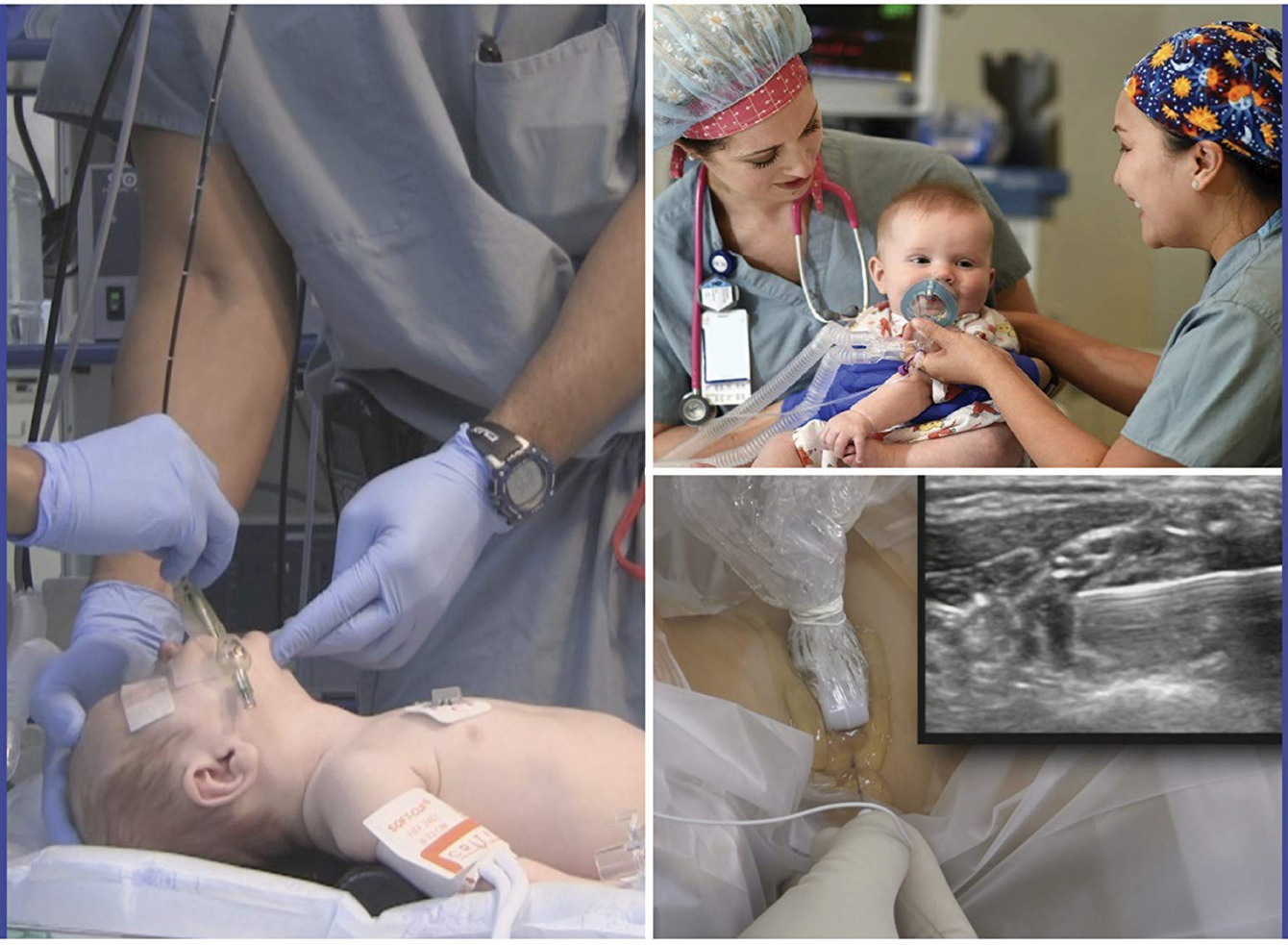
GREGORY'S PEDIATRIC ANESTHESIA

SIXTH EDITION



EDITED BY
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Wiley Companion Digital Edition

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Gregory's Pediatric Anesthesia

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WILEY Blackwell

Edition History
(5e, 2012) Blackwell Publishing Ltd; (4e, 2002, 3e, 1994, 2e, 1989, 1e, 1983) Churchill Livingstone

Registered Offices
John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Office
9600 Garsington Road, Oxford, OX4 2DQ, UK

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Library of Congress Cataloging-in-Publication Data

Names: Andropoulos, Dean B., editor. | Gregory, George A., 1934– editor.
Title: Gregory's pediatric anesthesia / edited by Dean B. Andropoulos, George A. Gregory.
Other titles: Pediatric anesthesia
Description: Sixth edition. | Hoboken, NJ : Wiley-Blackwell, 2020. | Includes bibliographical references and index.
Identifiers: LCCN 2019025692 (print) | LCCN 2019035827 (ebook) | ISBN 9781119371502 (cloth) | ISBN 9781119371526 (adobe pdf) | ISBN 9781119371519 (epub)
Subjects: MESH: Anesthesia | Pediatrics–methods | Infant | Child
Classification: LCC RD139 (print) | LCC RD139 (ebook) | NLM WO 440 | DDC 617.9/6083–dc23
LC record available at https://lccn.loc.gov/2019025692
LC ebook record available at https://lccn.loc.gov/2019025693

Cover images: Baby in the lap of a nurse © Kim P. Nguyen, Meghan E. Duggan, Julie E. Nicholson; Pediatric anesthesia procedure © Thomas Shaw; Pediatric surgery with ultrasound procedure © Thomas Shaw
Cover design by Wiley

Set in 9/11.5pt Palatino by SPi Global, Pondicherry, India

10 9 8 7 6 5 4 3 2 1

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Preface

Since the publication of the fifth edition of *Gregory's Pediatric Anesthesia*, both knowledge and practice have advanced in myriad ways. This sixth edition addresses these changes with significant updates and additions to all chapters, reflecting the most recent important literature in pediatric anesthesia. Significantly more figures and tables in nearly all chapters allow us to better illustrate the important principles in each area. Key points boxes have also been added after major sections in each chapter to enhance learning. New chapters have been added addressing the pediatric perioperative surgical home and anesthesia for non-cardiac surgery in congenital heart disease. Several extensive chapters from the fifth edition have been divided into two chapters to allow more space and detail: these cover development of the cardiovascular system and physiology of the cardiovascular system, anesthesia for trauma and anesthesia for burns, and anesthesia for otolaryngologic surgery and anesthesia for ophthalmologic surgery. The very popular case studies have been updated in all the clinical chapters.

The use of ultrasound for anesthesia procedures has increased exponentially in recent years, and this sixth edition has major extensive updates in ultrasound-guided regional anesthesia, with detailed descriptions and ultrasound images of the sonoanatomy for all the major blocks of the upper and lower extremities and trunk. Expanded use of point-of-care ultrasound for vascular access, including peripheral venous cannulation, for assessment of the heart and lungs, and for the airway and gastric contents are exciting new uses of this modality and are presented in detail.

Pediatric anesthesia is truly an international field and this edition's authors include those from the USA, UK, Canada, France, Germany, and Australia, giving a global perspective on practice in our ever-changing discipline. The History of Pediatric Anesthesia chapter was authored by Professor Kester Brown, who was the Director of Anaesthesia at the Royal Children's Hospital in Melbourne, Australia from 1974 to 2000. Professor Brown also traveled extensively around the world to teach and train anesthetists in many countries; the chapter reflects his extensive personal knowledge of the history of our field and its international roots. Sadly, Professor Brown passed away in November 2018; he will be remembered as one of the pioneers of pediatric anesthesia who trained hundreds of clinicians all over the world and who was a role model of professionalism, compassion, scientific curiosity, and outstanding clinical skill. He is missed by all in the community of pediatric anesthesiologists.

We would like to thank the editorial team at Wiley, including Publisher Claire Bonnett, Senior Project Editor Jennifer Seward, Senior Production Editor Nick Morgan, freelance project manager Nik Prowse, freelance copy-editors Ruth Hamilton Swan and Jane Andrew, and Editorial Assistant Bobby Kilshaw. This team of experts has been an absolute pleasure to work with and made many suggestions to improve the content and presentation of the enormous amount of material in this textbook.

Finally, as we acknowledged in the preface to the fifth edition, we thank our students, residents, and fellows for teaching us as much, or more, than we taught them. Their insightful questions, thoughts, and prodding is what academic medicine is about. This probing forces us all to get out of our comfort zone and think differently. We also thank the surgeons and nurses for their support. Most of all, we thank the patients and their parents for giving us the privilege of caring for them and for their continuing to teach us every single day. They are the best teachers!

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George A. Gregory

List of Abbreviations

α1-ATD	α1-antitrypsin deficiency
AA	artery-to-artery
AAA	asleep/awake/asleep
AAG	α1-acid glycoprotein
AAGA	accidental awareness under general anesthesia
AAP	American Academy of Pediatrics
ABA	American Board of Anesthesiology
ABC	ATP-binding cassette
ABP	arterial blood pressure
ACA	anterior cerebral artery
ACD	active compression-decompression device
ACE	angiotensin-converting enzyme
ACEi	angiotensin-converting enzyme inhibitor
ACGME	Accreditation Council for Graduate Medical Education
ACh	acetylcholine
AChR	acetylcholine receptor
ACL	anterior cruciate ligament
ACLS	advanced cardiac life support
ACO	accountable care organization
ACP	antegrade cerebral perfusion
ACRM	anesthesia crisis resource management
ACS	acute chest syndrome/abdominal compartment syndrome/ American College of Surgeons
ACTH	adrenocorticotropic hormone
ADAPT	Approaches and Decisions in Acute Pediatric TBI (trial)
ADH	antidiuretic hormone
ADHD	attention deficit hyperactivity disorder
ADP	adenosine diphosphate
ADPKD	autosomal dominant polycystic kidney disease
AED	automated external defibrillator
aEEG	amplitude-integrated EEG
AFP	α-fetoprotein
AGB	adjustable gastric band
AGP	α1-acid glycoprotein
AHA	American Heart Association
AHG	antihuman globulin
AHI	apnea-hypopnea index
AHT	abusive head trauma
AI	artificial intelligence
AICD	automatic implantable cardiac defibrillator
AIMS	anesthesia information management system/s
AIRS	Anesthesia Incident Reporting System
AKI	acute kidney injury
ALARA	as low as reasonably possible
ALCAPA	anomalous origin of the left coronary artery from the pulmonary artery
ALI	acute lung injury
ALL	acute lymphocytic leukemia
ALS	Advanced Life Support
ALT	alanine aminotransferase
AMC	arthrogryposis multiplex congenital
AML	acute myeloid leukemia
AMM	anterior mediastinal mass
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid
AN!	Anesthesia Now!
ANH	acute normovolemic hemodilution
ANP	atrial natriuretic peptide
AoDP	aortic diastolic blood pressure
AoV	aortic valve
AP	anterior–posterior
APCC	activated prothrombin complex concentrate
APL	adjustable pressure limiting
APM	alternative payment model
APRICOT	Anaesthesia PRactice In Children Observational Trial
APSF	Anesthesia Patient Safety Foundation
aPTT	activated partial thromboplastin time
AQI	Anesthesia Quality Institute
AR	adrenergic receptor/anesthetic room
ARB	angiotensin receptor blocker
ARDS	acute/adult respiratory distress syndrome
ARF	acute renal failure
ARPKD	autosomal recessive polycystic kidney disease
ARR	absolute risk reduction
ARVD	arrhythmogenic right ventricular dysplasia
ARVD/C	arrhythmogenic right ventricular dysplasia/cardiomyopathy
ASA	American Society of Anesthesiologists
ASC	ambulatory surgery center
ASCA	anti-*Saccharomyces cerevisiae*
ASD	atrial septal defect/autism spectrum disorder
ASIS	anterior superior iliac spine
ASO	arterial switch operation
AST	aspartate aminotransferase
AT	antithrombin
ATLS	Advanced Trauma Life Support
ATP	adenosine triphosphate
AUC	area under the curve
AV	arterial-venous/atrioventricular
AVC	atrioventricular canal
AVM	arteriovenous malformation
BBB	blood–brain barrier
BC	bronchogenic cyst
BDG	bidirectional Glenn
BDL	balloon dilation laryngoplasty
BiPAP	bi-level positive airway pressure
BIS	Bispectral Index
BMD	Becker muscular dystrophy
BMI	body mass index
BP	blood pressure
BPCA	Best Pharmaceuticals for Children Act
BPD	bronchopulmonary dysplasia
bpm	beats/min
BPS	bronchopulmonary sequestration
BSA	body surface area
BSEP	bile salt export pump

BT	bleeding time
B-T	Blalock–Taussig (shunt)
BUN	blood urea nitrogen
CA	cardiac arrest
cAMP	cyclic adenosine monophosphate
CAS	central anticholinergic syndrome
CAV	coronary artery vasculopathy
CBC	complete blood count
CBF	cerebral blood flow
CBFV	cerebral blood flow velocity
CBV	cerebral blood volume
CCAM	congenital cystic adenomatoid malformation
CCAS	Congenital Cardiac Anesthesia Society
CCL	cardiac cycle length
CCLS	Certified Child Life Specialist
CCTGA	congenitally corrected transposition of the great arteries
CDC	Centers for Disease Control and Prevention
CDH	congenital diaphragmatic hernia
CDS	clinical decision support
cEEG	continuous EEG
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
cGMP	cyclic guanosine monophosphate
CGRP	calcitonin gene-related peptide
CHCT	caffeine–halothane contracture test
CHD	congenital heart disease
CHEOPS	Children's Hospital of Eastern Ontario Pain Scale
CHF	congestive heart failure
CIOMS	Council of International Organization and Medical Sciences
CIRCI	critical illness-related corticosteroid insufficiency
CK	creatine kinase
CKD	chronic kidney disease
CLABSI	central line-associated bloodstream infection
CLD	chronic lung disease
CLE	congenital lobar emphysema
cLMA	classic laryngeal mask airway
CM	cardiomyopathy
C_{max}	maximum plasma concentration
CME	continuing medical education
cMEP	cortical motor evoked potential
$CMRO_2$	cerebral metabolic rate of O_2
CMS	Centers for Medicare and Medicaid Services
CMV	cytomegalovirus
CN	cranial nerve
CNI	calcineurin inhibitor
CNS	central nervous system
CO	cardiac output/carbon monoxide
COG	Children's Oncology Group
COX	cyclo-oxygenase
CP	cerebral palsy
CPAM	congenital pulmonary airway malformation
CPAP	continuous positive airway pressure
CPB	cardiopulmonary bypass
CPD	citrate, phosphate, dextrose
CPOE	computerized physician order entry
CPP	coronary/cerebral perfusion pressure
CPR	cardiopulmonary resuscitation
CrCL	creatinine clearance
CrCP	critical closing pressure
CRF	case report form/chronic renal failure
CRP	C-reactive protein
CRPS	complex regional pain syndrome
CRRT	continuous renal replacement therapy
CSF	cerebrospinal fluid
CSI	Cerebral State Index
CSV	Children's Surgery Verification
CT	closure time/computed tomography
CTFR	cystic fibrosis transmembrane conductance regulator
CUF	conventional ultrafiltration
CVA	cerebrovascular accident
CVC	central venous catheter
CVP	central venous pressure
CVR	CPAM volume ratio
CXR	chest x-ray
CYP	cytochrome P450
DA	dopaminergic
DAS	distal arthrogryposis syndrome
dB	decibel
DBS	double-burst stimulation
DC	direct current
DCD	cardiac (or circulatory) death/donation after cardiac death
DCM	dilated cardiomyopathy
DDAVP	1-deamino-8-D-arginine vasopressin
DEX	dexmedetomidine
DHCA	deep hypothermic circulatory arrest
DHPR	dihydropyridine receptor
DI	diabetes insipidus
DIC	disseminated intravascular coagulation
DILV	double-inlet left ventricle
DKA	diabetic ketoacidosis
DLCO	diffusing capacity for carbon monoxide
DLT	double-lumen tube
DMD	Duchenne muscular dystrophy
DNA	deoxyribonucleic acid
DORV	double-outlet right ventricle
DPPC	dipalmitoyl phosphatidylcholine
DS	Down syndrome
DSMC	data safety monitoring committee
d-TGA	dextro-transposition of the great arteries
DUF	dilutional ultrafiltration
EA	emergence agitation/esophageal atresia
EACA	ε-aminocaproic acid
EAT	ectopic atrial tachycardia
EB	epidermolysis bullosa
EBV	estimated blood volume/Epstein–Barr virus
ECC	emergency cardiovascular care
ECF	extracellular fluid
ECG	electrocardiogram
ECLS	extracorporeal life support
ECMO	extracorporeal membrane oxygenation
ECoG	electrocorticography
ECPR	extracorporeal cardiopulmonary resuscitation
ECW	extracellular water
ED	emergence delirium/emergency department
EDMD	Emery–Dreifuss muscular dystrophy
EDV	end-diastolic volume
EEG	electroencephalography
EF	ejection fraction
EGD	esophagogastroduodenoscopy
EGDT	early goal-directed therapy
eGFR	estimated glomerular filtration rate
EHR	electronic health record
EMA	European Medicines Agency
EMG	electromyography
EMLA	eutectic mixture of local anesthetics
EMO	Epstein Macintosh Oxford
EMR	electronic medical record
EMS	emergency medical services
ENaC	epithelial sodium channel
ENS	enteric nervous system
ENT	ear, nose, and throat
EP	evoked potential
EPA	Entrustable Professional Activity
EPO	erythropoietin
ERAS	enhanced recovery after surgery
ERCP	endoscopic retrograde cholangiopancreatography
ERF	established renal failure
ESR	erythrocyte sedimentation rate

ESRD	end-stage renal disease
ESRT	evoked stapedius reflex threshold
ERT	enzyme replacement therapy
ET	endothelin/end-tidal
$ETCO_2$	end-tidal carbon dioxide
ETT	endotracheal tube
ETV	endoscopic third ventriculostomy
EVD	external ventriculostomy drain
EXIT	*ex utero* intrapartum treatment
F_A	alveolar fraction
FAST	focused assessment with sonography for trauma
FC	fibrinogen concentrate
FCC	fetoscopic cord coagulation
FDA	Food and Drug Administration
FDAMA	FDA Modernization and Accountability Act
FET	end tidal fraction
FETO	fetal endoscopic tracheal occlusion
FEV_1	forced expiratory volume in 1 second
FFP	fresh frozen plasma
FGFR	fibrous growth factor receptor
FHF	first heart field
FHR	fetal heart rate
FiO_2	fraction of inspired oxygen
FISH	fluorescence *in situ* hybridization
FLACC	face, leg, activity, cry, and consolability (scale)
fMRI	functional MRI
FNHTR	febrile non-hemolytic transfusion reaction
FOB	fiberoptic bronchoscope
FRC	functional residual capacity
FS	fractional shortening
FVC	forced vital capacity
FVL	factor V Leiden
FWA	Federal Wide Assurance
G	Gauss
GA	gestational age/general anesthesia
GABA	γ-aminobutyric acid
GABAA	γ-aminobutyric acid receptor, A subunit
GAS	General Anesthesia compared to Spinal Anesthesia (Study)
GCP	Good Clinical Practice
GCS	Glasgow coma scale
GER	gastroesophageal reflux
GERD	gastroesophageal reflux disease
GFR	glomerular filtration rate
GH	growth hormone
GI	gastrointestinal
GP_i	globus pallidus internus
HAV	hepatitis A virus
Hb	hemoglobin
HbF	fetal hemoglobin
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCM	hypertrophic cardiomyopathy
Hct	hematocrit
HCV	hepatitis C virus
HES	hydroxyethyl starch
HFOV	high-frequency oscillatory ventilation
HFPV	high-frequency percussive ventilation
HHS	US Department of Health and Human Services
Hib	*Haemophilus influenzae* type b
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HLHS	hypoplastic left heart syndrome
HME	heat and moisture exchanger
HMWK	high-molecular-weight kininogen
HOCM	hypertrophic obstructive cardiomyopathy
HPV	hypoxic pulmonary vasoconstriction/human papillomavirus
HR	heart rate
HSA	human serum albumin
HSCT	hematopoietic stem cell transplantation
5-HT3	5-hydroxytryptamine-3
HTLV	human T-lymphotrophic virus
HTR	hemolytic transfusion reaction
HUS	hemolytic uremic syndrome
IAP	intra-abdominal pressure
IBD	inflammatory bowel disease
IBW	ideal bodyweight
IC	*in vitro* contracture (test)
ICD	implantable cardioverter-defibrillator
ICD-9	*International Classification of Diseases*, 9th edition
ICF	intracellular fluid
ICN	intensive care nursery
ICP	intracranial pressure
ICU	intensive care unit
ICW	intracellular water
ID	internal diameter
IDMs	infants of diabetic mothers
I:E	inspiratory:expiratory
IE	infective endocarditis
Ig	immunoglobulin
IHCA	in-hospital cardiac arrest
IHPS	idiopathic hypertrophic pyloric stenosis
IIS	interictal spikes
IJ	internal jugular
IJV	internal jugular vein
IL	interleukin
IM	intramuscular
IN	intranasal
IND	Investigational New Drug
iNO	inhaled nitric oxide
INR	international normalized ratio/interventional neuroradiology
INSS	International Neuroblastoma Staging System
IO	intraosseous
IOP	intraocular pressure
IPPV	intermittent positive pressure ventilation
IRB	institutional/investigational review board
ISHLT	International Society for Heart and Lung Transplantation
ITD	impedence threshold device
IU	international unit
IV	intravenous
IVC	inferior vena cava
IVH	intraventricular hemorrhage
JRA	juvenile rheumatoid arthritis
JVP	jugular venous pressure
LA	local anesthetic/left atrium
LBW	lean bodyweight
LC	locus coeruleus
LCR	laryngeal chemoreflex
LD50	median lethal dose
LDH	lactate dehydrogenase
LDLT	living donor lobar transplant
LED	light-emitting diode
LES	lower esophageal sphincter
LFCN	lateral femoral cutaneous nerve
LHR	lung to head ratio
LIC	low income countries
LiDCO	lithium dilution cardiac output
LITT	laser interstitial thermal therapy
LMA	laryngeal mask airway
LMIC	low middle income countries
LMWH	low molecular weight heparin
LOH	loss of heterozygosity
LOR	loss of resistance
LPS	lipopolysaccharide
LR	lactated Ringer's (solution)
L-R	left-to-right
LSMT	life-sustaining medical treatment
LV	left ventricle

LVAD	left ventricular assist device
LVEDP	left ventricular end-diastolic pressure
LVMI	left ventricular mass index
LVNC	left ventricular non-compaction
LVOT	left ventricular outflow tract
LVOTO	left ventricular outflow tract obstruction
MABL	maximum allowable blood loss
MAC	minimum alveolar concentration
MAP	mean arterial pressure
MAT	multifocal atrial tachycardia
MATE	multidrug and toxin extrusion transporter
MCA	middle cerebral artery
MCS	mechanical circulatory support
MDI	metered dose inhaler
MDR	multidrug-resistant
MEG	magnetoencephalography
MELD	model for end-stage liver disease
MEN2	multiple endocrine neoplasia type 2
MEP	motor-evoked potential
MER	microelectrode recording
MET	Medical Emergency Teams
MH	malignant hyperthermia
MIBG	metaiodobenzyl guanidine
MIPS	Merit-based Incentive Payment System
MIS	minimally invasive surgery
MMC	migrating motor complex/myelomeningocele
MMF	mycophenolate mofetil
MODS	multiple organ dysfunction syndrome
6-MP	6-mercaptopurine
MPAP	mean pulmonary artery pressure
MPD	maximum permissible dose
MPOG	Multicenter Perioperative Outcomes Group
MPP	myocardial perfusion pressure
MR	magnetic resonance
MRI	magnetic resonance imaging
MRI/A	magnetic resonance imaging and angiography
MRP	multiple drug resistance-associated protein
MRSA	methicillin-resistant *Staphylococcus aureus*
MS	molar substitution
MTD	maximal tolerated dose
MTHFR	methylenetetrahydrofolate reductase
mTOR	mammalian target of rapamycin
MTP	massive transfusion protocol
MUF	modified ultrafiltration
MVO_2	mixed venous oxygen saturation
MW	molecular weight
NAC	N-acetylcysteine
NACOR	National Anesthesia Clinical Outcomes Registry
NAD	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
NAT	nucleic acid testing
NCA	nurse-controlled analgesia
nCPAP	nasal continuous positive airway pressure
NCS	non-convulsive seizures
Nd:YAG	neodymium:yttrium-aluminum garnet
NDA	New Drug Application
NE	norepinephrine
NEB	neuroendocrine bodies
NEC	necrotizing enterocolitis
NEHI	neuroendocrine hyperplasia of infancy
NF	neurofibromatosis
NFκB	nuclear factor κB
NGT	nasogastric tube
NICU	neonatal intensive care unit
NIPPV	nasal intermittent positive pressure ventilation
NIRS	near-infrared spectroscopy
NMB	neuromuscular blocking drug
NMBA	neuromuscular blocking agent
NMDA	N-methyl-D-aspartate
NNT	number needed to treat
NO	nitric oxide
NORA	non-operating room anesthesia
NPH	nephronophthisis/neutral protamine Hagedorn (insulin)
NPMODS	new and progressive multiple organ dysfunction syndrome
NPO	nil per os
NPPE	negative pressure pulmonary edema
NRL	natural rubber latex
NRP	Neonatal Resuscitation Program
NS	normal saline
NSAID	non-steroidal anti-inflammatory drug
NSQIP	National Surgical Quality Improvement Program
NTCP	Na^+/taurocholate co-transporting polypeptide
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OAVS	oculo-auriculovertebral spectrum
OCT	organic cation transporter
OELM	optimal external laryngeal manipulation
OHCA	out-of-hospital cardiac arrest
OHRP	Office for Human Research Protections
OI	osteogenesis imperfecta
OIB	Oxford inflating bellows
OLV	one-lung ventilation
OMV	Oxford miniature vaporizer
OPTN	Organ Procurement and Transplant Network
OR	odds ratio/operating room
OSA	obstructive sleep apnea
OSAS	obstructive sleep apnea syndrome
OSCE	Objective Structured Clinical Examination
PA	pulmonary artery/pulmonary atresia
PABD	preoperative autologous blood donation
PAC	premature atrial contractions
$PaCO_2$	partial pressure of CO_2 in arterial blood
PACU	postanesthesia care unit
PAED	Pediatric Anesthesia Emergence Delirium (scale)
PALICC	Pediatric Acute Lung Injury Consensus Conference
PALS	pediatric advanced life support
PaO_2	partial pressure of oxygen in arterial blood
PAS	periodic acid–Schiff
PBS	prune belly syndrome
PC	protein C
PCA	patient-controlled anesthesia/postconceptual age
PCC	prothrombin complex concentrate
PCRA	patient-controlled regional anesthesia
PCWP	pulmonary capillary wedge pressure
PD	pharmacodynamic/peritoneal dialysis
PDA	patent ductus arteriosus
PDE	phosphodiesterase
PEA	pulseless electrical activity
PEC	Program Evaluation Committee
PEEP	positive end-expiratory pressure
PEFR	peak expiratory flow rate
PEG	percutaneous endoscopic gastrostomy
PELD	pediatric end-stage liver disease
PELOD	PEdiatric Logistic Organ Dysfunction (score)
PET	positron emission tomography
PEVPPS	Preverbal, Early Verbal Pediatric Pain Scale
PFC	persistent fetal circulation
PFIC	progressive familial intrahepatic cholestasis
PFO	patent foramen ovale
PFT	pulmonary function test
PG	prostaglandin
PGD	primary graft dysfunction
PGE1	prostaglandin E1
P-gp	P-glycoprotein
PH	pulmonary hypertension
PHBQ	Post Hospitalization Behavior Questionnaire
PICC	percutaneously/peripherally inserted central catheter
PiCCO	pulse-contour analysis of the arterial waveform

PICOT	Population, Intervention, Comparison, Outcome, Timeline
PICU	pediatric intensive care unit
PIPP	premature infant pain profile
PIV	peripheral intravenous catheter
PK	pharmacokinetic/prekallikrein
PKA	protein kinase A
PKC	protein kinase C
PLV	protective lung ventilation
P-MODS	Pediatric-Multiple Organ Dysfunction Score
PN	parenteral nutrition
PNAM	presurgical nasal alveolar molding
PNB	peripheral nerve block
PNEC	pulmonary neuroendocrine cells
PO	per os
POAH	preoptic anterior thalamus
POCA	Pediatric Perioperative Cardiac Arrest (registry)
POCUS	point-of-care ultrasound
POLST	physician order for life-sustaining treatment
PONV	postoperative nausea and vomiting
POV	postoperative vomiting
POVL	postoperative visual loss
PPH	portopulmonary hypertension
PPHN	persistent/primary pulmonary hypertension of the newborn
PPIA	parental presence at induction of anesthesia
ppm	parts per million
PPROM	preterm premature rupture of membranes
PPV	positive pressure ventilation
PQRS	Physician Quality Reporting System
PRA	panel reactive antibody
PRAE	perioperative respiratory adverse event
PRAN	Pediatric Regional Anesthesia Network
PRBC	packed red blood cells
PREA	Pediatric Research Equity Act
PRIS	propofol infusion syndrome
PRS	Pierre Robin sequence
PS	protein S
PSH	perioperative surgical home
PSRC	Pediatric Sedation Research Consortium
PT	prothrombin time
PTLD	post-transplant lymphoproliferative disorder
PTP	post-transfusion purpura
PTSD	post-traumatic stress disorder
PTT	partial thromboplastin time
PUBS	percutaneous umbilical blood sampling
PUV	posterior urethral valves
PV	postoperative vomiting/pulmonary valve
PVB	paravertebral block
PVC	premature ventricular contractions/polyvinyl chloride
PVO_2	pulmonary venous O_2 content
PVR	pulmonary vascular resistance
pVT	pulseless ventricular tachycardia
QL	quadratus lumborum
Qp:Qs	ratio of pulmonary to systemic blood flow
RA	right atrium
RAE	Ring–Adair–Elwyn
RAP	right atrial pressure
RBBB	right bundle branch block
RBC	red blood cell
RCM	radiocontrast media/restrictive cardiomyopathy
RCP	regional cerebral perfusion
RCT	randomized controlled trial
RDS	respiratory distress syndrome
REC	research ethics committee
REM	rapid eye movement
RF	radiofrequency/rheumatoid factor
RFA	radiofrequency ablation
RFID	radiofrequency identification
rFVIIa	recombinant activated factor VII
R-L	right-to-left
RLFP	regional low-flow perfusion
ROP	retinopathy of prematurity
ROSC	return of spontaneous circulation
RPGN	rapidly progressive glomerulonephritis
RR	relative risk
RRT	renal replacement therapy
RSI	rapid-sequence induction
RSII	rapid-sequence induction and intubation
rSO_2	regional oxygen saturation
RSV	respiratory syncytial virus
RV	right ventricle/residual volume
RVOT	right ventricular outflow tract
RYGB	Roux-en-Y gastric bypass
SAE	serious adverse event
SAFEKIDS	Safety of Key Inhaled Anesthetics in Children (study)
SAH	subarachnoid hemorrhage
SaO_2	percent arterial oxyhemoglobin saturation
SAR	specific absorption rate
SCD	sickle cell disease
SCFE	slipped capital femoral epiphysis
SCh	succinylcholine
SCIWORA	spinal cord injury without radiological abnormalities
SCPA	superior cavopulmonary anastomosis
SCT	sickle cell trait/sacrococcygeal teratoma
$S_{CV}O_2$	central venous oxygen saturation
SD	standard deviation
SFLP	selective fetoscopic laser photocoagulation
SGA	small for gestational age/supraglottic airway
SGS	subglottic stenosis
SHF	second heart field
SIADH	syndrome of inappropriate secretion of antidiuretic hormone
SIDS	sudden infant death syndrome
SIOP	International Society of Pediatric Oncology
SIRS	systemic inflammatory response syndrome
$SjvO_2$	oxygen saturation in jugular venous bulb
SLC	solute carrier
SNP	sodium nitroprusside
SOFA	Sequential Organ Failure Assessment
SOS	Shikani optical stylet
SPA	Society for Pediatric Anesthesia
SPECT	single photon emission computed tomography
SPLIT	Studies in Pediatric Liver Transplantation
SR	sarcoplasmic reticulum
SSCG	Surviving Sepsis Campaign Guidelines
SSEP	somatosensory-evoked potential
SSRI	selective serotonin reuptake inhibitor
STN	subthalamic nuclei
STS	Society of Thoracic Surgeons
SV	single ventricle
SVAS	supravalvar aortic stenosis
SVC	superior vena cava
SVL	Storz video laryngoscope
SVR	systemic vascular resistance
SVT	supraventricular tachycardia
T	Tesla
TA	tranexamic acid/tricuspid atresia
T&A	tonsillectomy and adenoidectomy
TACO	transfusion-associated circulatory overload
TA-GVHD	transfusion-associated graft versus host disease
TAH	total artificial heart
TAP	transversus abdominis plane
TB	tuberculosis
TBI	traumatic brain injury/total body irradiation
TBSA	total body surface area
TBV	total blood volume
TBW	total body water/total bodyweight
TCD	transcranial Doppler ultrasound
TCI	target-controlled infusion
TCPC	total cavopulmonary connection

TEE	transesophageal echocardiogram
TEF	tracheoesophageal fistula
TEG	thromboelastography
TF	tissue factor
TFPI	tissue factor pathway inhibitor
TGA	transposition of the great arteries
TGF	transforming growth factor
THAM	tris(hydroxymethyl)aminomethane
THRIVE	transnasal humidified rapid insufflation exchange
TIVA	total intravenous anesthesia
TLR	Toll-like receptor
TLV	total lung volume
T_{max}	time to maximum concentration
TMJ	temporomandibular joint
TNF	tumor necrosis factor
TOF	tetralogy of Fallot/train-of-four
TOI	tissue oxygenation index
tPA	tissue plasminogen activator
TPN	total parenteral nutrition
TPTN	transpulmonary thermodilution
TRALI	transfusion-related acute lung injury
TRAP	twin reversed arterial perfusion (sequence)
TRICC	Transfusion Requirements in Critical Care (trial)
TRIM	transfusion-related immunomodulation
TSC	tuberous sclerosis complex
TSH	thyroid stimulating hormone
TT	thrombin time
TTN	transient tachypnea of the newborn
TTP	thrombotic thrombocytopenic purpura
TTTS	twin–twin transfusion syndrome
TV	tricuspid valve
TXA	tranexamic acid
UBF	uterine blood flow
UDP	uridine diphosphate
UDPGA	uridine diphosphate glucuronic acid
UDPGT	uridine diphosphate glucuronyltransferase
UDT	undescended testes
UGT	UDP-glucuronosyltransferase
UNOS	United Network for Organ Sharing
UPJ	ureteropelvic junction
URI/URTI	upper respiratory tract infection
US	ultrasound
UTI	urinary tract infection
UVJ	ureterovesical junction
VA	veno-arterial/ventriculo-arterial/Veterans Administration
VACTERL	vertebral, anal, cardiac, tracheoesophageal, renal and limb anomalies
VAD	ventricular assist device
VAE	venous air embolism
VAS	vesicoamniotic shunt/visual analog scale
VATS	video-assisted thoracoscopic surgery
VCFS	velocardiofacial syndrome
VEGF	vascular endothelial growth factor
VEPTR	vertical expandable prosthetic titanium rib
VF	ventricular fibrillation
VGAM	vein of Galen aneurysmal malformation
VHL	von Hippel–Lindau
VIP	vasoactive intestinal polypeptide
VMI	visual motor integration
VO_2	maximum oxygen uptake
VSD	ventricular septal defect
VT	ventricular tachycardia
VTi	velocity time integral
VUR	vesicoureteric reflux
VV	veno-venous
vWD	von Willebrand disease
vWF	von Willebrand factor
vWF:RCo	ristocetin co-factor assay
WB	whole blood
WBC	white blood cell
WEB	wire-guided endobronchial blocker
WFSA	World Federation of Societies of Anaesthesiologists
WHO	World Health Organization
Wu	Woods unit
WUS	Wake Up Safe
ZBUF	zero-balance ultrafiltration

CHAPTER 1

Ethics and Professionalism in Pediatric Anesthesia

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Introduction

The key to the ethical practice of pediatric anesthesia is: *Treat every child and family with the grace and consideration with which you would want your child and family treated*. Here are seven maxims:

1. *Remember that surgery is a big deal*. Reminding yourself that this banal case is a lifetime event for the child and family helps you be kind and respectful to the child and family. It boosts your ability to mitigate the production pressure that hurries you to induce anesthesia before the premedication has taken effect, inadequately prepare a nervous adolescent for insertion of an intravenous catheter, or skirt safety guidelines.
2. *Meet the needs of the child and family*. Focus on process by being patient, calm, flexible, and nonjudgmental. Anxious, sleep-deprived parents receiving complicated information may need to hear it several times to understand it or may react strongly to the seemingly unremarkable. Interact with the intent of determining their needs, whether it be the extent of information, the preferences for decision making, or the need for reassurance. Respond directly to questions.
3. *Be humble*. As a professional, it is tempting to believe you know what is best. But many of the choices families make reflect values, anxieties, and personal, family, and community experiences that are difficult for you to know, much less appreciate. Denigrating families for choosing what you believe to be a less optimal albeit acceptable choice ravages professionalism and mars interactions with all patients. If you think a decision is unacceptable, consult with respected colleagues before pursuing administrative or legal interventions.
4. *Assume responsibility for the children and their families*. "Own" care for the child and family to ensure that every little thing goes as well as possible. This includes: bringing a chair for the third adult; finding someone to answer questions unrelated to perioperative clinical care; doing a thorough preoperative evaluation; making the extra effort to insert the IV in a way that does not impede the dominant hand; always using the optimal anesthetic technique; being alert for errors in the operating room unrelated to you; and ensuring children and families are physically and emotionally well postoperatively. If you would do it for your child, you should do it for every child.
5. *Serve patients*. Medicine is a noble service profession. For the most part, patients' preferences, values, and needs supersede ours. Our values become relevant only after thorough, thoughtful, and careful consideration and consultation.
6. *Hone your mastery*. Strive to provide first-rate care, critically consider what you know and how you know it, and seek help freely [1].
7. *Use empathic behavior*. Clinicians need to overtly communicate that they understand and appreciate the perspective and experience of the child and family [2]. An effective way to communicate empathy is a heartfelt "I wish things were different" [3].

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

Although clinicians may think of medical ethics in dramatic terms – withdrawing life-sustaining therapy, allocating organs for transplant – medical ethics floods our daily practice. Consider the clinician who recommends postponing surgery in an infant because of a borderline upper respiratory infection. Should they be flexible if the infant has missed three surgical dates for non-medical reasons? How should they respond to a parental request to proceed? Within these seemingly medical decisions lie the ethical components of informed consent and obligations to the child and family. How do we decide how much weight to give the parents' strong desire to proceed? Does it matter why they want to proceed (guilt over missing the previous appointments? Concern about their child's health? Convenience because grandma is in town to care for siblings? Concern about being able to get time off from work again? Scheduling because the child will spend the summer with an out-of-town parent, effectively delaying the operation until fall? etc.). Should we even consider the effects on the family? What if there is concern that the parents will not reschedule surgery?

Ethical dilemmas occur when clinicians are faced with "oughts" – that which a physician is bound by duty to do – that conflict. In the above example, clinicians ought to base proceeding with surgery solely on the child's best interest, which may include the effects of the upper respiratory infection and the likelihood that the child will get a timely operation. Medical ethics provides the process by which to resolve these apparently conflicting "oughts."

Resolving ethical dilemmas is not a matter of being a moral person. Identifying, diagnosing and managing ethical conflicts requires the same extent of expertise that is required to identify, diagnose, and manage myocardial ischemia. Training and experience in resolving ethical dilemmas enables ethics consultants to identify the dilemma and critical facts, apply ethical principles and case-based analysis, articulate precise questions, and have the moral imagination to create more palatable solutions.

Despite erstwhile efforts, fewer than 51% of pediatric residents correctly answered questions about some aspects of patient confidentiality, genetic testing, pediatric assent and the ethical similarity of withholding and withdrawing potentially life-sustaining medical treatments (LSMT) [4].

Deficits like these highlight the importance of ethics committees and their consultation services. Clinicians may find consultation services particularly helpful with concerns about disagreements among families and clinicians, appropriate decision-making roles for adolescents, decisions about end-of-life care, and professional obligations [5,6].

Members of ethics committees include representatives from throughout the hospital such as chaplains, administrators, social workers, nurses, and physicians. Many committees also include local community representatives. Depending on local practice, consultations may be performed by an individual, a small group, or the entire ethics committee. Most ethics consultation services permit anyone with standing to request a consultation, which fundamentally includes all clinicians who participate in the care of the patient [5]. Most services enter a written report into the clinical record. The standard of care is that ethics consultation services advise only and have no formal authority. A committee with a strong record, however, has substantial informal authority. The case study provides an example of an ethics consultation.

The law is not a desirable substitute for resolving ethical dilemmas. The law represents a lower bound for acceptable behavior, whereas ethics articulates a standard to which we should aspire. Pragmatically, the law does not provide clear guidance because most law surrounding ethical dilemmas is case law. In addition, the frequently adversarial legal process may pollute future family–clinician–hospital relations. Crude statutes and regulations are unable to govern complex medical care.

KEY POINTS: THE ETHICAL PRACTICE OF PEDIATRIC ANESTHESIA

- Pediatric medical ethics is a broad and changing field
- Identification, diagnosis, and management of ethical issues requires expert knowledge, experience, and skill
- Anyone involved in a patient's care can request an ethics consultation

The informed consent process for children

The doctrine of informed consent centers on the belief that patients have a right to self-determination. The right to self-determination is actualized through the legal concept of competency. Except in specific situations, minors are not legally competent to consent for healthcare. But minors do have varying degrees of decision-making capacity, and minors should be included in medical decision making to the extent permitted by the child and situation (Box 1.1) [7].

The process of pediatric informed consent depends on the age and development of the child (Table 1.1). The concepts

Box 1.1: Elements of consent and assent as defined by the American Academy of Pediatrics [7]

Elements of informed consent for medical decision making

- Provision of information about the following:
  - Nature of the illness or condition
  - Proposed diagnostic steps and/or treatments and the probability of their success
  - The potential risks, benefits, and uncertainties of the proposed treatment and alternative
  - Treatments, including the option of no treatment other than comfort measures
- Assessment of patient and surrogate understanding and medical decision-making capacity, including assurance of time for questions by patient and surrogate
- Ensure that there is voluntary agreement with the plan

Practical aspects of assent by pediatric patients for medical decision making

- Help the patient achieve a developmentally appropriate awareness of the nature of the condition
- Tell the patient what to expect with tests and treatments
- Make a clinical assessment of the patient's understanding of the situation and the factors influencing how they respond (including whether there is inappropriate pressure to accept testing or therapy)
- Solicit an expression of the patient's willingness to accept the proposed care

Table 1.1 Graduated involvement of minors in medical decision making

Age	Decision-making capacity	Techniques
Under 6 years	None	Best interest standard Harm threshold standard
Ages 7–11 years	Developing	Informed permission Informed assent
Ages 12–18 years	Cognitive skills developed Maturity developing	Informed assent (approaching informed consent as developmentally appropriate) Informed permission
Mature minor	Developed, as legally determined by a judge, for a specific decision	Informed consent
Emancipated minor	Developed, as determined by a situation (e.g. being married, in the military, economically independent)	Informed consent

This broad outline should be viewed as a guide. Specific circumstances always must be taken into consideration. When children are in the upper range of an age bracket, limited or full inclusion of a more developmentally advanced technique, such as the use of assent for a 6-year-old, may be appropriate.

of best interest, informed permission, and assent are used when considering pediatric informed consent. For convenience, the term "parent" will be used to describe the child's surrogate decision maker. Parents are not always the legal surrogate decision maker and parental authority may be limited in adolescents. The term "decision makers" will refer to those involved in the specific decision and may include parents, children, and their advisors.

The primary lesson of this chapter should be to respect the experiences and opinions of children. The American Academy of Pediatrics emphasizes that "no one should solicit a patient's views without intending to weigh them seriously. In situations in which patients will have to receive medical care despite their objections, the patient should be told that fact and should not be deceived." [8].

The best interest standard and informed permission

Informed consent can be given only by the patient. Some advocate for the term "informed permission" for when the parent provides legal consent and ethical decision making for the child, to emphasize that the consent is not by the patient [8]. This conceptual framework highlights the ethical limits of parental decision making. It does not affect the legal obligation to obtain informed consent from the parents as defined by local statutes.

Children younger than the age of 7 typically have insufficient decision-making capacities to participate effectively in the informed consent process. When children cannot effectively participate, or when parents are unable to base a decision on previous interactions with the child, the best interest standard traditionally guides decision making. This standard requires determining who will make the decision and what is in the child's best interest. Best interest does not mean the best care as defined by the clinicians. There are often several acceptable options, and clinicians rely on parents to determine which one is in the child's best interest. Parents are given considerable latitude in decision making because society values the role of family, parents want the best for their children, and families often have to live with the result of the choices. Although parents may be wrong in determining the preferences of their child's future self, many accept that parental values serve as a reasonable approximation of those future values [9].

Parental decisions should be scrutinized if they appear to fall outside of the boundaries of acceptable care. Boundaries are determined by the extent and likelihood of potential harms by the intervention or its absence, the likelihood of success, and the overall risk-to-benefit ratio.

The harm threshold standard may be more accurately named and conceptually useful than the best interest standard for determining whether to limit parental decision making. The harm threshold standard bases decisions on whether a parental choice threatens the health and safety of the child [10–12]. Many clinicians probably use a form of this standard to identify the borders of unacceptable decision making.

When parents appear to choose unacceptable treatments, clinicians should consult with colleagues to assess the acceptability of the decision and, if necessary and appropriate, to participate in the discussion. Seek to resolve disagreements without resorting to legal intervention. But the state has an interest in protecting those who cannot protect themselves. If other options have failed, clinicians should initiate an evaluation if they believe parents to be choosing unacceptable treatments.

Informed assent: the role of the child

Children should participate in decision making to the extent their development permits [7]. Decision-making capacity for children is based on the ability to understand and recall the information, to reason, which includes evaluating the risks and benefits of the options presented, to appreciate the effect of the decision on themselves, which requires advance abstract thinking, and to make a choice. Neurobiological evidence suggests that these abilities change with age and experience and are frequently present by the age of 12 [13].

For children between the ages of 7 and 11, clinicians should seek both informed permission from the parent and assent and participatory decision making from the child. Common decisions in which children participate include whether a 6-year-old wants sedation prior to an inhalation induction, whether a 10-year-old wants inhalation or intravenous induction of anesthesia, and whether an 11-year-old wants a peripheral nerve catheter for postoperative analgesia.

Clinicians should assume that adolescents 12 years and older have sufficient decision-making capacity to fulfill the ethical obligations of informed consent. Their decision-making capacities are affected, however, by their personality,

the situation, emotional impulsiveness, and a tendency to undervalue long-term consequences. The tendency to take risks increases in emotional situations. For these reasons, the influence an adolescent has on decision making is tempered by the adolescent's maturity and the risks of the decision. Decisions are considered higher risk when they include an increased likelihood of permanently lost opportunities that have noteworthy consequences. For example, delayed scoliosis surgery may increase the extent of the curve, subsequently impairing cardiopulmonary function. These impairments can affect the quality of life, future morbidity, and lifespan. In determining the extent of risk in a decision, the quality and relevance of the data must be rigorously considered.

Emancipated minors and the mature minor doctrine

Emancipated minors are minors who have a statutory right to legally consent for their own healthcare decisions. States often award this status to patients who are in the military, who are married, who have children, and who are economically independent. To be declared a mature minor, the patient must be determined by a judge to be legally and ethically capable of giving legal consent in a specific situation. Judges consider mature minor status based on the extent of the risk in the decision and the developmental maturity and age of the child.

Disclosure

The legal standard for most of the United States is the reasonable person standard, which declares that the information disclosed should satisfy the hypothetical reasonable person.

It is ethically, morally, and legally unclear as to what satisfies the reasonable person standard for informed consent for pediatric anesthesia. Children and families differ about the type and depth of information they want to receive, their desire to participate in making decisions, and their goals of the informed consent discussion [14]. For example, some want information to make decisions, some want information because they feel obligated to be informed, or some want reassurances that everything will go well, which often results in wanting less information. Sociodemographic characteristics do not reliably predict preferences for disclosure and decision making. These preferences may change given the surgery, stress, and other factors present that day.

A better approach is for the clinician to communicate only the necessary information based on the child's medical status, the risks of the procedure, and the availability of acceptable clinical options, and then seek to meet the informational and decision-making needs of the child and family by asking if they want to know more [15]. This does not burden those tepid about further information while meeting the needs of those who seek a more complete discussion. Patient-driven interactions likely reduce malpractice lawsuits. The likelihood of being sued based on informed consent malpractice issues is very rare. But the improved satisfaction that comes from patient-driven interactions (or, more simply, from listening to and responding to the decision makers' needs and requests) leads to decreased complaints and lawsuits in general [16].

Postoperative nausea and vomiting (PONV) is an archetype of the issues clinicians may want to routinely communicate unless explicitly deferred. PONV is: (1) of great concern to parents; (2) addressable by early use of medications; (3) modifiable by behavioral and eating strategies; and (4) relevant to seeking postoperative medical interventions. Yet, in one study, PONV was discussed in only 36% of preoperative discussions [17].

The literature varies in what must be told to patients and is rarely prescriptive [18]. Practices vary, even within the same institution. For example, in a 2012 observational study of consent for pediatric anesthesia, the five most commonly discussed risks per conversation were nausea and vomiting (36%), sore throat (35%), allergy (29%), hypoxia (25%), and emergence delirium (19%) [17]. Trainees discussed about three risks in each conversation as compared to attendings who discussed only one. Nearly a third of interactions used only general statements about anesthesia risk without further information about their nature, ramifications, or incidence. It is unclear whether these variations are appropriate responses to decision makers' needs or baseline variations in standards.

Adjunct techniques, like regional analgesia, require a modification of the "meet the decision makers' needs" approach. Consider extensive knee surgery in an otherwise healthy young adolescent. Because decision makers understand that general anesthesia is essential for the surgery to proceed, they may defer more thorough risk information because it will not sway their decision. But in this child, regional analgesia is an option but not a necessity. Decision makers should be aware that regional analgesia is not essential to the surgery, and, because there is a greater role for choice, decision makers should be more extensively informed about the risks and benefits.

Patients have difficulty understanding quantitative risks. Table 1.2 describes strategies for communication [19–21].

Informed refusal

Refusal of a significant recommendation requires clinicians to more fully inform decision makers about the risks, benefits, and alternatives than if the decision makers were following the recommendation. This helps ensure that decision makers are as knowledgeable as possible about the risks of selecting a less desirable path.

Children with significant decision-making capacity (perhaps around the age of 10 years but certainly by the age of 12 years) might refuse non-emergent procedures. Clinicians should respect this refusal of assent and conscientiously avoid pressuring the child. Coercing or manipulating a child into having a procedure damages the child's trust of the medical profession and impairs future cooperation with their care. Maintenance of trust is particularly important in children with chronic medical conditions.

Strategies for resolving conflicts center on maintaining communication, clarifying misunderstandings about the anesthetic and surgical experience, and decreasing the anxiety of both the child and parents. The goal is to resolve the problem without impairing the relationships among the child, parents, and clinicians. Clinicians may want to emphasize that nothing will happen without the child's approval, *but only if that is true*. Moving the discussion away from the preoperative area or letting the child dress in street clothes will often reduce stress and improve communication.

Clinicians should recognize the distinction between using pharmacologic agents to calm an anxious adolescent to enable

Table 1.2 Communicating quantitative risk to patients [19–21]

Understanding quantitative risks may help patients make decisions. Presentation is key to understanding. Consider a patient who is concerned about PONV. They want to know the relative risks of PONV in regional anesthesia (30%) versus general anesthesia (50%).

Approach

1. Use language at the 8th grade level.
2. Use absolute risks and frequencies.
3. Avoid relative descriptions like "regional anesthesia decreases the rate of PONV by 50% compared to general anesthesia."
4. Because patients have different abilities, data should be presented in a variety of ways cautiously. Too much information too quickly is confusing.

Verbal presentations	Analysis
"With regional anesthesia, there is a 30% chance of PONV. With general anesthesia, there is a 50% change of PONV"	• Relies on an understanding of percentages that is not universally present
"With regional anesthesia, there is a 30% chance of PONV, which is *3 out of 10 patients*. With general anesthesia, there is a 50% change of PONV, which is *5 out of 10 patients*"	• Adds a frequency (*3 out of 10 patients; 5 out of 10 patients)* ◦ Presents a second avenue to understanding ◦ Is often easier to understand
"With regional anesthesia, there is a 30% chance of PONV, which is 3 out of 10 patients. With general anesthesia, there is a 50% chance of PONV, which is 5 out of 10 patients. That means that *2 more patients out of 10* will have postoperative vomiting if we use general anesthesia	• Adds a direct comparison using an absolute number (*2 more patients out of 10*), which is often helpful • Increases the language complexity • Possible solutions ◦ Present information in smaller chunks, which makes it easier to understand ◦ Use pictorial representation

Pictorial presentations — **Analysis**

Pictorial representation #1

- Clinician can draw ten dots and fill in the appropriate number
- Described as the number of patients out of 10 who will have PONV with that type of anesthesia

	1	2	3	4	5	6	7	8	9	10
Regional anesthesia	■	■	■	□	□	□	□	□	□	□
General anesthesia	☒	☒	☒	☒	☒	□	□	□	□	□

Pictorial representation #2

- One line can be used to compare two treatments
- The additional patients who will have PONV can be circled or highlighted

	1	2	3	4	5	6	7	8	9	10
Regional anesthesia General anesthesia	■	■	■	☒	☒	□	□	□	□	□

proceeding and using pharmacologic agents to manipulate the adolescent into proceeding. Consider the 15-year-old who becomes overwhelmingly anxious and refuses surgery. It would be inappropriate to unilaterally administer midazolam to gain cooperation. On the other hand, it is wholly appropriate to seek the adolescent's assent to receive sufficient anxiolysis so they may undergo the procedure. Time, respect, and simple strategies often resolve issues satisfactorily and efficiently.

Children of Jehovah's Witnesses

Jehovah's Witnesses interpret biblical scripture to mean that anyone who accepts blood will be "cut off from his people" and not receive eternal salvation [22]. Adults may refuse potentially life-sustaining transfusion therapy. The presumption is that they are making an informed and voluntary decision. Courts commonly authorize necessary perioperative transfusions for children of Jehovah's Witnesses. The courts base these decisions on the doctrine of *parens patriae,* the obligation of the state to protect the interests of incompetent patients.

Clinicians should directly address perioperative transfusion therapy when caring for a child of Jehovah's Witnesses. The child and family should be informed that, as with all patients, attempts will be made to follow the family's wishes within the standard of care. Because refusal of transfusion therapy is deemed a "matter of conscience," the clinicians should clarify acceptable interventions. Deliberate hypotension, deliberate hypothermia, and hemodilution are often acceptable techniques. Synthetic colloid solutions, dextran, erythropoietin, desmopressin, and preoperative iron are usually acceptable. Some Jehovah's Witnesses will accept blood removed and returned in a continuous loop, such as cell saver blood. The family should be informed that in unexpected critical situations requiring transfusion, the clinician will transfuse while concomitantly or later seeking legal authorization. Clinicians should be familiar with the hospital's preferred mechanism for obtaining legal authorizing. In instances where the likelihood of requiring blood is high, or the local judiciary is not that familiar with case law for Jehovah's Witnesses, clinicians may choose to obtain the court order preoperatively if there is a palpable likelihood of transfusion.

Elective procedures may be postponed until the child is of sufficient age and maturity to decide about transfusion therapy. But delays may increase the risk of morbidity or the quality of outcome. Factors affecting whether to proceed

include the quantitative and qualitative changes in risks and benefits.

Reasonable people disagree as to whether clinicians should change their transfusion triggers for a child of a Jehovah's Witness. On one hand, when to transfuse is often a judgment call, affected by the child's baseline health, clinical findings, lab values, expectation of future blood loss, knowledge of surgeon and procedure, risk tolerance, and gestalt. Given that, it may be reasonable to transfuse later than normal. On the other hand, although clinicians acknowledge transfusion triggers vary, they presumably transfuse only when necessary. In this analysis, changing transfusion triggers provides less optimal care, which is inconsistent with the obligation to treat the child of a Jehovah's Witness like any other child.

When an adolescent wishes to refuse perioperative transfusion, the minor needs to articulate sufficiently mature reasons, be properly engaged with the religion, and understand ramifications to self and family about possible outcomes. A private conversation is necessary to assess for coercion or manipulation. Ethics consultations are particularly useful in making these determinations. When brought to court, judges often determine whether adolescents may refuse transfusion by the likelihood of significant benefits like 5-year survival and the practicality of initiating and maintaining transfusion therapy. Children as young as 14 have been given the right to decline transfusion therapy, even when they had a high probability of 5-year survival.

When arrangements are made to honor an adolescent's preferences to refuse transfusion, plans must be made to ensure other perioperative and postoperative clinicians are willing to honor the agreements, as well as to ensure a plan is in place to honor the agreement in case the child needs to return to the operating room urgently.

Emergency care

Emergency therapy is considered desirable and should be given to the minor who does not have a parent available to give legal consent or informed permission [23]. Clinicians should err on the side of treating if they are unsure whether to wait for parental consent.

Emergency therapy becomes more complex when adolescents nearing the age of majority refuse to assent to care. Urgency may not permit the extended evaluation necessary to determine whether the minor has sufficient decision-making capacity. Clinicians should use the best interest standard to guide therapy acutely. Consider a 15-year-old with an acute cervical fracture who refuses emergency stabilization. Forgoing cervical stabilization may cause irrevocable harm. The typical adolescent's decidedly short-term outlook and overvaluation of physical abilities make it unlikely that the adolescent possesses sufficient decision-making capacity in the acute situation. It is hard to imagine honoring an adolescent's refusal of emergent therapy in this case.

The temporarily impaired parent

Chemically intoxicated parents may be disruptive, dangerous, and incapable of fulfilling surrogate responsibilities. Clinicians should use the least restrictive means to protect patient and parent confidentiality while ensuring the safety of the child, the impaired parent, and others present.

Although it seems ethically and legally prudent to postpone routine treatment until informed permission and legal consent can be obtained from an unimpaired parent, clinicians should weigh the benefits of postponement with the risk that impaired parents may not reliably return. It may be in the child's best interests to proceed with a routine procedure even though the impaired parent is unable to give informed permission and legal consent. Consultation with legal, risk management, and ethics colleagues may help.

Consent for pediatric procedures without direct benefits

Pediatric clinicians may encounter children undergoing bone marrow donation for siblings who would benefit from hematopoietic stem cell transplantation [24]. The stem cell donor receives no direct medical benefit from the donation. The major risks of donation are the anesthetic and the potential need for transfusion.

The benefit of donation is commonly considered to be the psychosocial benefit of helping a family member. Pediatric donors report that the benefits of donations outweigh the physical harm [25]. As can be expected in such a complex dynamic, however, donation can result in moderate post-traumatic stress. Some donors felt they did not have a choice about being a donor and that they may be responsible for unsuccessful transplants.

Given the risks and benefits and the unique position of families in society, the American Academy of Pediatrics believes it is ethically permissible for minors to donate bone marrow when certain requirements are met, including a close relationship between donor and recipient, considerations of the risks of bone marrow donation, a likelihood of benefit to the recipient, and an absence of a suitable medically equivalent adult relative. Parental consent and patient assent is needed. Independent advocates for potential donors have been used to minimize the potential for inappropriate parental influence [26].

Genetic testing and biobanking

While genetic testing can provide the substantial benefits of confirming a diagnosis, determining carrier status, or testing for disorders of late onset, it can also harm by informing people about their genetic lineage without their consent or adequate preparation.

Whether to test is particularly hazardous with children. Genetic testing may affect personal psychosocial development and business and insurance opportunities and removes the opportunity to choose whether to obtain that genetic information. Testing should be performed only when there are immediate medical benefits to the child or when there are medical benefits to a family member and no expected harm to the child. Otherwise, testing should be deferred until the child can display an understanding of the consequences of genetic testing.

Consent for biobanking, the keeping of tissues for genetic research, is problematic, assuming that the revisions to the more than 25-year-old Common Rule begin as expected in 2018. The Common Rule is the core ethics regulations governing human research in the United States. The revision permits

using broad consent for biobanking [27,28]. Within some limitations, broad consent permits the use of tissues without additional permission from the donor [29]. One of the problems with broad consent is that donors or their surrogates may be consenting to unknown unimaginable risks [29]. No matter the protections, privacy is always at risk [30]. Consequences can include denial of life insurance, and, potentially in the future as health insurance laws change, denial or exorbitant premiums for health insurance.

Children should be involved in the consent process for biobanking to the developmentally appropriate extent [31]. The issues of consent change when the child reaches adulthood. One potential solution is to require biobanks to contact donors when they reach adulthood to either require the now adult to opt in for biobanking or provide the opportunity to opt out. This is not being done routinely [32].

KEY POINTS: THE INFORMED CONSENT PROCESS FOR CHILDREN

- Respect the "experience, perspective, and power of children" [8]. Legitimately involve children to the developmentally appropriate extent. Avoid pro forma solicitations
- Prioritize meeting the child and family's informational, decision-making, and emotional needs during the informed consent process
- Use verbal and pictorial strategies to quantify risks
- Under certain circumstances, adolescents may refuse potentially life-sustaining transfusion therapy for religious reasons
- Genetic testing and biobanking can lead to unforeseen consequences for the donor and their relatives

Forgoing potentially life-sustaining treatment

Children, like adults, have the right to limit LSMT when the likelihood and quality of potential burdens outweigh the likelihood and quality of potential benefits, as defined by the child and family [33]. Benefits include a prolonged acceptable quality of life. Burdens include intractable pain, disability, emotional suffering, or effects that diminish the child's quality of life.

The term "life-sustaining medical treatment" is preferred to the older term "do not resuscitate" to emphasize that treatment preferences range along a continuum instead of being binary. "Potentially" acknowledges the uncertain effectiveness of the treatments.

Perioperative limitations on potentially life-sustaining treatment

Limiting perioperative potentially LSMT allows children to have an opportunity to receive beneficial therapy without being forced to accept unwanted burdens [33,34]. Treatments may include procedures that increase quality of life, enable living at home, improve ability to interact, improve pain management, decrease pain, and treat non-terminal problems or urgent problems unrelated to the primary problem. Potential burdens from procedures may arise from resuscitation attempts, post-resuscitation medical care, or resultant functional or cognitive decrements. These burdens may make further resuscitation or intensive care therapy not "worth it." Considering both short- and long-term potential benefits and burdens helps clinicians understand the child's perspective, which improves honoring preferences.

The American Society of Anesthesiologists, the American Academy of Pediatrics, and the American College of Surgeons mandate reconsideration of existing limitations on LSMT before going to the operating room or procedure area.

Reconsidering the order prior to surgery requires clarifying the goals for the procedure and end-of-life care through discussions with the child, parents, and relevant clinicians such as surgeons and primary care physicians. Children should be involved in a developmentally appropriate manner. In practice, the reconsideration of LSMT for the perioperative period should result in either full resuscitation or a goal-directed approach toward perioperative resuscitation.

Goal-directed approaches permit decision makers to guide therapy by prioritizing outcomes (e.g. "I don't want to suffer in the ICU for two weeks before I die.") rather than specific therapies (e.g. cardiopulmonary resuscitation) [35]. Clinicians can guide the discussion by exploring acceptable burdens, desirable benefits, and the likelihood of the ranges of outcomes. Clinicians should explain the differences between ward and operating room resuscitation, emphasizing the idea that a dedicated clinician with understanding of the end-of-life goals and the ability to make a real-time assessment of the clinical problem as well as the ability to institute treatment immediately will be present throughout. Box 1.2 lists additional information to include in the discussion.

Operating room clinicians use their clinical judgment to determine whether and to what extent resuscitation will help achieve these goals. The decision about whether to use a certain intervention, such as chest compressions, will likely be more consistent with the end-of-life goals if the decision to

Box 1.2: Components of the discussion for perioperative limitations on potentially life-sustaining medical treatment (LSMT) [33–35]

- Planned procedure and anticipated benefit to child
- Description of advantages of perioperative LSMT as compared to ward LSMT
- Likelihood of requiring resuscitation
- Reversibility of likely causes that require resuscitation
- Description of potential interventions and their consequences
- Chances of successful resuscitation including differences between outcomes to witnessed and unwitnessed arrests
- Ranges of outcomes with and without resuscitation
- Responses to iatrogenic events
- Intended and possible venues and types of postoperative care
- Use of postoperative trials of therapy
- Postoperative timing and mechanisms for reinstitution of previous limitations of LSMT
- Establishment of an agreement through a goal-directed approach or revocation of the do-not-resuscitate order for the perioperative period
- Documentation

institute is made when the etiology of the event is known. This model encourages the ethically redoubtable strategy of trialing therapies. A trial of chest compressions that do not achieve specific goals provides evidence that continuing the therapy would be inconsistent with the goals of end-of-life care. Witnessed arrests in the operating room often have a better outcome than unwitnessed arrests due to the more immediate intervention and the greater likelihood that the cause of the arrest is known.

Most decision makers choose to use a goal-directed approach that authorizes temporary therapeutic interventions to manage quickly and easily reversible events, but reject those interventions that will likely result in permanent sequelae, such as neurologic impairment, from receiving potentially LSMT. For example, a brief bradyarrhythmia that responds to intravenous epinephrine and chest compressions would be consistent with the authorization to treat events that are temporary, easily reversible, and unlikely to have significant sequelae. On the other hand, if the bradyarrhythmia resulted in an extended resuscitation, continued therapy would require unacceptable burdens that in any case would be unlikely to achieve the patient's return to previous functional status. In that case, it would be appropriate to cease resuscitation efforts.

This common goal-directed preference can be documented as "The patient desires resuscitative efforts during surgery (and in the postanesthesia care unit (PACU)) only if the adverse events are believed to be both temporary and reversible in the clinical judgment of the attending anesthesiologists and surgeons."

The goal-directed approach requires determining when the child returns to their previous status for LSMT. Given that the goal-directed approach requires intimate knowledge and that it is intended to respond to the vicissitudes of anesthesia and surgery, the perioperative agreement is often discontinued when the patient is discharged from the PACU.

Clinicians should also discuss whether to try a postoperative trial of therapy before concluding that the burdens of continuing therapy outweigh the benefits. A trial of therapy allows decision makers and clinicians to determine how well a treatment achieves a defined agreed-upon goal, rather than presuming whether the therapy would work [3]. Trials may be limited by time or other factors. Trials permit children to tolerate a relatively small amount of burden, such as brief mechanical ventilation, to see if it would accomplish their defined goals. This information guides further decision making with greater certainty of burdens and benefits.

In pediatrics, precisely defining and documenting postoperative plans is often less essential, because parents are often available in the postoperative period to make decisions regarding therapy. Parents are often cognitively capable of participating in discussions of withdrawal of therapy because they have already grappled with analyzing the benefits and burdens of end-of-life care. The presence of parents permits greater trials of perioperative resuscitation while still respecting the decision to limit the burdens. However, developmentally appropriate conversations with the patient are essential when a child is able to participate in these discussions. A child's preferences should be incorporated into decision making similar to obtaining assent.

Resist the hegemonic instinct to overreact to iatrogenic events. Decision makers chose to limit care because they do not want the burden of undesirable outcomes. Iatrogenic issues do not supersede agreed-upon preferences for limitations on potentially LSMT unless knowledge of the event makes the associated burdens and benefits of treatment consistent with the agreed-upon plan.

That said, putting aside personal feelings about an iatrogenic event is hard. But children and families care about how they are, not how they got there.

Physician orders for life-sustaining treatment

A physician order for life-sustaining treatment (POLST) promotes the honoring of resuscitation preferences by giving the preferences the power of a physician order. This order is valid across in- and out-of-hospital locations [36]. As compared to other advance directives, which can be prepared without professional medical guidance, POLSTs ensure the advice of a physician on how to achieve end-of-life care preferences. POLSTs document preferences for LSMT, other medical interventions, and management of artificial nutrition [37]. POLST documents appear to improve communication and honoring of preferences, particularly across settings [38–40].

Perhaps the biggest impediment to POLSTs is physician unfamiliarity [41]. From the perioperative clinician's point of view, it should be taken as if the child has a duly authorized limitation of LSMT. It should thus undergo required reconsideration.

Barriers to honoring perioperative limitations on life-sustaining treatment

Although honoring limitations on LSMT is improving in the main, clinicians still poorly honor end-of-life care preferences [36,42,43]. Clinicians remain inadequately informed about policies, law, and ethics, hindered by sabotaging systems and poisoned by lore and misinformation [44–48].

Insufficient early identification and communication about a child who needs a perioperative reconsideration of LSMT, such as one with a POLST, limits the ability to find the right clinicians, have a robust discussion, and reach an agreement satisfactory to the child, family, and clinicians. Children having minor surgery or those who have not had a preoperative visit are more likely to remain unidentified until the day of surgery.

Lore and break room gossip reinforce the incorrect perception that honoring perioperative limitations on LSMT may result in being sued [49]. Statutes that address requirements for limitations on LSMT often include immunity provisions that protect clinicians from liability. Given the right of children to avoid inappropriate treatment, and the lack of judgments against clinicians who honor properly documented LSMT, the risk of honoring limitations on LSMT is likely to be lower than the risk of not honoring it.

Barriers that are less obvious include the natural desire to avoid most risk, particularly what is incorrectly perceived as a significant risk for little benefit [49]. Many clinicians like to avoid ambiguous situations in which they

have little experience making judgments and in which they are more prone to private or public criticism. These concerns can lead to anticipatory regret, letting an uninformed or overactive imagination create a fictional horrifying outcome that makes honoring limitations too risky. Clinicians overcome these honest but inappropriate feelings by reality testing with experts, seeking to become more skilled in these areas, and remembering that clinicians serve patients.

Potentially inappropriate interventions

Most of the confusion surrounding the concept of futility comes from imprecise terminology. Futile therapy should be viewed as treatments that cannot accomplish a specific physiological goal. In that sense, dilemmas about whether to use futile therapy rarely arise. Interventions with a low likelihood of success, on the other hand, may be considered potentially inappropriate but they cannot be considered futile. An intervention may be considered potentially inappropriate if there is "no reasonable expectation" that a significant defined endpoint will be reached, the burdens to the child, feasibility, or, at times, cost [50].

At the clinician level, discussions about inappropriate interventions center on the benefits and burdens to the child. Qualitative and quantitative considerations should be defined carefully and clinicians should explain whether the information used to form the estimation is based upon intuition, clinical experience, or rigorous and sufficiently relevant scientific studies. Complicating matters is the dubiety in predicting the likelihood and range of outcomes of therapeutic interventions in very young children. In the end, in the absence of national standards, decision making for a child regarding inappropriate care should be based on the benefits and burdens on the child and not on cost [51]. Hospitals should have established processes for resolving conflicts [52].

Perioperative clinicians encounter cases that seem to be inappropriate treatments. Aside from differences in core values and beliefs, parents have other influences that encourage them to seek seemingly inappropriate care (Box 1.3). Understanding these factors helps clinicians be empathetic.

Box 1.3: Why are we doing this case? Factors that affect parental desire to seek seemingly inappropriate care

Parents seek seemingly inappropriate care for personal, familial, and societal reasons. These latent factors influence decision making.

- Unrealistic expectations about prognosis or effectiveness of treatment
  - Previously incorrect prognoses about their child ("Won't live past age 2")
  - Local rumors about "miraculous" cures
  - Public stories about "miraculous" cures
- Influence/disapproval from insufficiently informed family
  - Fear of damaging personal reputation in their community
  - Fear of subtle ostracism
  - Internal or external pressure not to damage family reputation
- Guilt
  - Responsible for previous actions (e.g. left with "irresponsible" relative)
  - Responsible for "delaying" treatment because they "missed' something
  - Vague but wholly wrong feeling that it was their fault
  - Emotional overtones of "causing death"
- Mistrust of clinicians, hospitals, or medical systems
  - Personal disturbing individual interactions
  - Legitimate and illegitimate stories and events engendering distrust
  - Coming from communities that have experienced organizational prejudice (e.g. racial, gender, ethnic, socioeconomic, etc.)
- Inadequate education/guidance from clinicians
  - No clearly identified clinician coordinating care
  - Inadequate communication among clinicians
  - No process to address LSMT with family
  - Breakdown of communication among family and clinicians
  - Well-meaning but poorly considered comment by a peripheral clinician (sometimes medical student) on to which families latch

LSMT, life-sustaining medical treatment.

What would you do in my situation?

Parents may ask clinicians what they would do in the same situation. Clinicians should attempt to determine what the parent is asking before directly answering this question.

If they are asking for help making a decision, either because of difficulty managing the complexity of information or because of uncertainty, it is important to clarify the goals or values of the parents. Clinicians can then answer the question, "If that were my goal, I would do this, because…." Explaining why allows parents to apply their own values to the reasoning.

If parents are unsure about how to weigh competing values, it is appropriate for clinicians to share their values, with the caveat that many other approaches are acceptable and that the parents' values take priority. Clinicians can explain that to parents: "My job is to help you make one of the several reasonable choices that fits your values. Let's discuss how we can apply your values to this decision."

If parents are looking for reassurance for a reasonable decision that is not the one the clinician would have chosen, clinicians can respond by affirming both the appropriateness of the decision and the naturalness of feeling uncertain [53]. Admitting uncertainty about the "right" thing to do confirms to the parents the difficulty of the decision.

Organ procurement after cardiac death

In organ procurement after death by neurological criteria, the child is declared dead before going to the operating room. In organ procurement after cardiac (or circulatory) death (DCD), a child in whom the decision has been made to withdraw potentially LSMT is brought to the operating room and then treatment is withdrawn. If the child is declared dead by cardiac status within a pre-established time, organ procurement proceeds. Although widely accepted, concerns about DCD include whether the dying process is altered by interventions to facilitate organ procurement. See Chapter 30 for more information about organ donation after cardiac death.

KEY POINTS: FORGOING POTENTIALLY LIFE-SUSTAINING TREATMENT

- Children have the same right as adults to limit potentially LSMT, but predictions about the likelihoods and range of outcomes are less reliable
- Orders for limitations for LSMT must be reconsidered for the perioperative period. They may be honored under a goal-directed approach
- Trials of therapy increase the likelihood of honoring preferences for end-of-life care. Trials allow decision makers to test the assumption that a treatment may achieve specific goals while permitting it to be withdrawn if the treatment becomes too burdensome
- Desires for what appear to be inappropriate treatment come from values, beliefs, perceptions, personal experience, and community history
- Work with children and families to apply their values to decision making

Special circumstances in pediatric anesthesia

Research in pediatric patients

The anesthesiologist Henry K. Beecher was one of the first to recognize that research in pediatric patients requires greater oversight than research in adults [54]. Research subjects requiring surrogate consent are vulnerable to abuse. Pediatric research exposes children to unknown risks of long-term harm because research interventions occur during growth and development of the child [55].

The increased risk of harm and lack of direct benefit to the child increase the obligation to obtain the developmentally appropriate assent from the child. This obligation is not always met, particularly in diseases that have a strong emotional overlay, like cancer [56,57]. Assent may be waived if there is the prospect of direct benefit to the child that is available only through participation in research. Although undesirable, assent also may be waived if the study exposes the child to no more than minimal risks or if the study could not sensibly proceed without the waiver [50,51].

Federal guidelines define four categories of pediatric research (Box 1.4). The hallmark of these categories is that potential benefits must increase commensurate with potential risks. Most controversy about pediatric research concerns the interpretations of minimal risk and minor increase over minimal risk [52].

Minimal risk is defined as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" [58,59].

The common interpretation is that minimal risk refers to risks encountered by healthy children in a safe environment, such as playing sports and riding in a car [59,60]. A previous competing interpretation, now out of favor, used the more relative interpretation of basing the standard of "daily life" on the events to which children enrolled in the research are routinely exposed. In other words, if a child enrolled in the study routinely receives lumbar punctures as part of therapy, then it may be acceptable to expose a child to the risk of a lumbar puncture for study purposes.

The category "*greater than minimal risk* and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition … which is of vital importance" defines when it is acceptable to expose a child to what is called "minor increase over minimal risk" [58]. "*Minor increase over minimal risk*" has been interpreted as pain, discomfort, or stress that is transient, reversible, and not severe [61]. Risk assessment is based on the combined exposure to risks throughout the study and the relationship between the risks and the patient population. For example, although drawing blood in healthy 15-year-olds may be considered acceptable, drawing blood from 15-year-olds with severe autism spectrum disorder may be unacceptable because their inability to understand may cause intolerable stress [62].

"Condition" is used to mean characteristics "that an established body of scientific or clinical evidence has shown to negatively affect children's health and wellbeing or to increase the risk of developing a health problem in the future" [62]. For example, consider a protocol to assess insulin resistance in obese children who do not have type 2 diabetes. If the investigator presented sufficient scientific support to the institutional review board that obese children are at increased risk of developing diabetes because of their obesity, then those obese

Box 1.4: Federal classifications for pediatric research [50]

1. Research not involving greater than minimal risk.
   a. IRB determines minimal risk
   b. IRB finds and documents that adequate provisions are made for soliciting assent from children and permission from one of their parents
2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.
   a. IRB justifies the risk by the anticipated benefit to the subjects
   b. The relation of the anticipated benefit to the risk is at least as favorable as that presented by available alternative approaches
   c. Adequate provisions for assent and permission from one of the parents
3. Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition (commonly known as "minor increase over minimal risk").
   a. IRB determines the risk represents a minor increase over minimal risk
   b. The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations
   c. The intervention or procedure is likely to yield generalizable knowledge … which is of vital importance for the understanding or amelioration of subject's disorder or condition
   d. Adequate provisions for assent and permission from both of the parents
4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

IRB, institutional review board.

children would be acceptable research subjects for this study. Svelte children would not be acceptable, because they would not be considered at risk for developing diabetes.

Stringent regulations certainly hinder necessary and beneficial research [56,57]. But regulations are often responses to previous transgressions. At some point, relaxation of regulations will reanimate the abuses that beget the regulations. It is difficult to identify that line until it is crossed.

Improving the institutional review board (IRB) process may minimize the inaccurate estimations of risk that hinder appropriate research and permit inappropriate research. An individual's intuition about the risk level of an activity is hampered by cognitive biases, such as familiarity, control of activity, and reversibility of the potential harms [63]. Systematizing evaluation of research risks may reduce inaccurate estimations of risk. One approach is to use a standardized scale to categorize the extent and likelihood of each potential harm and then compare the potential harms with comparative activities [64].

Socioeconomically disadvantaged children are overrepresented in clinical research [65]. Their environments may drive or worsen diseases such as reactive airway disease, and most research is performed in urban hospitals. Children in more economically settled situations get the benefit of the research without bearing proportionate risk. In addition, socioeconomically disadvantaged children and families may be more enticed to participate in research because of the commonly offered relatively inexpensive tokens of gratitude. But to socioeconomically disadvantaged families, what the researcher or IRB perceives as a minor gift can be a strong incentive to participate. See Chapter 4 for additional discussion about research consent and ethics.

Confidentiality for adolescents

Open discussion, the lynchpin to a successful adolescent–clinician relationship, occurs only when the adolescent believes in the openness and confidentiality of the discussion [66,67]. Confidentiality means the adolescent owns their information, and, as such, it may not be shared without the adolescent's permission [68]. The adolescent's emerging desire for autonomy and their cognitive decision-making abilities make them developmentally ready for this responsibility.

Clinicians are obligated to protect patient information from unauthorized and unnecessary disclosure. With adolescents, confidentiality is crucial for even the anodyne. Adolescents concerned about confidentiality withhold pertinent information and defer necessary treatment [66,67,69]. Clinicians may want to ask sensitive questions without the parents present. Squarely addressing confidentiality concerns often improves truthfulness.

But adolescent confidentiality is not absolute. Honoring an adolescent's preferences for autonomy may compete with the obligation to ensure the adolescent is making a reasonable decision. It is ethically justifiable to breach confidentiality only when complying with reporting statutes or when breaching confidentiality will prevent serious harm to the child or another. These decisions are not obvious, and clinicians should use patient, family, and case characteristics in consultation with ethics or legal consultations to determine the appropriateness of breaching confidentiality.

Confidentiality breaches occur by sloppy and insecure use of medical records and electronic communications, by discussing patients in front of other patients or uninvolved clinicians in public areas like elevators, hallways, and cafeterias, and by clinicians being forced to have public discussions with patients or families because of inadequate private facilities, such as in the family waiting room. The most common breaches were to clinicians uninvolved in patient care about patients' sexual activities, mental or other stigmatizing illnesses, and racial or ethnic backgrounds [70].

The pregnant adolescent

Hospitals and clinicians should have a defined approach to the preoperative adolescent who has a positive pregnancy test. As described previously, this information is the adolescent's and should only be shared with the patient's permission. State statutes may limit clinicians to informing only the adolescent about a positive pregnancy test [71,72]. In addition to ethical principles and practical reasons, these statutes are specifically present to address concerns about child abuse in pregnant adolescents.

Clinicians in possession of sensitive information should encourage the adolescent to share the relevant information with the parents. Involving adolescent specialists or social workers may facilitate communicating with the parents and receiving future care.

The ethical complexity increases logarithmically when pregnant adolescents do not want to inform their parents and it is appropriate to postpone the procedure [73]. Even though clinicians must postpone the case in a manner that does not breach confidentiality, the details of how the postponement is communicated affect the ability to maintain confidentiality. For example, clinicians can issue a terse communiqué to the parents that the procedure will be postponed. While this approach avoids explicit lying, its oddness may confuse parents and trigger a cascade of questions leading to a loss of confidentiality. On the other hand, clinicians may actively deceive, correctly reasoning that because parents have no right to that information, their primary obligation is to preserve confidentiality.

Albeit peculiar in a medical textbook, perhaps a short course in deception is useful [74,75]. Clinicians should try to avoid deception. But, when necessary, as a later resort to maintain confidentiality, it may be the least objectionable approach. It is perhaps easier to mitigate the sting of being deceptive by considering that, ethically, only the patient has the right to that information, and you are doing what is practically necessary to maintain confidentiality.

Clinicians should deceive in ways that will be successful, not require diagnostic or therapeutic interventions, and not unduly worry parents. For example, while intimating about unavailable operating room space and emergency surgeries may be useful, the excuse is rather weak if stated in the morning, when the family could offer to wait until one is available. Using a "new murmur" as an excuse may worry parents and cause unnecessary consultations. More simple deceits, such as postponement due to concerns about inadequate fasting or upper respiratory infections, tend to minimize unintended consequences.

The American Academy of Pediatrics supports confidentiality for adolescents seeking information about having an abortion [76]. Unless restricted by state law, adolescents may have abortions without parental consent. The rules surrounding parental involvement in elective abortions vary by state [71]. States may require either parental consent or notification prior to an elective abortion [71]. To ensure that adolescents can seek an abortion confidentially in states with parental involvement laws, states must have a judicial bypass procedure to preclude parental involvement. In a judicial bypass hearing, the judge interviews the adolescent to determine sufficient maturity to consent for an abortion. Even if the judge determines the adolescent insufficiently mature, the judge may grant permission for the abortion if the judge believes it is in the adolescent's best interest.

LGBTQI+ patients

Although the number of LGBTQI+ adolescents and the incidence of gender dysphoria are increasing, the specialization of care for these individuals means there is often clinical inexperience. LGBTQI (lesbian, gay, bisexual, transgender, transsexual, queer, intersex) is an insufficient term to describe the variations of preferences for gender identification or no identification. A person's genetic biology is called sex. Gender is a self-identified social construct of how a person presents themselves to those around them. Gender identification is unconstrained, and includes no gender, gender fluid and combined or unnamed genders. Because covering the spectrum would be unwieldy, the "+" is to indicate those unmentioned, without prejudice.

The wholly legitimate issue of gender variation or dysphoria in the prepubescent child is widely misunderstood and not infrequently grotesquely mocked. Different treatments are appropriate. Decisions about more definitive interventions are usually postponed until puberty, given the uncertain natural history [77]. Clinicians must be supportive in following the chosen treatment (e.g. support for gender transition) for their patient.

Being an adolescent is hard. Isolation, prejudice, and even implicit or explicit condemnation from parents and other family make the difficulty of being an LGBTQI+ adolescent unimaginable for those who have not had the experience. Because of these factors, LGBTQI+ children have higher rates of substance abuse, homelessness, suicidal ideation, and physical harm. Reprinted rather widely is part of the 2015 suicide note of Leelay Alcorn, who self-identified as transgender. This note exemplifies the isolation, shame, and pain. "Please don't be sad, it's for the better. The life I would've have lived isn't worth living in… because I'm transgender….I never told anyone and I just continued to do traditionally 'boyish' things to try to fit in." [78].

Clinicians should avoid heteronormative assumptions (asking if someone has a boyfriend or a girlfriend), identify preferred name (often incorrectly identified on records if the name has not been legally changed), identify preferred pronouns or use non-gender pronouns, although in conversation with children their name should be used, articulate the purpose of potentially awkward questions, and use genderless language.

KEY POINTS: SPECIAL CIRCUMSTANCES IN PEDIATRIC ANESTHESIA

- Adolescents deserve confidentiality for ethical and practical reasons. Clinicians are responsible for maintaining appropriate confidentiality
- Diligently assess yourself for personal but unintended behaviors that may lead to health or healthcare disparities, particularly across race, gender, and socioeconomic status. Develop strategies to minimize these actions
- Be cautious about seemingly innocuous language that makes presumptions that may hurt or shame adolescents

Professionalism in pediatric anesthesia

Advocacy and good citizenship

Physicians owe their ability to train, practice, and thrive to society's largesse. The implicit social contract therefore obligates physicians to manage matters within their sphere of influence, with a special obligation to address issues that "directly influence individuals' health" in the physician's community [79,80]. Community may refer to a physical location or a type of patient to whom the physician is particularly obligated. Pediatric anesthesiologists have a special obligation to further pediatric healthcare [81,82].

Pediatric anesthesiologists fulfill obligations to society by participating in activities that are consistent with the individual's "expertise, interests and situations" (Fig. 1.1) [80]. Pediatric clinicians in particular should address the healthcare disparities of quality of care and access to care seen across socioeconomic, racial, gender, geographical, and other cohorts that lead to the health disparities in morbidity and mortality [83,84].

Safety and quality care initiatives

Clinicians must work to improve safety. Clinically, clinicians need to actively support safety initiatives that seek to improve care such as the procedural time out and the Clean Hands Count initiative. Ignoring or bypassing inefficient, impractical, or harmful policies prevents developing a functional policy and leads to a dysfunctional culture of clinicians choosing which rules to follow [85]. Clinicians need to bring unsuccessful policies to leadership, who must be willing to honestly discuss and address concerns without blaming clinicians or demeaning them by declaring "try harder." Even one brush-off by leadership will chill future communication from the front lines.

Clinicians should do their best to improve care by reporting near misses or other potential risks. Clinicians are suspicious (sometimes rightly) of the trumpeted "blame free" approach to reporting potential errors or near misses [86]. To fulfill professional obligations of identifying potential risks, suspicious clinicians should reality test their perception or find a different way to highlight the risk. System flaws that lead to medical errors can only be identified by honest reporting and by participating in root cause analyses.

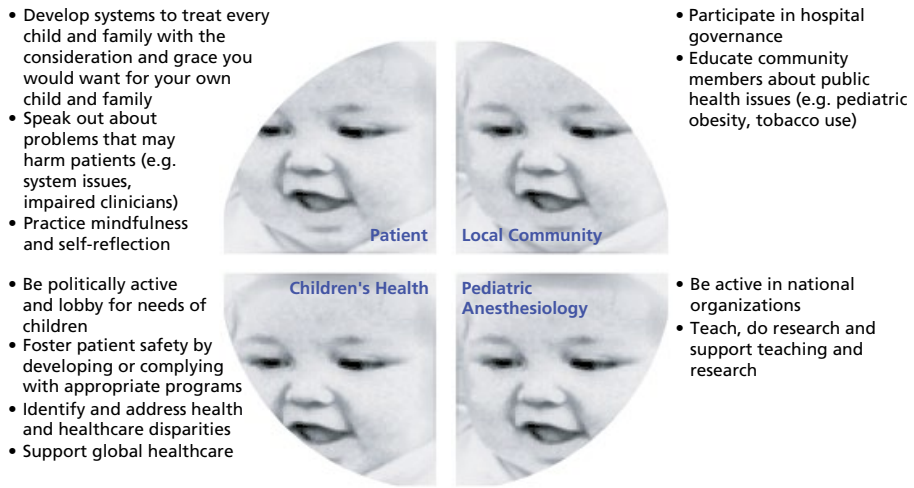

Figure 1.1 Obligations of pediatric anesthesiologists. Pediatric anesthesiologists are obligated to these four communities. Individual anesthesiologists are not expected to fulfill every obligation. "Units" of anesthesiologists such as private practice groups, academic departments, and state societies should fulfill these obligations collectively. A few examples are given.

Disclosure and apology

Although viscerally seductive, hiding medical errors violates informed consent principles, destroys trust when the error is inevitably revealed, and leads to legal action [87]. To be sure, it is understandable to want to hide a medical error. Clinicians foresee mercurial treatment by the hospital or legal system, do not receive adequate psychosocial support, and are inadequately educated about how to manage these conversations [88].

Children and parents wish to be informed about medical errors. Proper disclosure and apology can improve trust, communication, and respect and may give them a greater sense of control, which some research suggests may lead to better outcomes [89]. They also wish to receive appropriate apologies, even if it makes them more anxious.

Thoughtful full disclosure should commence upon recognition of the problem. Wise clinicians unskilled in disclosure and apology involve an expert. The expert can prepare clinicians by rehearsing process and content and by providing support for the clinician. The expert can arrange for continuing communication and provide emotional support for the family. Clinicians who make errors, sometimes referred to as "second victims" [90], may be understandably rattled and may not be able to provide emotional support. Clinicians should share what is known as quickly as reasonably possible, but they should not make assumptions about what is not known, particularly about fault. Decision makers should be informed about the medical implications of the event and any necessary treatment. Because disclosure is a process over time, the child and family should be given a contact person skilled in disclosure and apology who will be available to answer questions, arrange meetings, explain the results of the investigation, and describe plans to prevent comparable events.

Most arguments against apology about and disclosure of errors center on increasing the risk of being successfully sued and on protecting the patient from unnecessary anxiety regarding the event or future care. Upon examination, these arguments are weak. An apology is an expression of regret or sorrow. A sincere apology followed by actions consistent with regret is invaluable; an insincere apology is costly. Even though more than half the states have laws prohibiting the admission of apology or sympathy as evidence of wrongdoing, it is conceivable that an apology may increase the risk of being sued or losing a suit. But the best protection against being sued is a good patient–doctor relationship [16]. Hiding, dissembling, or being indifferent about an event destroys trust and galvanizes a lawsuit much more than a sincere apology.

For example, some recommend apologizing for the effect on the child but not taking responsibility for the actual event. This apology is appropriate for a rash caused by an appropriately administered antibiotic. But it seems bizarre not to take responsibility when a clinician errantly administers a neuromuscular blocking agent instead of an anti-cholinesterase agent when attempting to antagonize muscle relaxation. Although an investigation should be done to assess for system flaws that contributed to the error, not taking responsibility in that case (unless there was a good reason) would likely aggravate parents.

Parents are naturally sensitive about the perioperative experiences of their children. Clinicians should consider apologizing or at least sympathizing about unpleasant experiences such as multiple, painful attempts to insert an intravenous catheter or an out-of-control inhalation induction of anesthesia. These discussions can include an acknowledgment that it was a bad experience and recommendations for the future. For example, a clinician could say, "I am sorry the intravenous catheter took so many sticks," and "Next time, we should probably give oral sedation prior to attempting the intravenous catheter." These comments simply acknowledge what happened, express regret, and educate the family for the future.

"Communication-and-resolution," a transparent disclosure of injury or error presented with appropriate compensation, can lead to improved relationships with patients and families, better analysis of events to implement improvements, and possibly forestall legal action [91,92]. Defense of appraised care is essential for clinicians to participate in this system [93,94].

Production pressure

Production pressure is the ubiquitous "internal or external pressure on the anesthetist to keep the operating room schedule moving along speedily" [95]. As a consequence, clinicians may feel pressure to curtail preoperative discussions, inadvisably proceed with cases, or prematurely extubate the trachea to speed turnover. Clinicians should be aware of pressures to provide anesthesia inconsistent with their level of skill or to permit surgery in inappropriate settings. For example, the "routine" tonsillectomy for a child with achondroplasia may be too complex for some clinicians or some surgery centers. Clinicians have an obligation to their patients and to themselves only to provide care for which they are competent and to recognize when economic and administrative pressures induce them to do otherwise.

Suspicion of child maltreatment

Physicians are legally obligated to report even the suspicion of child maltreatment and may be criminally liable for not reporting it. It is natural to downplay concerns because of a hesitancy to inform authorities, particularly if the parents are from a socioeconomic class similar to the physician's. But child abuse should never be minimized as a one-time event. Early intervention minimizes disastrous consequences.

Children may be physically abused, sexually abused, emotionally abused, and neglected [96]. Clinicians may be the first to recognize child abuse because evidence of abuse frequently occurs on the arms, hands, head, face, neck, and mouth. Signs of abuse include bruises or burns in shapes of objects, injuries that fit a biomechanical model (e.g. a handprint), fractures in infants, and developmentally inappropriate injures that are not explained by the offered history. Child abuse might occur in the hospital during diagnostic or therapeutic care. Children with chronic cognitive delays or physical limitations are more prone to abuse [97]. Munchausen by proxy syndrome is a type of abuse in which parents either cause or fictionalize clinical problems in their children. The signs and symptoms of the resultant diseases are often difficult to explain coherently.

KEY POINTS: PROFESSIONALISM IN PEDIATRIC ANESTHESIA

- Pediatric clinicians have a societal responsibility to improve children's health through supporting professional or lay efforts in local, national, or international communities
- Disclose and apologize for medical errors promptly, factually, blamelessly, and with colleagues trained in disclosure and apology. Remember that clinicians are the "second victims" and deserve grace. Put in place systems to identify and support "second victims"
- Reject production pressure by treating each child as if they were your own

CASE STUDY

This case study is designed: (1) to emphasize that superficially defining cases such as "a 17-year-old wants to refuse transfusion therapy" overlooks relevant complexities; (2) to examine the process and relevant factors in determining maturity for medical decision making in an adolescent; (3) to provide an example of how dilemmas may be evaluated; and (4) to provide an example of the content in an ethics consultation. Characteristics of consultations include clarifying medical issues, identifying stakeholders and their relative extent of influence, defining the ethical questions and issues, and providing an assessment and recommendation.

Summary

Candace is a 17-year-old who has a rare type of rhabdomyosarcoma. She presents for resection of a tumor intertwined with major blood vessels. Candace is a Jehovah's Witness and wants to refuse receiving transfusion therapy during and after the resection of the tumor.

Medical questions

This type of rhabdomyosarcoma is too rare to reliably predict outcome. The best guess, though, is a 5-year survival of 5–10%. While there is a low likelihood of significant bleeding during the operation, the position of major blood vessels presents the possibility of sudden, rapid, and substantial bleeding.

Family

Candace is the daughter of Linda and Larry. Through a friend, Larry began exploring the Jehovah's Witness community 9 years ago and became baptized as a Jehovah's Witness 6 years ago. Linda describes herself as spiritual but has no interest in organized religion. She very much supports the authority of Candace's decision making.

Candace "was very skeptical the first month of learning about [the Jehovah's Witness religion]. I had friends who had 'found' religion … but it never made sense to me." Jehovah's Witness "made sense to me, in an easy to understand manner. This is it, this is the right religion." Following thorough study, at age 14 she chose to become a baptized member to show her dedication to being a Jehovah's Witness.

Candace leads an active high school life. She is a starting wing on the field hockey team, and she frequently participates in school theater productions. She leads bible study and weekly youth group meetings. She is an accomplished public speaker, speaking to groups "over 100 people" about being a Jehovah's Witness.

Linda and Larry like the person Candace has become. Candace, Linda, and Larry share decision making about family matters. They have the normal disputes about things like curfew.

Candace is an active participant in her care. She asks appropriate and extensive questions about options and short- and long-term implications.

In private discussions with Candace, she emphasized that she did not want to die. However, because she believes that Bible and God forbid taking blood, receiving blood would fill her with incredible guilt and sadness because she had disappointed her God. While she was concerned that taking blood would separate her from God, her primary concern was the overwhelming sense of failing her God. When asked whether being transfused forcibly or while unconscious would ease her conscience, she answered that she would feel the same because she had actively put herself in a position in which she could involuntarily receive blood. She equated being transfused forcibly while unconscious as "rape." She stated in a factual and calm way that "if I woke up and found I was getting blood, I would rip it out of my arm."

Candace coherently articulates her religious and spiritual faith. Her beliefs are consistent with the teachings of her chosen faith community. She views herself as able to reason and be responsible for acting on personal moral judgments. She can imagine separating from the Jehovah's Witness community if guided so by her conscience.

Ethical questions

1. If individuals of majority age have the right to refuse potentially life-sustaining transfusion therapy, do minors have this right?
2. What characteristics and criteria can be used to determine whether a minor possesses sufficient decision-making capacity and maturity to make this decision?
3. What issues should be discussed to ensure that their desired blood therapy wishes are followed?

Maturing adolescents are granted increasing authority in decision making. Relevant characteristics that give evidence of adolescent maturity and decision-making capacity include an understanding of their options and associated consequences, an internally coherent rationale, an ability to articulate their positions, an intellectual and emotional freedom to entertain alternate perspectives, and an indication of mature relationships with older individuals. Not all characteristics need to be present for an adolescent to be considered mature. The threshold for the evidence necessary to have decision-making capacity for a specific decision increases as the consequences of the decision increase.

Legitimate concerns about adolescents being overly influenced by short-term consequences should not be tainted by less relevant concerns that preferences may change as adolescents become older. Mature individuals are able to change their minds based on experience and evidence. That adolescents may change their mind as they mature does not invalidate current choices inasmuch as sufficient decision-making capacity is present.

Pragmatism affects considerations about whether to force adolescents to receive undesired healthcare. Adolescents are most capable of physical protest, either by yanking intravenous catheters or by not presenting for therapy. For example, Billy Best, a 16-year-old with Hodgkin lymphoma, ran away so that he would not have to complete his chemotherapy regimen [98].

Assessment

The ethics advisory committee believes that Candace meets the requirements of being a mature individual with substantial decision-making capacity who understands the gravity of her choice. Her active participation outside the Jehovah's Witness community indicates a wider view of the world rather than a more narrow view that may be present with exposure only to the Jehovah's Witness community. Given her beliefs and her extensive missionary and teaching activities, we believe that she has thoughtfully chosen to become a Jehovah's Witness. She has a loving and comprehensive relationship with her parents. Although her refusal of potentially life-sustaining therapy may lead to significant morbidity or death, we believe she exceeds the criteria to make these decisions.

Recommendations

1. The ethics committee believes that Candace should be considered primary decision maker.
2. We are aware that the surgeon requests a court order permitting Candace to be able to consent for refusal of potentially life-sustaining transfusion therapy. We encourage Candace and her family to seek as much information about this process as possible, including the process of seeking this status, the possible drawback of pursuing and securing mature minor status, the role of the parents after achieving this status, and the use of healthcare proxies. A court order may minimize chances that wayward individuals may transfuse Candace.
3. To ensure fidelity in regard to the hospital's implicit promise to honor her preferences, a cadre of clinicians committed to honoring Candace's wishes must be identified. Necessary clinicians include operating room nurses and technicians, anesthesiologists, trainee anesthesiologists, certified registered nurse anesthetists, surgeons, and postoperative nurses and physicians, particularly ICU physicians. Arrangements must be made to ensure willing clinicians in case of an emergent re-operation. The needs of these clinicians (e.g. to meet Candace) should be met.
4. This consultation is solely advisory. Our comments are restricted to the ethical interpretation of the issues facing Candace, her family, and the care team. You may wish to contact the Office of Legal Counsel for their input on existing regulations as well.

Postscript: A court order granted Candace the authority to make decisions about transfusion therapy. In informal conversation later, the judge declared that one of the primary considerations aside from Candace's maturity was the very low likelihood of survival. If her possible survival had been higher, they would have been much less likely to grant Candace the legal authority to make decisions about transfusion therapy.

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 2

History of Pediatric Anesthesia

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Introduction

History is different when written by people who were there at the time compared to that written more recently by people who rely on information derived from other sources. Insights into the use of clinical signs and acumen by older anesthesiologists, many of whom also had good technical skills unaided by modern equipment (for example, difficult and blind nasal intubation and locating nerves when injecting local anesthetics), help one to appreciate the developments that have taken place and how they managed before.

This chapter will mention events in the first hundred years of anesthesia but will cover mainly 1950–2000, the period of greatest change in children's anesthesia.

The beginning of anesthesia as a specialty and the first drugs used, 1842–1921

The first anesthetic agents had all been experimented with as party inhalations and observed to relieve pain when the inhalers were accidentally injured. Humphrey Davy had made the observation that led him to remark in 1799 that nitrous oxide might be useful to relieve surgical pain where no great effusion of blood took place. In 1824 Henry Hill Hickman thought that a gaseous inhalation might have the desired effect but selected ineffective carbon dioxide.

In 1844 Horace Wells, a dentist in Hartford, Connecticut, tried nitrous oxide successfully in his practice for extractions. Subsequently his public demonstration failed because his patient cried out, although he claimed he felt no pain.

Ether was used in 1842 by Crawford Long in Georgia to anesthetize several patients for surgical procedures, including children. As he did not report his cases for several years, until after William Morton performed his successful public demonstration with ether in Boston in 1846, he has not been given his due credit for inventing anesthesia. Neither has the chemist, William Clark, who had a tooth extracted painlessly as an experiment, after ether frolics, in January 1842.

The speed with which the news travelled around the world was remarkable considering the rate of sea travel at the time. William T.G. Morton's first successful public demonstration of anesthesia was held in Boston on 16 October 1846. The first anesthetics were given in Britain on 16 December and in Australia by Pugh (surgical) on 7 June 1847 and Belassario (dental) in Sydney about the same time.

In 1847 James Young Simpson, Professor of Midwifery in Edinburgh, introduced chloroform as an anesthetic, having previously used it and ether at dinner parties to exhilarate his guests. So the three agents that were to dominate anesthesia for the next century had been introduced. Later, ethyl chloride was often used for induction because of its rapid onset and short duration of action. It was first introduced in 1848 but did not come into general use until 1895. Embley reviewed its pharmacology in 1906 [1,2].

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

Figure 2.1 Pediatric Schimmelbusch masks (left), with gauze insert in the middle. Chadborne's modification is shown on the far right.

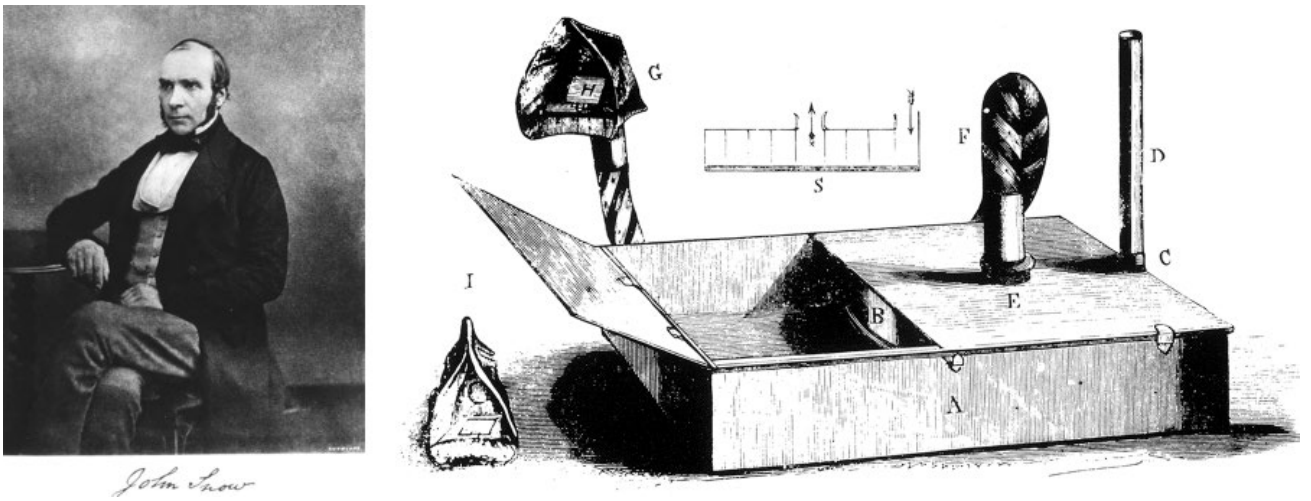

Figure 2.2 John Snow and his inhaler showing the waterbath (right).

These anesthetics were administered in many cases by open drop on to a handkerchief or on to gauze, which was later held in a wire frame such as the Schimmelbusch mask [3] (Fig. 2.1).

Ether was regarded as a relatively safe anesthetic. It has sympathomimetic properties, which sustain cardiovascular stability, and is a very potent bronchodilator that was used successfully to treat status asthmaticus before specific bronchodilators were available. It also produced secretions that liquefied sticky mucus so that it could be more easily sucked out. Secretions were usually a nuisance during anesthesia but could be controlled with atropine or hyoscine – a major reason for including these drugs in premedication. The smell was unpleasant and many children were sick but most often only vomited once. Guedel developed a scale of eye signs and breathing patterns which is a useful guide to the patient's depth of anesthesia during ether administration.

Ether is flammable. Electrical plugs were placed higher than 5 feet (150 cm) to minimize the possibility of ignition or explosion because ether is heavier than air. Ethylene was a weak anesthetic gas like nitrous oxide. Its use was limited because it was flammable and lighter than air and was dangerous with these electrical installations. Ether has continued to be used in many less affluent countries because it is cheap and relatively safe and simple to administer by trained nurses and medical assistants. These people provide an important service, particularly in many parts of Africa where medically trained personnel are scarce.

John Snow (Fig. 2.2) in London soon became the expert in the administration of anesthetics. He built a vaporizer that took into account several principles of vaporization of ether: baffles increased contact time between liquid and gas so that more vapor was taken up, and a warm waterbath surrounded it to prevent the liquid from cooling too quickly on vaporization. Snow also kept meticulous records of his cases and published large series with both ether and chloroform without fatalities. He recorded 145 cases of infants under 1 year who received chloroform, the youngest being 10 days old [4]. Many of these were for operations on cleft lip. He emphasized the importance of avoiding high concentrations. With chloroform he did not exceed 2%. He also noted that the effects of chloroform came on more rapidly in infants and children than in adults.

There was much discussion about the choice between ether and chloroform. The latter was sweet-smelling and caused less vomiting but was associated with more deaths, mostly cardiac but some due to liver failure. In 1896 there were 85 deaths in England, of which 65 occurred before surgery began. These statistics led the first anesthetist at the Melbourne Hospital, Edward Henry Embley (Fig. 2.3), to undertake a huge study on 284 dogs which showed that death was due to cardiac failure rather than respiratory failure as suggested by the Hyderabad Commissions in India. He also showed that some protection was offered by vagal section or atropine. Another feature of the study was that half the animals received

Figure 2.3 Edward Henry Embley.

morphine and curare 40 years before curare's introduction into clinical anesthesia. The animals were ventilated via tracheostomy prior to the administration of chloroform. The results were published in 20 pages of the *British Medical Journal* in April 1902 [5]. In 1905 Embley published another major paper on ethyl chloride, used for over half a century to induce anesthesia. Embley was appointed as lecturer in anesthetics at Melbourne University in 1901. He must have been one of the earliest academic appointments in anaesthesia in the world.

The first recorded death with chloroform was that of Hannah Greener, a 15-year-old girl who succumbed during induction like so many others afterwards [6]. It was probably because her heart, sensitized by chloroform, was exposed to high levels of circulating catecholamines (she was very anxious). After the development of the electrocardiogram (ECG) by Levy in 1911 it was shown that this combination could cause ventricular fibrillation. There were no defibrillators then.

Premedication

The purpose of premedication was to reduce patient anxiety and thereby reduce the amount of anesthetic drugs needed, and to reduce secretions, particularly with ether (atropine or hyoscine). Forty years ago heavy premedication with an opiate, atropine, or hyoscine with or without a hypnotic was often used. Children did not like injections and nurses did not like giving them so there was a change to oral (or nasal) administration in about the 1980s. Now, with increasing parental involvement and more day-of-surgery admissions, many anesthesiologists rarely use premedication. It has been shown that preschool children are as calm when their parents are present as with premedication if they are not there [7].

Local anesthesia

The discovery of the local anesthetic properties of cocaine on the eye by Koller in 1884 led to the development of other local anesthetic drugs such as amylocaine (1904) and procaine (1905).

Local and regional anesthesia was developed initially by surgeons. August Bier in Germany performed spinal anesthesia and had two children among his first six patients (1898) [8]. Spinal anesthesia became popular in some centers and, by 1907, 2000 cases were reported from France and another 1000 by Bier's group in Germany.

In 1920 Gaston Labat, a French surgeon, spent a year at the Mayo Clinic teaching regional anesthesia and writing his well-known book *Regional Anesthesia: Its Techniques and Clinical Applications* [9].

Fidel Pages (Madrid, 1921) introduced epidurals [10]. Mario Dogliotti (Turin, Italy, 1933) has been credited with popularizing this technique [11].

KEY POINTS: THE BEGINNING OF ANESTHESIA

- Crawford Long in Georgia used ether in the first recorded anesthetics starting in 1842, including children
- Horace Wells first used nitrous oxide for dental extraction in 1844 in Hartford, Connecticut
- William T.G. Morton staged the first successful public demonstration of anesthesia, with ether, in 1846 in Boston
- James Young Simpson introduced chloroform as an anesthetic for labor and delivery in 1847 in Edinburgh, Scotland

Early regional anesthesia in children, 1909–1933

Papers relating specifically to regional anesthesia in children began to appear in the early twentieth century. In 1909–10 Tyrell Grey, Medical Superintendent of Great Ormond Street Hospital for Sick Children in London, published three papers on spinal anesthesia in children, each covering 100 cases [12]. The patients were not anesthetized but comforted by a nurse who knew them. Spread of the local anesthetic was controlled by increasing specific gravity of amylocaine with glucose. The patient benefits were absolute anesthesia, no surgical shock, analgesia was localized to the area of the block, and postoperative vomiting was minimal. The surgical advantages were good operating conditions, easy access to the abdomen, the gut was contracted, the surgery was quicker, and the spinal anesthesia could be administered by the surgeon himself. There was less pain and feeding could be started sooner.

In 1945 Etherington-Wilson was well known for the use of baricity in determining the height of spinal block. He included 30 patients between 16 days and 3 years of age when describing his methods of calculating dosage in a series of 1600 patients [13]. Successful experience with spinal anesthesia was also reported by Stephen and Slater in Montreal (1949) [14] and Leigh and Belton [15].

If one knew this and had read the positive reports of its use in sick infants it should not be surprising that many years later Abajian et al advocated spinal anesthesia as an effective form of anesthesia in neonates and premature infants, especially as it does not cause hypotension in that age group [16,17]. A major problem of general anesthesia in this age group was postoperative apnea. This can be largely overcome by retaining less diffusible nitrogen in the lungs by inhaling air, thus stabilizing the alveoli. Déry et al demonstrated the importance of this in maintaining functional residual capacity in adults [18]. The same applies to infants and babies but, although effective, the method has not been widely practiced in neonates.

In 1920 Farr, in Minneapolis, reported 129 spinals in children with nine failures. Many were for pyloromyotomies [19]. In 1932 Marian from Bucharest, Romania, reported 653 spinals in children, mainly with 4% procaine, with 15 failures [20]. Interest continued and spread. In 1935, Balacesco, also from Bucharest reported 1241 spinals in children with good results – only some older children (older than 15 years) had headaches. He used amylocaine and later 4% procaine [21].

Spinals were used in children as young as 2 weeks of age in Toronto by 1933 [22]. They had also done four thoracic cases. The patients were mostly premedicated with pentobarbitone and morphine, and the needle was inserted at L4–5 as it had been recognized that the spinal cord reached lower in infants but, conveniently, the intercristal line between the iliac crests at the level where the needle was inserted, was also a segment lower than in older children. Junkin, in Toronto, made two important observations: that hypotension was less than in adults and headaches were uncommon in children [22].

Caudals were introduced for cystoscopies and urethral surgery in children 4–14 years old by Meredith Campbell (1933) [23]. In 1936 Sievers reported the use of peridural block for cystoscopy [24].

Harry Curwen in Durban, South Africa, presented a paper on caudal anesthesia in 92 neonates in 1950 [25]. Armando Fortuna led the development of regional anesthesia in Brazil. He wrote several papers relating to caudal anesthesia and its safety, even in poor-risk children, and then produced a good historical review of regional anesthesia in children in 2000 [26,27].

By the 1970s caudal anesthesia was being used in several parts of the world including Australia, Britain, France, and Mexico [28–31].

The French Paediatric Anaesthetic Society, ADARPEF, analyzed 224,409 cases done with regional or local blocks: 50% were caudals [32]. There were eight dural perforations, four accidental spinals, two inadvertent vascular injections with convulsions, and one rectal penetration. Another reported complication is syringe swap and the incorrect drug being given. This can be disastrous if a toxic substance is injected. The same society later published another review of 24,005 cases (1982–91), mostly caudals followed by lumbar epidurals and spinals [33]. This paper caused some concern because there were five patients with serious neurological sequelae, three of whom died. They were all less than 2 months old. Three had tetraplegia, one had hemiplegia, and one had cardiac arrest with brain damage. Dalens et al suggested that the injection of air could cause problems [34], as it did in some of these catastrophes [35].

When large numbers of failures are recorded (25%) [21] or there are many serious complications it suggests that the knowledge of technique or dose was inadequate or the operators were careless [36]. For example, textbooks previously described performing femoral nerve block by fanwise injection lateral to the femoral artery. It is more accurate to insert a short beveled needle vertically lateral to the femoral artery and feel the resistance of two "pops" as the needle penetrates fascia lata and fascia iliaca. If it is easy to inject, the tip is in the correct place [37]. Otherwise withdraw the needle with pressure on the syringe plunger until it is easy to inject – occasionally the two fascial layers are fused. The other aid to finding depth is that there is resistance to injection while the needle tip is in muscle but it is easy to inject into spaces where nerves often lie [38].

KEY POINTS: EARLY REGIONAL ANESTHESIA IN CHILDREN

- Tyrell Grey of Great Ormond Street Hospital in London published three papers on spinal anesthesia in children in 1909–10
- In the 1920s and 1930s there were four major case series of spinal anesthesia in children in over 2000 patients
- The first caudal anesthetics in children were reported by Meredith Campbell in 1933

Delivery systems and anesthetic machines, 1916–1937

Many varieties of inhalers were developed before gas, oxygen, and ether machines such as the one produced by Gwathmey came into being in the early twentieth century. Edmund Boyle, at St. Bartholomews Hospital (Barts) in London, dissatisfied with the older methods of anesthesia, obtained a Gwathmey machine from the United States in 1916. As it developed gas leakage problems at joints he decided to make his own machine beginning about 1917. Initially this provided oxygen, nitrous oxide, and ether. This continued to develop as the Boyle machine, which became widely used around the world [39]. In the United States Forreger and then Heidbrink machines were developed. As all these progressed, flowmeters and vaporizers improved and became more accurate. By the 1950s Lucien Morris had developed the copper kettle vaporizer [40] and Cyprane had made the Fluotec with split gas flow and temperature compensation to provide accurate lower concentrations of halothane. It was then modified for other agents [41].

Another important addition was carbon dioxide absorption with soda lime, introduced in a circle system by Dennis Jackson (1915) [42]. Waters developed the to and fro system using his canister which had a small pediatric version [43]. These avoided the use of high gas flows and were particularly useful with cyclopropane which was an expensive and explosive agent. It also required special flow meters.

Anesthetic machines such as the Boyle evolved, and variations remained in use for six to eight decades (Fig. 2.4). Jeffrey Cooper in Boston designed a brilliant delivery system with electronic feedback safety features [44] which suffered commercial suppression. Rod Westhorpe (see Fig. 2.11H) and colleagues in Melbourne produced a machine with many ergonomic features such as height adjustment, sloping light emitting diode (LED), flow meters, and gas delivery from either side (Fig. 2.5). It did not get past prototype development before the new concept workstations were introduced which combined anesthesia delivery, ventilator, and monitors. They were revolutionary.

Pediatric anesthesia delivery systems

For infants and small children low-resistance circuits were desirable to minimize work of breathing. In 1937 Philip Ayre (Fig. 2.6) introduced his T piece which had the advantages of low resistance (no valves), simplicity, and allowing controlled ventilation away from the operative field in patients who were intubated, particularly for cleft lip and palate and neuro surgery. His original T piece was part of an older Philips circuit which had a gas delivery tube entering the side but turning a right angle to face the expired gas flow. He recognized that the patients did better this way because the flow creates slight resistance to expiratory flow which would tend to keep the alveoli open – actually it was a form of continuous positive airway pressure (CPAP). Unfortunately when the T piece was manufactured it was made with the fresh gas flow tube entering at right angles. About 40 years later an acute-angled fresh gas inflow was made and Portex made a similar device in plastic, thus restoring the original benefit of slight CPAP.

The volume of the expiratory limb of the T piece should exceed tidal volume to avoid air dilution. For controlled ventilation the expiratory limb is occluded to force fresh gas into the lungs. The tidal volume then depends on the fresh gas flow rate and the duration of occlusion (flow generator).

Ayre was an unusual man: he had alopecia, wore a ginger wig, and had had a cleft lip and palate repair which left him with a honking voice that mesmerized the children during induction. He gave about 2000 anesthetics while he was still a medical student [45]!

Later, Jackson Rees from Liverpool, England, added an open-ended bag to increase versatility (Fig. 2.7). With spontaneous ventilation it acted as a respiratory monitor but it could

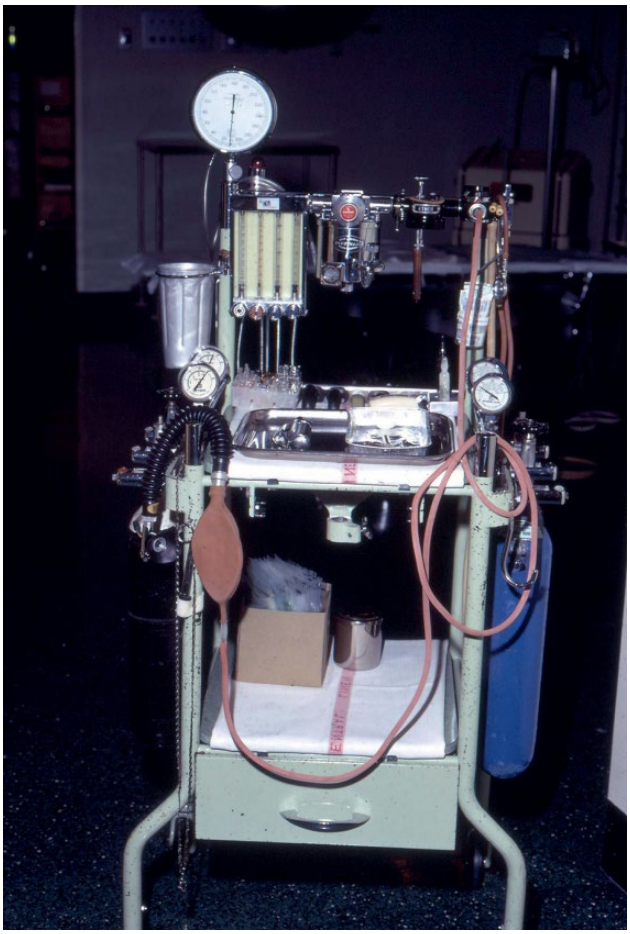

Figure 2.4 CIG Boyle machine, 1963.

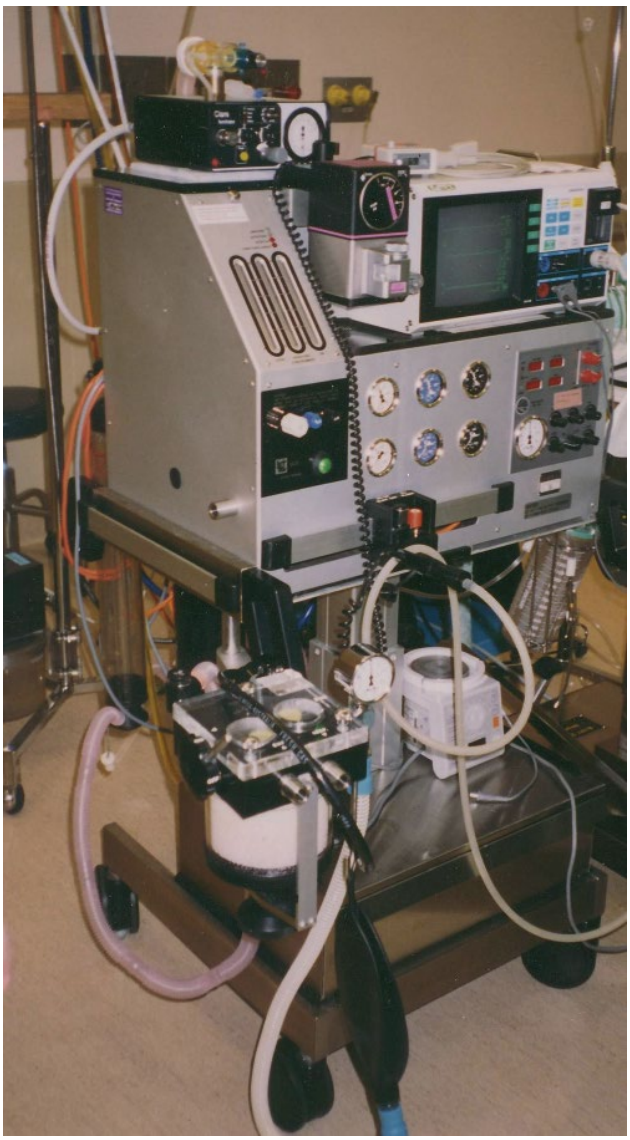

Figure 2.5 Ergonomic anesthetic machine with Claire ventilator and monitor on top.

Figure 2.6 Philip Ayre, Newcastle upon Tyne, England.

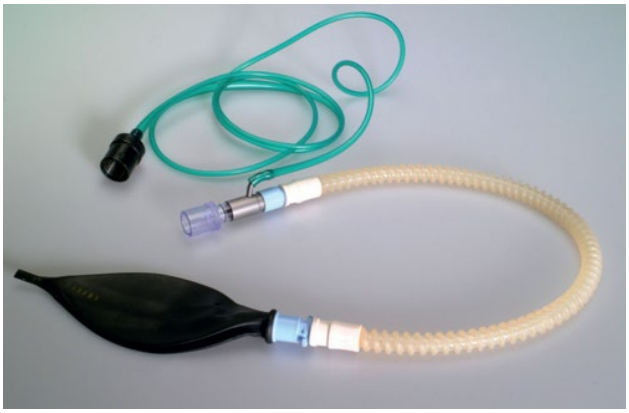

Figure 2.7 Jackson Rees T piece modification with his prolonged intubation tube attached.

be used for controlled ventilation as demonstrated in Figure 2.8. It was important to use three fingers to squeeze the bag because using four caused thenar muscle fatigue.

Other low-resistance devices used more in North America were the Lewis–Leigh and Stephen–Slater one-way valves. They allowed fresh gas to flow to the patient but during expiration a flap valve stopped the inflow and directed the gas out of the circuit.

The Bloomquist pediatric circle with miniaturized soda lime canisters and narrow tubing were used in North America, while Ian McDonald in Melbourne made a similar miniature circuit. They had valves which increased work of breathing and so were better used with controlled ventilation. The circle system conserved the expensive gas, cyclopropane, and reduced the risk of fire.

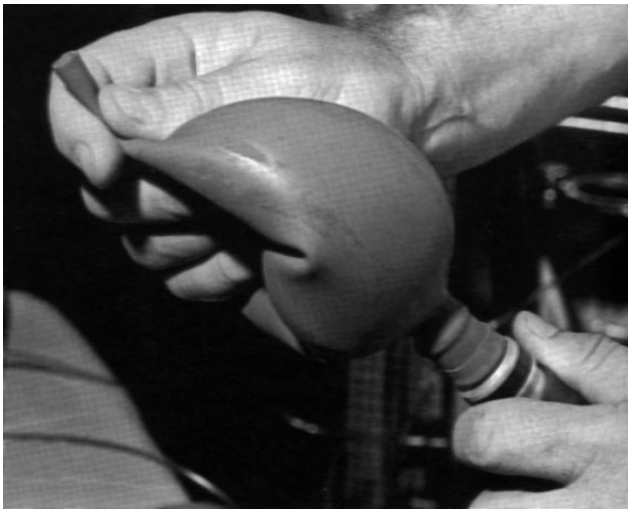

Figure 2.8 Ventilating with the open-ended bag of the Jackson Rees T piece. Three movements are required. (1) Close open end with thumb and index finger. (2) Squeeze bag with the other three fingers (shown). (3) Stop squeezing and allow expiration.

KEY POINTS: DELIVERY SYSTEMS AND ANESTHETIC MACHINES

- Anesthesia machines delivering oxygen, nitrous oxide, and ether were developed as early as 1916–17
- Carbon dioxide absorption with soda lime was introduced by Jackson in 1915
- The Ayre T piece was introduced in 1937 specifically for pediatrics

New drugs in the 1930s, 1940s, and 1950s

Several new anesthetic drugs were introduced in this period. Cinchocaine/dibucaine (1929) was a longer-acting local anesthetic which was widely used to extend spinal anesthesia. Vara-Lopez from Burgos, Spain, reported 438 spinals in children using cinchocaine/dibucaine in 1942 [46].

The short-acting barbiturates, hexobarbital and thiopental, were introduced in 1932 and 1934. Although many continued to induce anesthesia using inhaled agents, thiopentone was the favored intravenous induction agent for over 60 years. There were circumstances in which the usual dose (about 5 mg/kg) needed to be modified. It was often avoided in neonates but could be used in small doses – 2–3 mg/kg. The infant dose was higher and declined after 2 years with age [47,48]. Premedication reduces anxiety and the sympathetic response. An anxious child will have an increased cardiac output and muscle blood flow with proportionately less of the cardiac output going to the brain so that more drug is needed to induce anesthesia. The opposite situation prevails when the patient is hypovolemic, usually due to blood loss. If the usual dose is given, the concentration in the reduced blood volume is greater and a greater proportion of cardiac output and the drug goes to the brain and heart. Onset of anesthesia is quicker and myocardial depression is more likely to occur.

Cyclopropane is a gas, discovered in Toronto but introduced to clinical anesthesia by Waters in 1934 [49]. It was not only flammable but explosive. There was an explosion in Chile that killed five staff and the patient. Cyclopropane had a low blood:gas solubility (0.47) and provided rapid induction and emergence. Deep anesthesia could be reached quickly and the muscles relaxed so that patients could be intubated and good operative conditions achieved. This facilitated the development of thoracic surgery before muscle relaxants were introduced. Cyclopropane had sympathomimetic properties so that blood pressure was maintained even when some blood had been lost. The downside was hypotension when the vasoconstrictive action wore off.

Cyclopropane was popular for children because of the rapid, smooth induction. In inexperienced hands laryngeal spasm during emergence could be a problem but after three or four spasms one soon learnt how to deal with that complication – *continuous* positive pressure on the bag full of oxygen would force oxygen into the patient with the slightest opening of the vocal cords. It was a matter of timing whether one extubated the child while still deeply anesthetized or nearly awake. Ralph Waters taught to turn on nitrous oxide and discontinue cyclopropane near the end of an anesthetic to reduce the tendency to spasm. The use of cyclopropane declined after the introduction of halothane.

Trichloroethylene (Trilene) was a dry cleaning agent. Langton Hewer, in London, introduced it as an anesthetic in 1941. It had several good points including low cost, potent analgesia (good for obstetrics and peripheral procedures), and non-flammability. Its minimum alveolar concentration (MAC) was 0.17%. Unlike other inhalational agents it was a poor hypnotic and increased muscle tone, resulting in rapid shallow breathing (like restrictive lung disease). Unlike other inhalation anesthetics it increased consumption of non-depolarizing muscle relaxants when used with them. This was thought to be due to an effect on muscle spindles increasing muscle tone which reduced chest wall compliance.

Trichloroethylene was found to have neurotoxic effects when used with soda lime which, in those days, contained 5% potassium hydroxide [50]. The exothermic reaction of this compound with carbon dioxide produced toxic breakdown products, affecting most commonly the trigeminal nerve. Potassium hydroxide was later replaced with sodium, calcium, or barium hydroxide in soda or baralyme (80% calcium hydroxide and 20% barium hydroxide) which were safer.

Trichloroethylene was used in a few pediatric centers as an adjunct in neurosurgery, as an agent which did not cause cardiovascular changes during cardiac catheterization, and in primitive situations where it could even be used instead of nitrous oxide which, being a gas, was too expensive or not readily available in less affluent countries.

High concentrations had to be avoided otherwise rigidity, prolonged sleep, and a high incidence of postoperative vomiting occurred, especially if narcotics were used as well. One could just detect the smell when 1 MAC was delivered. Trichloroethylene was very cheap but it was discontinued when the manufacturing plant needed to be replaced.

Lidocaine (lignocaine) was synthesized by Lofgren and Lundquist in Sweden in 1946. It became widely used. Despite its shorter action (about 1½ h) it was used by infusion, if necessary, for longer cases in less affluent countries where cost mattered and new drugs were too expensive. About 18 years later it was found to have antiarrhythmic effects on the heart.

More recently longer-lasting local anesthetics such as bupivacaine were introduced (1963) which led to a rekindling of interest in nerve blocks and regional anesthesia. Although newer agents with claimed advantages have been introduced, bupivacaine was safely used thousands of times by keeping to safe doses (3 mg/kg) and avoiding intravascular injection. Moore suggested convulsions were unlikely below plasma levels of 4 μg/mL. He recorded 5.1–5.4 μg/mL in one case [51]. In another report 7.5 μg/mL was recorded during unexpected convulsions because the plunger of the syringe was pulled back to ascertain the absence of blood. The 12-year-old patient was ventilated with oxygen until she recovered. Although a decrease in heart sounds occurred, indicating a transient decrease in cardiac output, no dysrhythmias were detected [52].

KEY POINTS: NEW DRUGS IN THE 1930S, 1940S, AND 1950S

- Cyclopropane was introduced into practice by Waters in 1933
- Trichloroethylene was first used by Hewer in 1941
- Lidocaine was synthesized by Lofgren and Lundquist in 1946

Neonatal anatomical and physiological factors in relation to anesthesia and monitoring

There are some important anatomical points relevant to ventilation of infants and small children [53]. Looking at a chest radiograph, small infants' ribs are more horizontal which prevents an increase in antero-posterior diameter, also, lacking the bucket handle movement of older children and adults prevents increases in transverse chest diameter. The consequence is that a baby's tidal volume is more dependent on diaphragmatic movement. Anything that splints the diaphragm such as air in the stomach or abdominal distension diminishes tidal volume. Gentle ventilation will avoid stomach distension.

In tracheo-esophageal fistula, positive pressure ventilation, if used, must be gentle (low pressure), particularly if a lower esophageal fistula is large. In the early years (1960s) the size was sometimes estimated by the air in the fistula on a lateral chest radiograph. If it was more than 2 mm across, it indicated that inflating the stomach was a potential hazard.

Another observation when looking at a neonatal chest radiograph is that the left bronchus comes off the trachea at a greater angle (47°) than the right bronchus (30°) [54]. Adriani and Griggs [55] stated in 1954 that the angles were equal, a point that was assiduously reproduced in textbooks for many years.

When an endotracheal tube is inserted too far, it is usually on the right side. Many people think this is because the right bronchus is in a more direct line from the trachea or that the right bronchus and lung are larger, but it is mainly due to the fact that the tip of the bevel of the tube is on the right. The

practical implication is to turn the tube so that the point of the bevel is on the left if one is aiming for left endobronchial intubation. In the days before endoscopic placement of tubes was available these were important points for the anesthesiologist to know.

Anesthetic dead space must be kept to a minimum and hence the Rendell-Baker–Soucek low dead space mask was developed. Some anesthesiologists cut endotracheal tubes to reduce dead space but this is unnecessary and even undesirable when controlled ventilation is used because of the tendency to overventilate.

Babies breathe faster and have more rapid heart rates so that more oxygen is delivered to the tissues to satisfy their higher metabolic rate and oxygen consumption. Cardiac output is heart rate dependent because stroke volume varies little. Also, the heart rate slows in response to hypoxia (unlike adults) so that cardiac output is adversely affected.

Fifty years ago monitoring was simple and depended more on observation of clinical signs. Anesthesiologists could glean most of the essential information from these. The pulse would indicate rate, rhythm, volume, and character (e.g. bounding, soft).

The stethoscope, either precordial or esophageal, provided valuable information about ventilation and correct placement of the tube as well as heart rate, rhythm, and intensity of heart sounds. The last are created by heart valve closure and will be softer if stroke volume or myocardial contractility is reduced. The sounds give a sensitive indication of changing cardiac output (provided the stethoscope has not become loose) and, more recently, it is a quick way of telling whether a falling oxygen saturation is a patient or probe attachment problem.

Capillary refill was a useful indicator of peripheral perfusion. It would decrease when there was blood loss and with cold temperatures. Skin color could indicate adequacy of hemoglobin; for example, if it was low, the skin exhibited pallor. Cyanosis was a rather late sign of hypoxia, particularly if the hemoglobin was low. This is why the introduction of the pulse oximeter was such an important development in anesthesia.

Over the years fluid and electrolyte therapy has improved. Initially it was felt that babies needed to be kept hydrated and needed glucose for energy. Pediatricians gave 5% glucose in water or 4% glucose in 1/5 normal saline which provided inadequate sodium resulting in hyponatremia.

An important difference between neonates and small infants compared to older children is that the extracellular (ECF) and smaller intracellular (ICF) fluid compartments are larger, which makes them sicker than older patients if they become dehydrated (easy loss from ECF and less fluid in the ICF to buffer losses in the ECF) (Fig. 2.9).

The kidneys, including the cortical nephrons which control sodium reabsorption, are not fully developed at birth. While much water is reabsorbed in the proximal tubules, the urine osmolality (700 mOsm/L in neonates compared with 1400 mOsm/L in adults) is adjusted by water reabsorption in the loops of Henle where interstitial urea is less (nitrogen is being used for tissue building). This information was only reported in the 1960s and early 70s.

Nowadays a balanced electrolyte solution (e.g. Hartmann's, lactated Ringer's) is a commonly used intraoperative fluid in children. Normally the stress of surgery will ensure an adequate blood sugar level in children. Some glucose may be added to the intravenous fluids in premature babies because glucose and glycogen storage may be insufficient at birth. Neonates require less fluid during the first few days. One calculation for daily fluid requirement was:

- 0–7 days: day of life/7 × 100 mL/kg
- 0–6 months: 100 mL/kg
- 1–13 years: weight (kg) – age (years) × 90 mL/kg.

Total parenteral nutrition (TPN) was a concept developed in the 1970s, advocated because it shortened length of stay in ICUs by providing essential calories, nutrients, and fluids. The savings offset the cost of TPN.

Heat loss may be greater because infants have large heads that contribute to their greater surface area:body weight ratio. They are poorly insulated with less subcutaneous fat, they do not shiver, and they have a narrower thermoneutral range, i.e. ambient temperature where heat loss is minimal. Steps such as a warming blanket beneath the baby on the operating table, wrapping in foil, warmed humidification, and the use of overhead heaters were used to prevent cooling. Before these steps were taken, outcomes of surgery were less favorable.

There have been many developments in physiology, some of which also affect the handling of drugs, which impact on pediatric anesthesia. A better understanding of these has helped improve the care of children and the results of surgery.

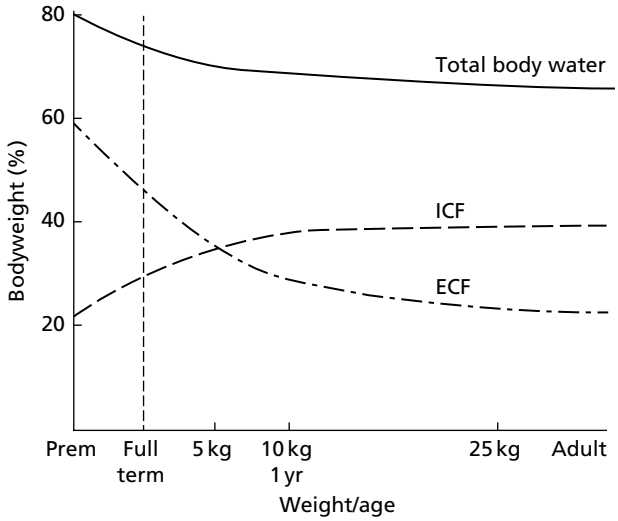

Figure 2.9 Changes in intracellular and extracellular fluid compartments (ICF and ECF) during the first months of life. *Source:* Adapted from Cheek [125] and Friis-Hansen [126].

KEY POINTS: NEONATAL ANATOMICAL AND PHYSIOLOGICAL FACTORS

- Small infants' ribs are more horizontal, preventing "bucket handle" movement and making tidal volume more dependent on the diaphragm
- In early years monitoring was by clinical observation only: skin color, capillary refill, pulse
- Balanced electrolyte solutions, preservation of body temperature, and neonatal pharmacology have contributed significantly to survival in neonatal anesthesia

Early anesthesiologists interested in children: pediatric anesthesia emerges into the specialist era, 1920s to 1950s

During the transitional years (1920–1950) when doctors who gave anesthetics first began to take a special interest in children, particularly babies, changes began to occur mainly in some of the more progressive children's hospitals. Pediatric surgery was beginning to expand but success was only possible when anesthesia improved and there was still a long way to go.

Pediatric anesthesia refers to anesthesia for children of all ages. In the first 100 years it was part of the amalgam of anesthesia generally, with few references to studies in children who were regarded as miniature adults. Few doctors devoted their practice to anesthesia, mostly doing some general practice as well. Before World War II few people took a special interest in children's anesthetics. In countries like Canada, Britain, Australia, and New Zealand, doctors, sometimes young and inexperienced, gave the anesthetics while in the USA and Europe nurses were often involved. Betty Lank was one who made an outstanding contribution, working with Robert Gross in Boston for 20 years from 1936.

Canada

Charles Harold (Robby) Robson (Fig. 2.10A) [56,57] came from British Columbia. He graduated in medicine at McGill in Montreal in 1913. He interned at Montreal General and trained in anesthesia at Royal Victoria Hospital before going to France in World War I, later becoming Senior Consultant Anesthetist to the Canadian Army.

In 1919 he returned to Canada and became Chief Anesthetist at the Hospital for Sick Children (HSC), Toronto, where he remained until he retired in 1951. Adenotonsillectomy constituted about a third of cases. Anesthesia was mainly open drop ethyl chloride and ether. Robson had a special skill of tactile intubation when necessary – he used his fingers to guide the tube into the trachea. He became Clinical Demonstrator in 1935, published one paper on "anesthesia for children" in 1936 and made a movie on the hazards of the immediate postoperative period. He was a frequent speaker on pediatric anesthesia and trained a generation of anesthesiologists, including five who became department heads. He was probably the first pediatric anesthetist to have such a major influence on the field and has been called the grandfather of pediatric anesthesia in Canada.

In 1927, Charles Junkin joined the staff of HSC but like many doctors involved with anesthesia in those days he anesthetized adults and children and also did general practice. In 1945 he became a full-time pediatric anesthetist and went on to become Chief from 1951 to 1960 [58].

At the conclusion of World War II the department was enlarged by better trained and more experienced full-time anesthetists coming back from the war, such as Norman Park, who was joined by others in Toronto including Code Smith, a wonderful pharmacology teacher who made the subject more interesting by discussing structure–action relationships of drugs (notably barbiturates and local anesthetics). This made the subject easier to follow and remember. He was mainly a neuroanesthetist.

Digby Leigh (Fig. 2.10B) [58], also from British Columbia, graduated in Montreal (McGill) in 1932. He began surgical training until Wesley Bourne, later the first Professor of Anesthesia in Montreal and Canada, persuaded him to change to anesthesia. He spent three years with the legendary Ralph Waters at Madison, Wisconsin, the first Professor of Anesthesia in the USA (1937), before returning to become Chief at the Montreal Children's Hospital in 1940. He developed a non-rebreathing valve and an infant circle absorber so that cyclopropane could be administered in a closed circuit.

During the war, Leigh with Wesley Bourne and Harold Griffiths (later first President of the World Federation of Societies of Anaesthesia – WFSA) each organized 3-month anesthesia courses for doctors in the armed forces before they went overseas. Many of these trainees went on to become part of the rapid expansion of specialists after the war. Digby Leigh established the Montreal Diploma of Anesthesia course which set the pattern for training in Canada. In 1947 he moved to Vancouver where he set up a department which supplied the total service for Vancouver General and Children's Hospitals. Among those who went with him was Eric Webb, a brilliant clinical teacher who also inspired an interest in the history of anesthesia among trainees. Leigh later went to Lagos, Nigeria, as part of a Canadian initiative to help establish training in that country. Others who accompanied Leigh were Horace Graves, Harold Kester, John Poole, and Herb Randall. The last also trained with Waters and had a limited practice until he was 92 (possibly the oldest anesthesiologist still to practice).

Leigh produced the first textbook on pediatric anesthesia in North America with Kay Belton, Supervisor of Pediatric Anesthesia at Vancouver General Hospital (1949) [59]. It is an interesting book, first discussing the care of the child in hospital, and later including a chapter on local anesthetic blocks including caudals and spinals, which were used in about 10% of their cases.

In 1954 Digby Leigh moved to Los Angeles Children's Hospital, having failed in his request for a separate department and chair of anesthesia in Vancouver. He started the annual weekend courses on pediatric anesthesia that were run for many years by Wayne Herbert. Later his idea of half-day release for teaching trainees was taken to Australia. His influence on teaching and training both generally and in pediatrics was immense. He was regarded as father of pediatric anesthesia in Canada.

C.R. Stephen followed Leigh as chief at Montreal Children's Hospital until 1950, when his colleague H.M. Slater succeeded him when he moved to Duke, North Carolina [57]. They had developed the Stephen–Slater non-rebreathing valve.

Children's hospital anesthetic departments and major hospitals with separate pediatric sections began to acquire more and more full-time pediatric anesthesiologists although in many places general anesthesiologists performed children's anesthetics as part of their practice. The full-timers were largely responsible for leading the way in the advances in the specialty, which was developing from the 1950s onwards.

In 1954 Ruston, working in Hamilton, Ontario, reported on epidural anesthesia for Infants and children, and 10 years later updated their experience [59,60].

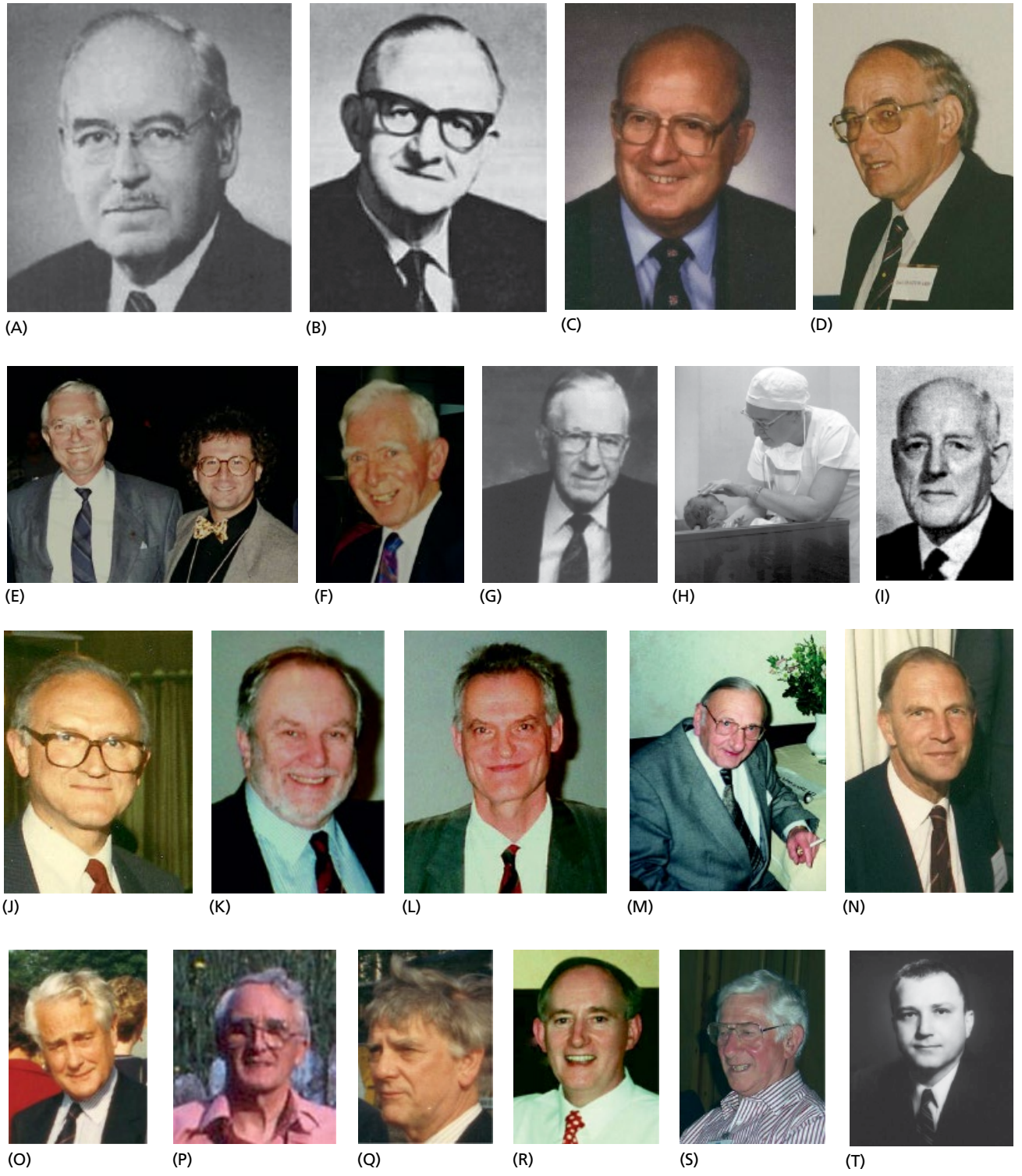

Figure 2.10 Prominent pediatric anesthetists: Canada, USA, and Britain. (A) Charles Robson, Toronto; (B) Digby Leigh, Montreal, Vancouver, Los Angeles; (C) Alan Conn, Toronto; (D) David Steward; Toronto, Vancouver, Los Angeles; (E) Robert Creighton (left), Jerrold Lerman (right), Toronto; (F) Tom McCaughey, Winnipeg; (G) Robert Smith, Boston; (H) Virginia Apgar, Columbia, New York City; (I) Robert Cope, London; (J) William Glover, London; (K) David Hatch, London; (L) Ted Sumner, London; (M) G. Jackson Rees, Liverpool; (N) Gordon Bush, Liverpool; (O) Gerry Black, Belfast; (P) Harold Love, Belfast; (Q) Peter Morris, Manchester; (R) George Meakin, Manchester; (S) Ted Armitage, Brighton; (T) Arthur Keats, Houston, TX.

During the 1960s and 1970s the next group of leading contributors in Canada included Alan Conn (Fig. 2.10C), Chief at HSC Toronto, who went on to become Chief of Intensive Care with a special interest in near drowning. He was succeeded by David Steward (Fig. 2.10D), who was a very active teacher and editor of his well-known *Handbook of Pediatric Anesthesia*. One of his interests was anesthesia for ex-premature infants. He later opened up Vancouver Children's Hospital before concluding his clinical career as Chief at Los Angeles Children's Hospital. He was succeeded by Bob Creighton and

then Jerry Lerman (Fig. 2.10E), who was an enthusiastic researcher.

Many others specialized in the field. Jeremy Sloan was a cardiac anesthetist at HSC who came from South Africa. Later he contributed to international standards committees. Harold Davenport was chief at the Montreal Children's Hospital before moving to Vancouver for a short period. He then returned to England. He authored a small book about pediatric anesthesia. Tom McCaughey (Fig. 2.10F) became well known as chief at Winnipeg Children's Hospital.

United States of America

Robert Smith (Fig. 2.10G) [4], after war service in Europe where he became involved in anesthesia, was appointed Chief of Anesthesia at the Boston Children's Hospital in 1946. Previously anesthesia at this hospital had been given by nurses including Betty Lank, who made special equipment such as small blood pressure cuffs and masks for infants and children. Smith was interested in patient safety and was an advocate of the use of appropriately sized endotracheal tubes and of wrapping babies to prevent heat loss. In the 1950s he pioneered the use of the precordial stethoscope.

Robert Smith was a great teacher and trained people from all over the world. He had a calm demeanor and never roused antagonism. He produced a famous, comprehensive book in 1959 called *Anesthesia for Infants and Children*. He was regarded as the father of pediatric anesthesia in the USA [61].

Virginia Apgar (Fig. 2.10H), having trained with Ralph Waters, became Director of Anesthesia at the Babies Hospital in New York in 1938. Following her research on neonatal resuscitation she became known around the world for the APGAR scoring system (1953) which she developed to assess the condition of babies at birth and soon afterwards: skin color, pulse, reflex irritability, muscle tone, and respiration each scored as 0, 1 or 2. It was simple and had predictive value – a score below 5 indicated that the baby was in trouble. Later in her career she moved to Johns Hopkins University where she took an interest in birth defects [62].

There were others who contributed to the development of pediatric anesthesia such as Robert McQuiston at Chicago Children's Hospital and Herbert Rackow and Ernest Salanitre at the Babies Hospital at Columbia Presbyterian Medical Center in New York [63]. They established departments that advanced training and practice of pediatric anesthesia after World War II. The latter had research interests in the uptake and elimination of inhalational agents and the risk of cardiac arrest in infants and children.

Margot Demming was the first full-time pediatric anesthesiologist in Philadelphia. She observed that infants required higher concentrations of inhalational agents than adults [64]. Many others followed such as Jack Downes, also in Philadelphia, who was involved in the early days of intensive care [65]. Some places benefitted by the immigration of established pediatric anesthesiologists like Digby Leigh and C.R. Stephen from Canada, and elsewhere.

United Kingdom

In Britain, Great Ormond Street Hospital for Sick Children in London appointed Robert Cope as head anesthetist in 1937 (Fig. 2.10I) [66]. Others joined him such as Sheila Anderson, Bill Glover (Fig. 2.10J), and later David Hatch (Fig. 2.10K) who became the first Professor of Paediatric Anaesthesia in the United Kingdom. David Hatch, with Ted Sumner (Fig. 2.10L), produced a valuable book on neonatal anaesthesia.

Liverpool became influential later when people like Jackson Rees (Fig. 2.10M), Gordon Bush (Fig. 2.10N; the first editor of *Pediatric Anesthesia*), Alan Stead, and Tony Nightingale joined the group there. People from many parts of the world gained experience with them. Britain had many children's hospitals, and places like Glasgow (Douglas Arthur, Roddie McNicol – nerve blocks, especially the anterior approach to the sciatic nerve), Belfast (Harold Love, Fig. 2.10O; Gerry Black, Fig. 2.10P), Manchester (Peter Morris (Fig. 2.10Q), George Meakin (Fig. 2.10R) – muscle relaxants in children), Birmingham (Susan Jones) and others developed good reputations as their staff became well known. Even places like Brighton contributed through the work on caudal anaesthesia by Ted Armitage (Fig. 2.10S) and, in Derby, by Brian Kay. Many of the leaders became President of the Association of Paediatric Anaesthetists.

Jackson Rees was an enthusiast who was well recognized for his teaching, research, and constant search for new ideas [67]. He was largely responsible for the Liverpool technique: thiopental, d-tubocurarine, and rapid ventilation with nitrous oxide and oxygen. Many people incorrectly described it as hyperventilation but the method as he performed it was very rapid, small breaths ventilated with the bag he attached to the T piece on which he kept a slight positive pressure. Unwittingly he was using high-frequency ventilation and positive end-expiratory pressure (PEEP) long before the value of these were appreciated. He was guest lecturer to the Australian Society of Anaesthetists and ran a 2-week course in Melbourne in 1963. During his visit he saw the work with prolonged nasotracheal intubation, with ventilation if needed, that had developed in Adelaide [68] and Melbourne [69]. He returned to Liverpool via Toronto and conveyed his enthusiasm for what he had seen. He began pediatric intensive care in Liverpool and developed his special complex tube for nasal intubation.

In 1973 Britain led the way in Europe when the Association of Paediatric Anaesthetists of Great Britain and Ireland (APA) was formed. They had foreign members who were leaders in Europe and the rest of the world who were well represented at their meetings before other regular meetings had started [70]. These became an important step in building the bonds between pediatric anesthesiologists.

Australia

In Australia a handful of the more experienced general anesthetists took care of most of the babies and pediatric cases needing special care before and during World War II. These included Gilbert Brown (first President of the ASA – Australian Society of Anaesthetists) and Mary Burnell (Fig. 2.11A) who established pediatric anesthesia at the Adelaide Children's Hospital (later President of ASA and Dean of the Faculty of


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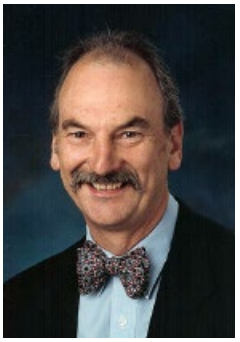
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Figure 2.11 Prominent pediatric anesthetists: Australia, New Zealand. (A) Mary Burnell, Adelaide; (B) Charles Sara, Sydney; (C) Margaret McClelland, Melbourne; (D) Bernard Brandstater, Australian working in Beirut, Lebanon (left) and Ian McDonald, Melbourne (right); (E) John Stocks, Melbourne; (F) attendees at the 1979 Australian Pediatric Anesthesia Meeting; (G) Robert Eyres, Melbourne; (H) Rod Westhorpe, Melbourne; (I) Peter Kempthorne, Auckland; (J) Brian Anderson, Auckland.

Anaesthetists), Gilbert Troup in Perth (1922–1947), and Andrew D. Morgan, the first specialist pediatric anesthetist to be appointed in Sydney in 1940. It was Morgan who provided anesthesia for the first lung lobectomy in 1942 and ligation of ductus arteriosus in 1947. He retired in 1957. Charles Sara (Fig. 2.11B), whose research interests were muscle relaxants, humidification, and the management of prolonged respiratory insufficiency, joined the department in 1957. Verlie Lines,

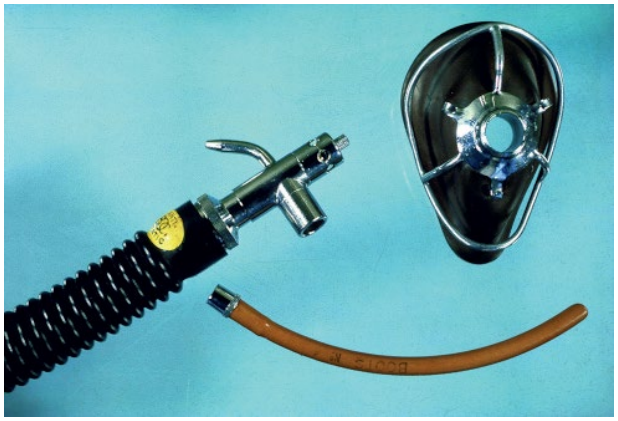

Figure 2.12 Pediatric anesthetic equipment designed by Margaret McClelland and Harry Adams.

who became their first full-time anesthetist in 1955, had a special interest in airway problems. In Perth, Douglas Wilson, who was part-time Honorary Director (1946–1956), made his own equipment and anesthetized most of the neonates there. In 1960 Nerida Dilworth began 30 years as Director, helped by part-timer Peter Brine who later became President of the Australian Society of Anaesthetists [71].

In 1946, Margaret McClelland (Fig. 2.11C) returned to Melbourne, having spent the war years in London giving anesthetics and gaining her Diploma of Anaesthetics. She was in demand immediately but spent some time at the Children's Hospital, eventually becoming the first Director of Anaesthesia (part-time in 1949, full-time in 1956). A training rotation with the Women's Hospital was started. As well as local trainees, others came from interstate and New Zealand. Providing good training and competent assistance in the form of anesthetic technicians, several of whom stayed 30–35 years, McClelland ensured that her concerns about the care of the children in hospital and anesthetic mortality were considerably improved. She collaborated with Harry Adams of Commonwealth Industrial Gases to make a range of equipment for pediatric use (Fig. 2.12) and initiated the use of new drugs including muscle relaxants.

Margaret McClelland was ably supported by Ian McDonald (Fig. 2.11D, right) and later by John Stocks (Fig. 2.11E). They began prolonged intubation and ventilation which led to the development of intensive care in Melbourne Children's Hospital, initially in half of the recovery room [69]. She also did research into hypothermia in relation to cardiac surgery and into anesthetic mortality. She retired in 1970, having also been President of the Australian Society of Anaesthetists in 1964.

She was succeeded by John Stocks, who was a quiet, diligent doctor, highly regarded by his colleagues [71]. He had become Director of Intensive Care in 1969. He wrote *Notes on Paediatric Anaesthesia* which were widely read and utilized. He had intended to write a book but unfortunately he died in 1974 from complications of cancer surgery when only 43. The book was eventually written by Kester Brown, who succeeded him as Director for the next 26 years. Brown was very involved in teaching, continuing education, and research. His co-author was Graham Fisk, who established the second pediatric anesthesia and intensive care units in Sydney and also became a leader in research and education in Australia. Geoff Barker succeeded Stocks as Director of Intensive Care. He had done training in Toronto and returned there later to become Chief of Intensive Care at HSC and eventually Professor of Critical Care in Toronto University.

Tess Brophy was another outstanding woman who advanced pediatric and neuroanesthesia in Queensland, later becoming Dean of the Australian and New Zealand Faculty of Anaesthetists.

By 1967 there were ten full-time and five part-time pediatric anesthetists in Australia who led the rapid changes that occurred during the next 20 years. It was noteworthy how many pediatric anesthetists held leading roles in the Australian Society or Faculty of Anaesthetists and how many were outstanding women. Kester Brown was involved with the WFSA for 20 years, the last four as President. He was able to promote pediatric anesthesia when he organized courses, lectured, and taught in many countries.

Many overseas anesthetists came to Australia for further experience – from 40 countries to Melbourne, and many others to Sydney, Adelaide, and Perth. The majority returned home, where they taught and raised the standard of anesthesia in their own countries.

Victor Mwafongo (Fig. 2.13A) returned to become Head Anaesthetist in Tanzania and later Director of Emergency Medicine. Radha Krishna (Fig. 2.13B) and then Ng Siew became heads of government anesthesia in succession in Malaysia. Rebecca Jacob (Fig. 2.13C, centre), who spent 2 years in Adelaide, became Professor at Vellore Christian Medical College, one of the major hospitals in India. She was also a leader in the Asian Society of Paediatric Anaesthesia which was started by Agnes Ng (Fig. 2.13C, right) from Singapore. Many others, like Dilip Pawar from India (Fig. 2.13C, left), had leadership roles.

During the following ten years (1970–1980) many able young men and women in Australia specialized in pediatric anesthesia (Fig. 2.11F). Many made outstanding contributions. Robert Eyres (Fig. 2.11G) performed cardiac anesthesia and pioneered epidurals in the Royal Children's Hospital in Melbourne. He did the first studies on blood levels of local anesthetics in children which showed that even with doses of 3 mg/kg bupivacaine the levels in caudals and epidurals did not exceed safe levels of 2 µg/mL [72]. Rod Westhorpe (Fig. 2.11H) became an expert on the history of anesthesia, was a leader in the Australian Patient Safety Foundation, and contributed to the development of an ergonomic anesthetic machine and the Claire ventilator. He also became President of the Australian Society of Anaesthetists. Johns Overton, Kennealy, and Vonwiller became the leaders in Sydney where Overton performed the first infant open heart surgery under deep hypothermia in 1969.

This section is included to show the development and some changes in practice during the years of pediatric anesthesia's evolution. In 1967 over 700 patients were managed for 24 h or more in the Royal Children's Hospital ICU in Melbourne. Mortality had begun to decline in neonatal conditions such as esophageal atresia (Fig. 2.14) and diaphragmatic hernia. In those days diaphragmatic hernia, which presented as a blue baby with a barrel chest and scaphoid abdomen because of the displaced abdominal contents, was treated as an emergency to prevent the gut

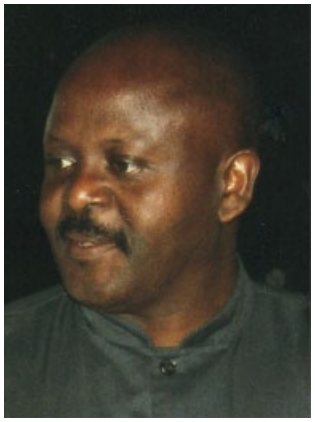
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Figure 2.13 Prominent anesthetists from Scandinavia, Europe, South Africa, Nigeria, South America, and Asia including Japan. (A) Victor Mwafongo, Tanzania; (B) Radha Krishna, Malaysia; (C) (left to right) Dilip Pawar, India, Rebecca Jacob, India, and Agnes Ng, Singapore; (D) Hans Feychting, Stockholm; (E) Alvar Swenson, Stockholm; (F) Barbro Ekstrom Jodal, Stockholm; (G) Krister Nilsson, Stockholm; (H) Toivo Suutarinen, Helsinki; (I) Gunnar Bo, Oslo; (J) Claude St. Maurice, Paris; (K) Isabel Murat, Paris; (L) Paolo Busoni, Florence (left), Bernard Dalens, Clermont-Ferrand (center), Elizabeth Giaufre, Florence (right); (M) Ottheinz Schulte Steinberg, Munich; (N) Josef Holzki, University Children's Hospital in Liege, Belgium; (O) Anneke Meursing, Rotterdam; (P) Harry Curwen of Durban, South Africa, with his paper on caudals in infants, 1950; (Q) Adrian Bosenberg, Durban; (R) Dorothy Ffoulkes Crabbe, Lagos, Nigeria; (S) Armando Fortuna, Brazil; (T) Carlos Riquelme, Chile; (U) Carlos da Silva, Brazil; (V) Seizo Iwai (left) and Mitsuko Satayoshi (right), Japan; (W) Hiroshi Sankawa, Japan; (X) Katuyuki Mitasaka, Japan; (Y) Genichi Suzuki, Japan; (Z) Maseo Yamashita, Japan; (A') Estela Melman, Mexico.

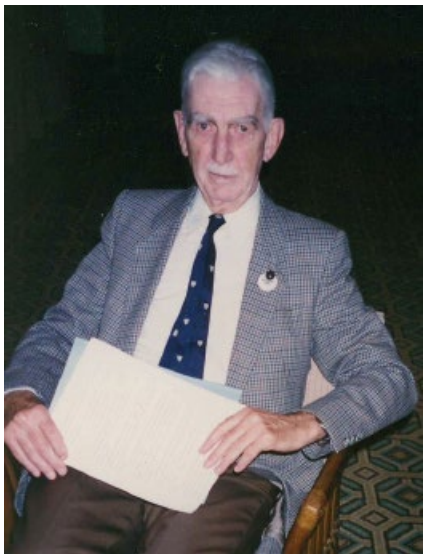
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Figure 2.13 (*Continued*)

distending with gas before the small abdomen was closed after the hernia was repaired. One infant operated on after 24 h had a red upper half of its body and a blue lower half after surgery. The lung was a reasonable size and the patient recovered. A clinical assessment of lung size was considered useful in prognosis. If it was one-third or less of normal size the outlook was poor. It is now recognized that if the lung on the compressed side was that small, the other lung would be compressed as well and pulmonary hypertension would occur. Over the years things changed with the advent of new technology: the use of ECMO (extracorporeal membrane oxygenation) and the treatment of pulmonary hypertension. Another factor that seemed to have a greater influence on poor survival was the patient becoming cold during transport to the hospital. When the baby was kept warm and had a reasonably developed lung, the outlook was good. An important point in the anesthetic management was not to try to inflate the small lung. It cannot be fully inflated. With time the lung grows once the compression is relieved.

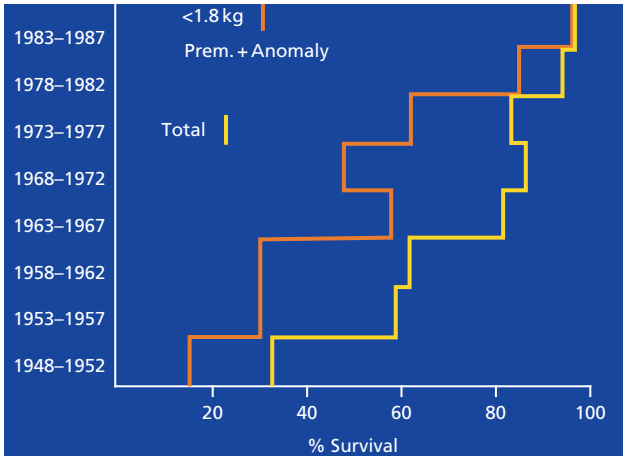


Figure 2.14 Improving results in esophageal atresia with the development of intensive care.

New Zealand

New Zealand did not have a children's hospital until Starship opened in Auckland in 1991. New Zealanders regularly came to Melbourne for some pediatric anesthesia training but Peter Kempthorne (Fig. 2.11I) was the first to return to do pediatric anaesthesia and neonatal intensive care. Brian Anderson (Fig. 2.11J), who did pediatric anesthesia training in Melbourne and Rotterdam, led the academic developments when the new hospital opened in Auckland.

Scandinavia and Europe

Anesthesia in Scandinavia remained the responsibility of the surgeon, who supervised specially trained nurses, until after World War II when the ether/chloroform era began to pass with the advent of new drugs and equipment [73].

In Sweden, Goran Haglund was appointed anesthesiologist at the Children's Hospital in Gotenburg in 1951, having spent a year training in Chicago. His experiences in the United States led him to conclude that critically ill patients with cardiovascular and respiratory problems would be better managed in one location. He opened the world's first multidisciplinary pediatric intensive care unit in 1955. But he did much more. Before that, he handled respiratory and fluid and electrolyte problems in part of the surgical ward. A positive–negative pressure ventilator was described in 1954, and in 1958 the team reported respirator treatment which included four newborns, two of whom had infant respiratory distress syndrome, probably another first. Haglund developed diagnostic and treatment skills for respiratory problems including bronchoscopies. He proposed the use of mouth-to-mouth breathing some years before Peter Safar's important publication. Haglund was a talented man and great contributor to the specialty [74,75].

In 1958 Hans Feychting (Fig. 2.13D) was appointed as the first pediatric anesthetist at the Children's Hospital in Stockholm. In 1961 he established a postoperative ward that over the next 5 years evolved into an intensive care unit for which he became well known. Later he played a role in establishing international standards for anesthetic equipment. Alvar Swenson (Fig. 2.13E) was appointed chief of pediatric anesthesia at Karolinska Sjukhuset in 1966. He had a special interest in ventilator treatment. Pediatric anesthesia was in good hands when these people were followed by Barbro Ekstrom Jodal (Fig. 2.13F), Krister Nilsson (an active researcher) (Fig. 2.13G), Gunnar Olsson (chronic pain), and others.

Toivo Suutarinen (Fig. 2.13H) served in the winter war with Russia in 1941. He became the father of pediatric anesthesia in Finland. He began training in surgery but recognized the need for good anesthesia, so changed. He went to the United States for 2 years (Chicago and Massachusetts General Hospital). Shortly after his return in 1956 he was appointed to the Children's Hospital in Helsinki where they developed high standards of surgery ably supported by good anesthesia and intensive care. He retired in 1981 to be followed by Olli Meretoja, a leading researcher on muscle relaxants in children.

Otto Mollestad was the first anesthesiologist in Oslo, Norway, in 1947. Signe Gullestad in Bergen was the first to have a special interest in children. It was not until the 1980s before Gunnar Bo (Fig. 2.13I) and some colleagues managed to get agreement to organize a small group to care for the infants and children at Rikshospitalet in Oslo.

Across Europe there were many children's hospitals. Paris had several, including Enfants Malades and St. Vincent de Paul, where Claude St. Maurice (Fig. 2.13J) and later Isabel Murat (Fig. 2.13K) worked. They were leaders in regional anesthesia. Later, Bernard Dalens (Fig. 2.13L, centre) published a definitive textbook on regional anesthesia in children. St. Maurice co-edited a book on local anesthesia in children with Ottheinz Schulte Steinberg (Fig. 2.13M) who trained with Bromage in Montreal. He worked in Starnberg, near Munich in Germany. The latter undertook one of the first studies on the spread of local anesthetic from caudal injection. He also introduced the technique of threading a caudal catheter up the epidural space in small children (who do not have obstructing ligamentous partitions in the epidural space) to the thoracic region if necessary. The idea was promoted further by Paolo Busoni (Fig. 2.13L, left) in Florence at Ospedale Pediatrico A. Meyer, where much of the surgery was done with caudal anesthesia [75]. Their common technique where appropriate was halothane induction, intravenous diazepam, and caudal block without continuing the general anesthetic. Their postoperative vomiting rate was a low 7%. Busoni also did a study with a psychologist, getting the children to draw their perception of their anesthetic. One drew the upper half of the body red and the lower half green.

Other Europeans who became well known by the 1970s included Professor Mickelson at Filitov Children's Hospital in Moscow where epidural anesthesia, including thoracic, had been used since the 1970s; Karl Rondio in Poland; Josef Holzki (Fig. 2.13N) at University Children's Hospital in Liege, Belgium; and Peter Dangel in Zurich. He was particularly involved in intensive care and was one of the early doctors involved in helicopter transport of very sick children. Much of the anesthesia was done by nurses trained in anesthesia.

Although there are several children's hospitals in the Netherlands, much of the pediatric work is done in university hospitals. Anneke Meursing (Fig. 2.13O) visited several major centers in Britain and America and spent 6 months in Melbourne in 1986 before she raised the profile of Sophia Children's Hospital in Rotterdam which, at the time, was the

largest in the Netherlands (Meursing A, personal communication, 2016). She introduced teaching and active research programs. She persuaded Jackson Rees, who had just retired, to come on regular visits from Liverpool to supervise their research. She also had people come from other countries to gain further experience. Several of these, such as Brian Anderson from New Zealand and Andrew Davidson from Melbourne, later became leaders in the field at home. All this development came to an end when Sophia was amalgamated into the University Hospital and the staff numbers were reduced so that the remaining ones had to limit their activities mainly to clinical service.

Anneke Meursing played a big role in anesthesia generally. She organized the first two European Pediatric Anesthesia Congresses in Rotterdam in 1986 and 1989, with the foundation of the Federation of European Associations of Pediatric Anaesthesia (FEAPA). She was secretary for the World Congress of Anaesthesia Organizing Committee for 1992 and thereafter was a WFSA Executive Committee member, Secretary and President of the WFSA.

Another European pediatric anesthesiologist who gained prominence was Sten Lindahl, who became Professor at Karolinska in Stockholm and later chairman of the Nobel Prize Committee for Physiology and Medicine.

South Africa

Harry Curwen (Fig. 2.13P, holding a typed copy of his 1950 paper [25]), in Durban, began a series of caudals in neonates and by 1950 he had done 92. He reported his experience at a South African meeting. He was uncertain whether the technique would be adopted but did suggest that it might be useful for practitioners working in smaller centers in relative isolation.

Red Cross Memorial Hospital was opened in Capetown in 1955, intended as a children's hospital open to all races. The Red Cross provided a large part of the funds to build it. Tom Voss became full time in charge of anesthesia in 1958 and became Associate Professor in 1968. He moved to Australia in 1977 and became the pediatric anesthetist at the new Westmead Hospital in Sydney in 1980. While he was in Capetown he was part of a team that had operated on five pairs of conjoined twins (Voss T, personal communication, 2016).

Adrian Bosenberg (Fig. 2.13Q) worked in Durban as a pediatric anesthetist and, following Schulte Steinberg's visit on sabbatical leave, used caudal catheters, threaded even to the thorax, in neonatal surgery. The advantage was that the patients could be nursed without ventilator care postoperatively with a catheter passed up to the thorax in an environment where there were not enough experienced nurses [76].

Dorothy Ffoulkes-Crabbe was a prominent anesthesiologist at Lagos University Teaching Hospital, Nigeria, who published a number of papers on airway management, regional anesthesia, and carbohydrate metabolism under anesthesia in children over a career spanning more than 30 years (Fig. 2.13R).

South America has many children's hospitals. One of these, Calvo McKenna in Santiago, Chile, is now a WFSA training center for pediatric anesthesia in the region. The first trainee was from Bolivia. Armando Fortuna (Fig. 2.13S) from Brazil reported his experience with caudals, mostly in poor-risk infants using lidocaine in 1963 [25,77]. He was a leader in the field, starting in the late 1950s. Carlos Riquelme (Fig. 2.13T) from Chile organized the first pediatric anesthesia symposium in Chile in 1984. He has been an outstanding teacher who has well thought out reasons for what he does. Carlos da Silva (Fig. 2.13U) in Brazil examined trainees by watching an anesthetic and then getting them to give reasons for how they conducted it.

Japan

The first recorded anesthetic in Japan was a herb mixture including mandragora called *Tsu Sen San*, administered by a surgeon, Hanaoka, in 1804. Its use in children over 5 for cleft lip repair was reported by Gencho Homma in 1837. Japan was an isolated country so anesthesia did not progress until after 1950. Mitsuko Satayoshi (Fig. 2.13V, right) established general anesthesia with intubation for the neonatal surgical pioneer, Keijiro Surugu, and was later joined by Seizo Iwai (Fig. 2.13V, left) when he returned from training with Digby Leigh in Los Angeles in 1961. National Children's Hospital was the first children's hospital when it opened in 1965. By 1990 there were 17. Seizo Iwai was the first head of the Anesthetic Department. The department began day surgery in 1966. Initially understaffed, this was improved and it became the leading center in the country [78].

Iwai became professor in Kobe in 1968 and was followed at Tokyo Children's Hospital by Hiroshi Sankawa (Fig. 2.13W) and later by Katuyuki (Kats) Miyasaka (Fig. 2.13X) who had spent several years at HSC Toronto. Miyasaka undertook early trials of sevoflurane. He was also involved in ten separations of conjoined twins and in planning a new paperless National Children's Hospital to which he managed to have a previously non-existent Emergency Department added.

The Japanese Society of Paediatric Anaesthetists was formed in 1971 to promote the transfer of knowledge. Genichi Suzuki (Fig. 2.13Y) was a major participant. Maseo Yamashita (Fig. 2.13Z) played a role in the Asian Society of Paediatric Anaesthesia after its establishment.

KEY POINTS: EARLY PEDIATRIC ANESTHESIOLOGISTS, 1920–1950

- Charles Robson in Toronto became the first recognized pediatric anesthesiologist in 1919
- Robert Cope in London was the first full-time pediatric anesthetist in the UK in 1937
- Robert Smith in Boston, starting in 1946, was the first full-time pediatric anesthesiologist in the United States, and the author of an early textbook
- Brown, Burnell, Troup, and Morgan established pediatric anesthesia in Australia in the pre-World War II years

The specialty of pediatric anesthesia develops further, 1950s to 1970s

From the 1950s through the 1960s and 1970s great changes took place. Anesthesia had become a recognized specialty, more and better equipment became available including endoscopes, which helped both anesthesiologists and surgeons, and operating microscopes, as well as a wide range of drugs

and adjuncts to resuscitation, all of which helped to cope with the demands of more difficult surgery. The introduction of polyvinyl chloride (PVC) tubes, intravenous butterfly needles and cannulae, and intensive pre- and postoperative care contributed to better survival.

More recently the advent of endoscopic surgery has brought about another major change in surgical practice to which anesthesiologists have had to adapt.

Cardiac surgery

Cardiac surgery began, tentatively at first, with the ligation of a patent ductus arteriosus by Gross in Boston in 1938. At Johns Hopkins Hospital, Merel Hamel and Austin Lamont were involved with Blalock and Helen Taussig in the development of their palliative operation for Fallot's tetralogy in 1944 [79].

Denton Cooley at Texas Children's Hospital was the most prolific cardiac surgical operator between 1955 and 1970. The most prominent pioneer anesthesiologist who worked with him was Arthur Keats [80] (Fig. 2.10T). He published many papers on related subjects such as anesthetic techniques, outcomes, premedication, airway management, induction and maintenance of anesthesia, arrhythmias and their intraoperative treatment, perfusion, and descriptions of the postoperative ventilator they made in 1958. He also described anesthesia for cardiac catheterization (1958) and the reversal of heparin with protamine in 1959. He made a great early contribution to the field. Another pioneer was W.O. McQuiston in Chicago who wrote one of the first papers on pediatric cardiac anesthesia in 1949 [81].

In 1969 and the 1970s corrective heart surgery was successfully carried out on infants under 10 kg down to neonates under deep hypothermia (18°C) with circulatory arrest by the technique suggested by Mori in Japan [82]. (Drew, in London, had earlier tried deep hypothermia but the technique did not catch on.) This was an exciting time. To see a heart gradually beginning to beat and become more regular with stronger contractions as it rewarmed after an hour or more of cardiac standstill was a most amazing experience. At least part of the success of the technique was due to adding CO_2 to the oxygenator before the pump was switched off. The aim was to maintain a corrected $PaCO_2$ for temperature (pH stat) but importantly it moved the oxygen–hemoglobin dissociation curve back to the right allowing greater release of oxygen to the tissues before circulatory arrest. Normally in hypothermia it moved far to the left.

Because the heart is vital to survival, anything that could help, such as drugs or technical support, was useful in the intensive care of these patients. Gradually more and more anesthesiologists specialized in this field and increasingly complex abnormalities were corrected. Cardiac surgery has become a subspecialty with its own experts and meetings.

Some patients were ventilated after cardiac surgery. In Toronto this began in 1961 [83], contributing to the beginning of their intensive care, initially in part of their recovery room.

The beginning of intensive care

In 1952 there was a pandemic of poliomyelitis. Copenhagen, Denmark, was badly hit and had many cases. Nearly 90% of the early cases with respiratory involvement died. Bjorn Ibsen [74,84], recently returned from anesthesia training in the United States, when the specialty was first recognized in Denmark, was invited to consult. He found that many patients were dying from CO_2 retention and respiratory failure. He instituted tracheotomy, suction, and hand ventilation by medical students and later dental students. They only had one iron lung and a few inefficient negative pressure cuirass ventilators. Eventually, after 165,000 h (equivalent to 1000 weeks or over 19 years) of hand ventilation, the epidemic passed and the respiratory mortality had been reduced to 25%. The first successfully treated patient was a 12-year-old girl. This episode was the start of the development of intensive care. It was also a stimulus for the developments of ventilators, and of acid base, pH, and $PaCO_2$ measurement by Paul Astrup, Ole Sigaard Andersen, and John Severinghaus [85].

Polyvinyl chloride endotracheal tubes and pediatric intensive care

The advent of PVC endotracheal tubes opened the door for the development of pediatric intensive care. In 1962 Bernard Brandstater (Fig. 2.11D, with Ian McDonald, when they met 50 years later), an Australian working in Beirut, Lebanon, reported the first cases of prolonged intubation. Most of his patients had tetanus but one had croup [86].

Tom Allen became Director of Anaesthesia at the Adelaide Children's Hospital in 1960 [68,87]. Having seen nasotracheal intubation used successfully in adults, he persuaded the physicians to try prolonged nasotracheal intubation in their more severe cases of croup (laryngotracheobronchitis). He was a leader in the field but there were others starting about the same time. In Melbourne, Ian McDonald ventilated a baby by hand overnight following a lobar lung resection in 1960. He and John Stocks suggested nasotracheal intubation as a step in decannulating a baby with a retained tracheostomy following esophageal atresia repair. After 5 days the tube was successfully removed. When they reviewed their first 60 cases of prolonged intubation, three had developed subglottic stenosis [69]. Ethylene oxide sterilization and organotin in the tubes were eliminated as possible causes. There was no tissue reaction when PVC was implanted under the skin. It was eventually concluded that pressure on the mucosa around the cricoid ring, the narrowest part of the larynx, from too tight a tube was the cause. None of the next 300 patients suffered this complication after it was recommended that a slight leak of gas around the tube should occur when positive pressure was applied. People working in that era would question the justification of cuffed tubes which have been advocated in recent years. The main reasons are cost and mucosal trauma from pressure from the cuff further down the trachea. A larger-diameter plain tube can be used instead, which fits comfortably through the cricoid ring and has proved satisfactory for many years. Such tubes mold, when warm, to the shape of the airway which, in that region, is almost circular. Also, where the cuff lies, the diameter of the trachea expands and contracts with each breath.

There were many other details that had to be worked through, which modern intensivists take for granted. When the normal humidifying mechanism in the nose is bypassed by a tube some form of humidification must be employed to prevent encrustation of secretions and tube blockage. There

was much debate over whether gas should be passed over heated water or a nebulizer, producing fine water droplets, should be used. The size of the droplets was critical: if they were too small (0.5–3 µm) they could reach the alveoli and "drown" the patient, whereas if too large (30 µm) they would fall out in the trachea and not reach the bronchi.

In time nebulizers lost out to humidification. The simplest form was a hot water tank over which the gas flowed. There were several hazards. The temperature had to be set so that it was about 35°C when it reached the patient. This maximized humidity and prevented burning and overheating. Loops in the tubing had to be avoided to prevent water condensation and obstruction to gas flow. Later, a heating wire was inserted into the tubing so that the required temperature that the patient received could be set at the humidifier. The problem was that at 35°C bacteria grew well while in the former hotter environment (55–60°C) they were killed. It was not just a matter of using antibiotics to treat infections because in those days a common pathogen, *Pseudomonas pyocyaneus*, was not susceptible to the available antibiotics. When infections and cross infection became problems the obvious solutions of strict hand washing and changing suction catheters had to be enforced.

Various methods were developed to hold the nasotracheal tube in place. Tunstall in Aberdeen, Scotland, devised a special clip [88]. Jackson Rees made a complex tube for good fixation (Fig. 2.7) but its cost and difficulty of insertion led to its abandonment. A commonly used method was to split two pieces of waterproof tape for half their length. Half of the first piece would be laid across the face just below the nose (Fig. 2.15). The other half was wound round the tube and fixed up the nose. The upper half of the second piece would be laid across the nose and the nasal part of the first tape used to hold it in position and prevent a downward pull on the tube. The lower half was wound around the tube and across the face. To protect the skin and add stickiness, tincture of benzoin compound was wiped on the face where the tape would be attached. The tapes had to be changed from time to time if they became wet with secretions. The most urgent emergencies were accidental extubation and tube blockage which required immediate removal, mask ventilation, and rapid reintubation.

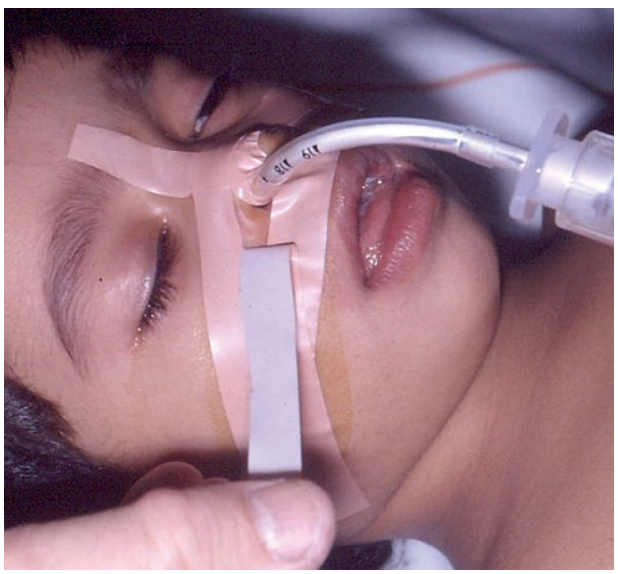


Figure 2.15 Fixing a nasal tube with waterproof strapping around the tube and up the nose to prevent downward pull. Another strap then fixes it. The whole is then covered with sticking plasters (not shown).

Figure 2.16 shows an ergonomic method of holding the mask with the mouth open to make it easier to ventilate with a mask.

Intubation technique must be proficient both for anesthesia and in intensive care, especially in infants in whom oxygen consumption is greater and hypoxia develops rapidly. A good ergonomic approach for infants and small children, which did not require someone to hold the head steady, is shown in Figure 2.17. Note the head being stabilized and the way the laryngoscope is held, allowing the left little finger to press the larynx back so that the tube can be seen passing between the vocal cords. It is advanced for 2–3 cm to avoid endobronchial intubation. (Tracheal length at birth is usually 4.5 cm at full term.) In nasal intubation the tube is passed through the nose and guided towards the larynx, which can be moved by pressure from the left little finger or by rotating the tube. Sometimes flexing the neck slightly as the tube is advanced will allow it to pass more easily.

Ergonomics is how to carry out tasks most efficiently with the least effort. Such ergonomic approaches made these techniques easier to teach and learn.

The question remained, "How long could a PVC tube be left in?" At the meeting at HSC, Toronto, in November 1964 a panel with Drs Leigh, Cope, and Jackson Rees were discussing 5–7 days when Tess Brophy, the leading pediatric anesthetist from Brisbane, rose and said that a child in Australia had been successfully extubated after 34 days. There was a stunned silence. Tubes have since been left in situ for much longer (6 months) but nowadays if very prolonged intubation is necessary a tracheotomy is done so the infant's facial muscles can develop [89].

Ventilators

The first positive pressure ventilator was developed by Crafoord in Stockholm in 1937. He was a thoracic surgeon. Many places did not have mechanical ventilators until after the late 1950s. Only a few used in the early days of the

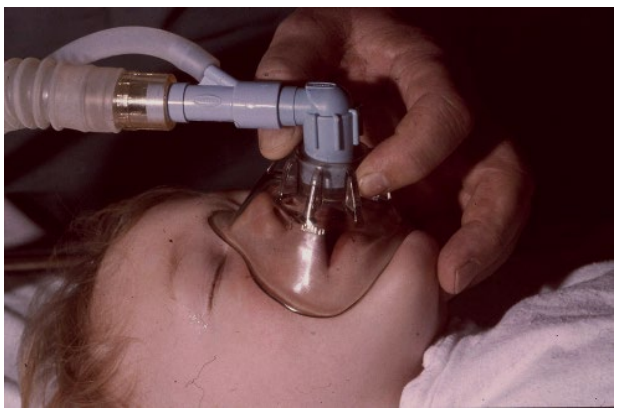
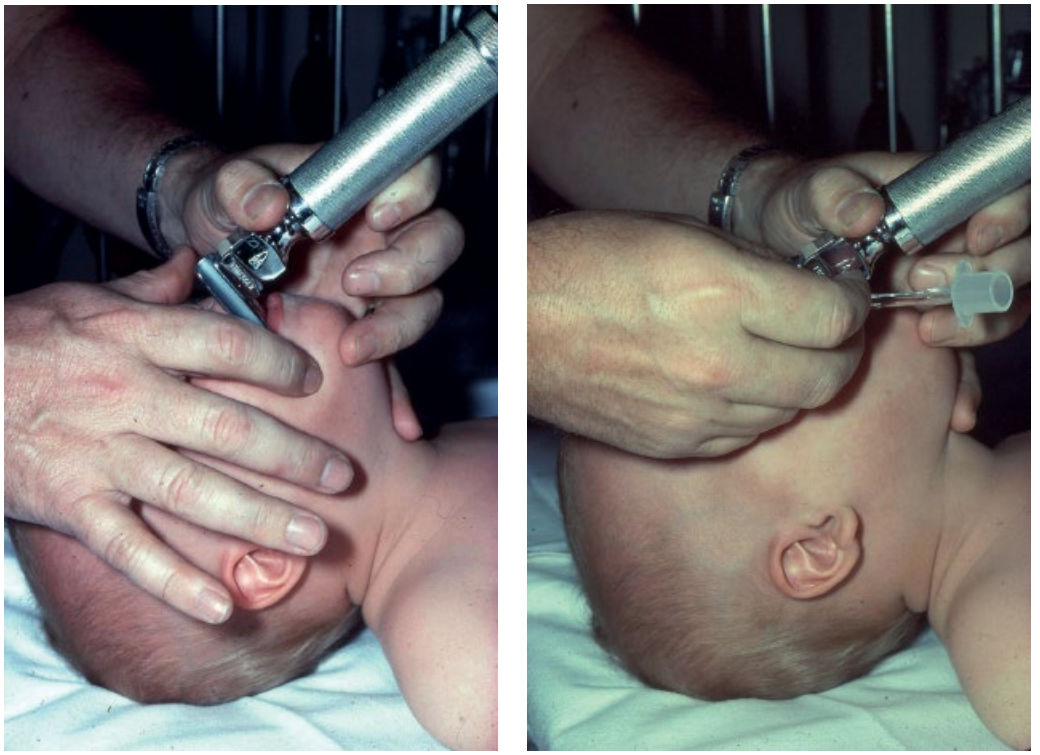


Figure 2.16 Ventilating with a low dead space mask. The mask is placed in the groove on the chin with the mouth open. It is then pressed gently on to the face by the thumb and index finger and the jaw is pulled forward by the little finger (note the Portex y connector).



(A) (B)

Figure 2.17 Intubation. (A) The neck is extended, the right thenar eminence fixes the forehead, and the right index finger opens the mouth to ease insertion of the laryngoscope. (B) Note how the laryngoscope is held so that the left little finger can reach to press the trachea backwards. The tube is inserted in the right corner of the mouth so that the trachea is visible. For nasal intubation the tube is inserted and guided towards the trachea with slight external rotation if necessary. Slight flexion of the neck sometimes helps.

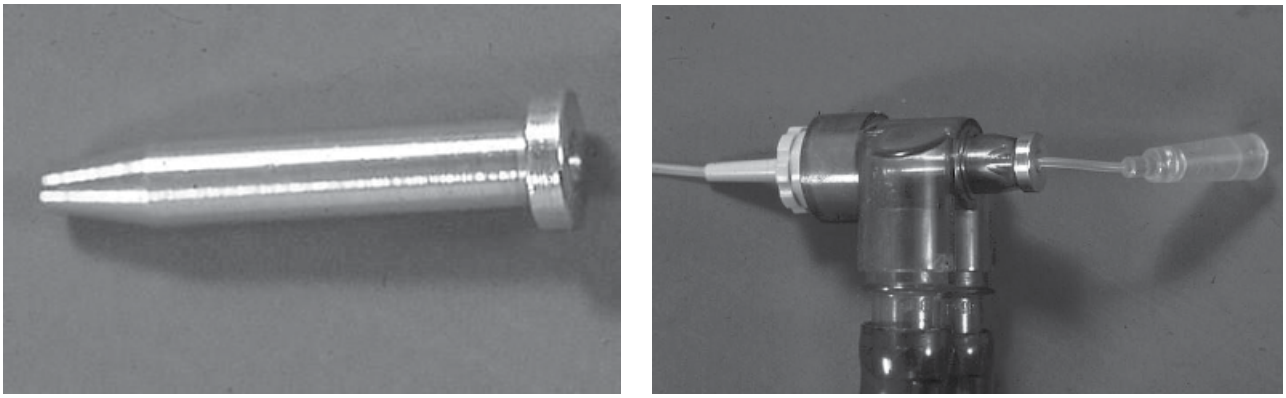
pediatric intensive care unit (PICU) will be mentioned here. With pressure-controlled ventilators (e.g. Bird Mark VIII or Bennett PR2) the pressure was adjusted to produce a suitable tidal volume. The ventilator could also have a time cycling mechanism in case it could not achieve the maximum inspiratory pressure. These required frequent adjustment. The volume-cycled ventilators (e.g. Engstrom) delivered the set volume provided there was not a significant leak around the tube.

The Engstrom ventilator was developed just prior to the polio epidemic that reached Sweden in 1953. It was a large machine driven by a large piston with an eccentric cam which produced a sine wave positive pressure curve. The inspiratory thrust was applied to squeeze the bag containing the gas in a polymethyl methacrylate cylinder. The amount delivered was determined by the amount added to the circuit and hence to the bag. It was volume controlled. The flow pattern was slow to start with, allowing flow into all parts of the lungs before the rate increased. The bag had to be empty before the sine wave reached the top of the curve. This provided time for the pressure to equilibrate while gas redistributed from easily ventilated areas to less well-ventilated ones with narrower airways and higher resistance to gas flow. Most other ventilators did not have this facility and hence the patient needed a periodic large inflation or "sigh" to prevent atelectasis. The main problem with the Engstrom ventilator was its large size.

Intermittent positive pressure ventilation (IPPV)

IPPV produces many physiological changes. Mean intrathoracic pressure is raised. The amount depends on the inspiratory:expiratory (I:E) ratio and the pressure applied. This reduces venous return, which causes a decrease in blood pressure in hypovolemic patients. Some ventilators had a negative expiratory phase to compensate. There was a strong divergence of views between those who thought a negative phase was useful because venous return was important and those who thought some positive expiratory pressure was desirable to prevent alveolar collapse and diminution of functional residual capacity in the lungs. In 1968 John Inkster from Newcastle upon Tyne, England, presented a paper and gave a workshop describing his valve to achieve the latter [90]. Professor Mary Ellen Avery of Montreal was there. She spoke of the concept of PEEP keeping the airways open at the Royal Children's Hospital Centenary meeting in Melbourne in 1970. About the same time George Gregory in San Francisco struck on the idea of using CPAP to keep the lungs inflated in premature babies with hyaline membrane disease (respiratory distress syndrome). Charlie Bryan, at HSC, Toronto, had similar ideas. Was there any transfer of information or had they all come to their ideas independently? Now it seems such an obvious solution to the problem which greatly expanded the field of neonatology and provided pediatric anesthesiologists with the challenges of anesthesia for very small babies with consequent conditions such as inguinal hernias, necrotizing enterocolitis and patent ductus arteriosus.

All was not over. CPAP raises mean intrathoracic pressure but in so doing it raises venous pressure required to get the blood back to the heart and maintain end diastolic volume. That leads to capillary pressure alterations so that more fluid is retained in the tissues – edema develops. Extra fluids are



(A) (B)

Figure 2.18 (A) The Stocks bullet. (B) Catheter inserted through the bullet, enabling suction while continuing ventilation.

needed to compensate for these losses from the circulation and to ensure an adequate stroke volume. CPAP or PEEP has to be adjusted to maximize the benefits to ventilation while minimizing the vascular problems. Another important problem arose. With improved alveolar ventilation FiO_2 increased, sometimes to the extent that oxygen toxicity in the lungs developed, sometimes causing death, and having the potential of causing retrolental fibroplasia and blindness [91]. Now the problem of hyaline membrane disease has been solved by the instillation of surfactant, the substance which was lacking, and which prevents alveolar collapse.

The Stocks bullet

Another problem was the effect of suction, which is necessary to remove secretions [92]. It is necessary to interrupt ventilation and oxygen supply with resultant drop in the patient's PaO_2. Like so many early anesthesiologists who had inventive minds, John Stocks designed a very simple device, the Stocks bullet, which fitted into the circuit where it attached to the tube (Fig. 2.18). A small hole through it allowed the passage of a suction catheter while ventilation continued during suction, thereby lessening the fall in PaO_2 and the amount of recruitment necessary after suction [93].

Airway obstruction

Airway obstruction is one of the great challenges of pediatric anesthesia. It can be life-threatening. In 1927 Scholes reported the use of O'Dwyer tubes [94], devised to treat diphtheritic obstruction, in 1175 patients. Eventually immunization solved the problem.

Laryngeal papilloma and obstructive cysts and nodules can create anesthetic challenges unless a tracheostomy is present. The operating microscope, laser, and inflating devices (bronchoflator) [95] have made these treatments easier [96].

Epiglottitis was a frightening condition to treat, especially if obstruction was nearly complete and the epiglottis looked like a cherry with maybe a bubble of air the only indication of the airway. Initially, tracheostomy was the treatment but intubation became the preferred method because the artificial airway was only needed for a few hours after the antibiotic was given until the swelling decreased [97]. Immunization against *Haemophilus influenzae* type B has virtually eliminated this disease.

Tracheal obstruction could be caused by a foreign body within it, stenosis in the wall, or compression from outside such as by an aberrant subclavian artery or a mediastinal mass. The latter tumors require a diagnostic biopsy to determine the most appropriate treatment. This can create a very hazardous anesthetic, especially if the patient cannot lie down because obstruction to the trachea, bronchus, or even the superior vena cava may occur in certain positions. In this situation careful positioning is important and experience suggests that ketamine, which maintains muscle tone, is the safest induction agent.

The development of pediatric intensive care was in the domain of anesthesiologists because of their expertise in airway management and ventilation. As critically ill patients with other conditions were admitted to ICU, staff from other specialties became involved and intensive care became a separate specialty in some countries. Originally anesthesiologists took their skills to intensive care but now it is important for those who want to become top-class pediatric anesthesiologists to spend some time working in intensive care so that they acquire expertise with the technical skills and equipment used when treating the sickest patients.

KEY POINTS: THE SPECIALTY DEVELOPS FURTHER

- Congenital cardiac surgery developed significantly from 1955 to 1970 with Denton Cooley and Arthur Keats in Houston
- Intensive care originated in the early 1950s under Ibsen during the polio epidemic in Denmark
- The Engstrom ventilator was one of the earliest ventilators, developed in Sweden in the early 1950s

Unraveling mysteries and challenges: malignant hyperthermia, massive hyperkalemia, and anaphylaxis

Unexpected situations created fear in anesthesiologists' minds, especially when the cause was unknown and treatment was not known. Jim Villiers in Melbourne (Fig. 2.19) was twice in this unenviable situation but succeeded in being the

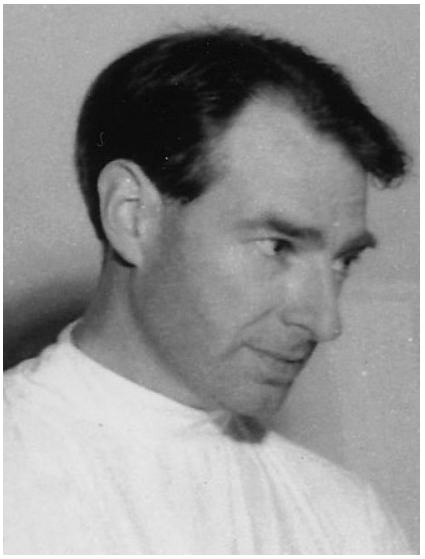


Figure 2.19 Jim Villiers.

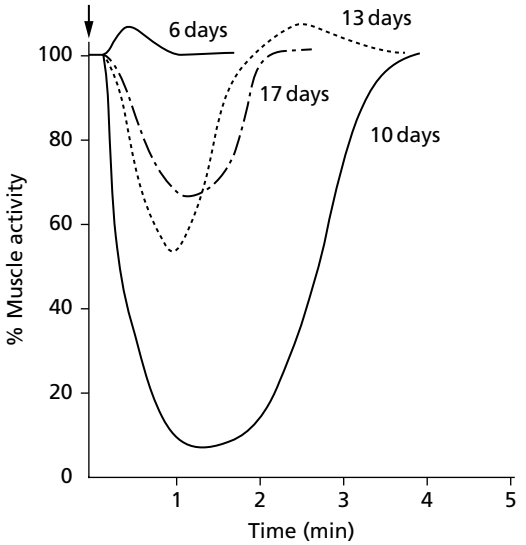


Figure 2.20 Electromyograph recordings following 0.1 mg/kg succinylcholine in a 6-year-old with 30% burns showing varied response and sensitivity during the first 2 weeks post burn.

first to keep his patients alive in both instances of newly described anesthetic "diseases": malignant hyperthermia, and massive hyperkalemia after succinylcholine administration.

The syndrome of malignant hyperthermia was described in 1962 by Denborough and colleagues after a 20-year-old male presented with a broken leg for manipulation and plaster. He had a family history of deaths associated with anesthesia but a cousin had recently survived. Preoperative enquiry and examination gave no clues to a problem but as soon as a halothane anesthetic started, the patient and the soda lime canisters began to get hot. There was still no clue but Villiers immediately discontinued the anesthetic and gave oxygen. The procedure was completed promptly and the patient was taken to the relatively new recovery room where, by good fortune, there were buckets of ice waiting to be used on a neurosurgical case. These were dumped on the patient who cooled and survived. They still did not know the cause. The patient was referred to physicians who worked out from the family history that the cause was genetic [98].

In 1965 a 13-year-old girl in Toronto was receiving Harrington rods for scoliosis when she arrested due to hyperthermia. She could not be resuscitated. It was before the use of dantrolene was discovered. The metabolic derangement is caused by excess calcium release on exposure to succinylcholine and halogenated inhalation agents leading to excessive muscle contraction, heat, increased oxygen consumption, carbon dioxide production, and acidosis. When the temperature reaches 44–45°C the buffering mechanisms fail and death ensues. Nowadays the early warning sign is a rising end-tidal CO_2 despite increasing ventilation, and effective treatment is with dantrolene infusion. It was a condition that terrified anesthesiologists and introduced regular temperature monitoring.

Jim Villiers had another first survival, described in 1960, in a 6-year-old girl with extensive burns who was given succinylcholine prior to intubation so that she could lie prone to have grafting undertaken on her back. Cardiac arrest occurred with no explanation [99]. The event preceded closed chest cardiac massage and the only defibrillator in Melbourne was several miles away at another hospital. The team opened the chest and massaged until the heart was beating 20 min later. They had no idea why the girl arrested. A week later the patient was intubated again for a dressing change with same response – cardiac arrest. The chest was opened and 25 min massage performed before eventual recovery. What had happened? No one knew, but the patient recovered and lived for at least another 50 years. Gordon Bush, a well-known Liverpool anesthetist, wrote a paper with several suggestions which led to some research in Vancouver [100]. The normal potassium response to succinylcholine had not been studied in humans but turned out to be minimal – a rise in serum potassium not exceeding 0.5 mmol/L, less in adults (TCK Brown, unpublished data). Badly burned patients in the Vietnam War were later shown to have massive increases in potassium [101]. Later, Brown showed that the rise in potassium in large burns was related to the dose of succinylcholine and to the size of the burn [102]. He confirmed the findings of Viby-Mogensen that the rise did not occur until about 10 days post burn [103]. Using small doses of 0.1 or 0.2 mg/kg (so as not to produce large rises in potassium) he showed electromyographically that a period of acute sensitivity to succinylcholine developed about 7–10 days post burn when transient paralysis followed these small doses [104] (Fig. 2.20). Although there was a short time when succinylcholine could be used, most anesthesiologists avoided the problem by not using the drug.

Anaphylaxis is another "out of the blue" experience. It can occur in response to a number of drugs but fortunately is rare. It can be serious, even lethal, but on the other hand can be less serious as with cremophor in the formulation of the induction agent, propanidid (1965). Althesin which, 10 years later, seemed to be the new wonder drug for induction and could be given by infusion because of its short action, was taken off the market because of the tendency to anaphylaxis, although usually mild.

Latex allergy then appeared. Avoidance of latex is essential if the patient or staff are latex allergic. It is desirable to avoid problems in unknown cases. Patients with spina bifida were

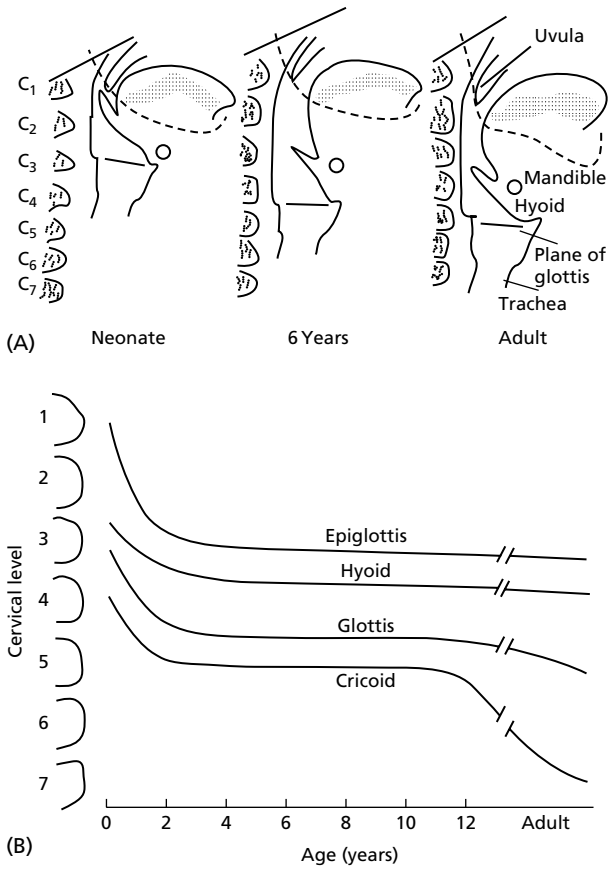


Figure 2.21 The position of the larynx (vocal cords) in relation to the cervical vertebrae during growth.

particularly prone to reactions because of their exposure to latex products like urinary catheters. With advocacy of anesthesiologists, patient groups, and others, latex products were gradually replaced by non-latex substitutes making the environment now virtually latex free.

Some other congenital abnormalities and genetic diseases caused difficulties for anesthesiologists. It is recognized that with early bone marrow transplantation or enzyme replacement some of these conditions will be rectified or disappear.

One example of how a problem was identified and managed will be given. Maintaining the airway and intubating patients with some forms of mucopolysaccharidoses (especially Hurler and Hunter syndromes) could be extremely difficult [105]. A lateral neck radiograph provided the clue. Normally the larynx in a baby lies opposite C3 and gradually descends to C4–5 by 3 years and C6 in adults [106] (Fig. 2.21). In mucopolysaccharidosis patients the upper cervical vertebrae are abnormal and the larynx is higher than expected so when a Guedel airway was used it pushed the epiglottis back over the entry to the larynx making ventilation more difficult. (Fig. 2.22). When intubation was attempted it was harder to align the higher larynx so the opening could be seen to insert the tube. This problem could be overcome by one person positioning the laryngoscope and forcefully pushing back on the larynx with his/her other hand to bring it into view while another guided the tube between the vocal cords. Because of the extreme difficulty this task was undertaken in some

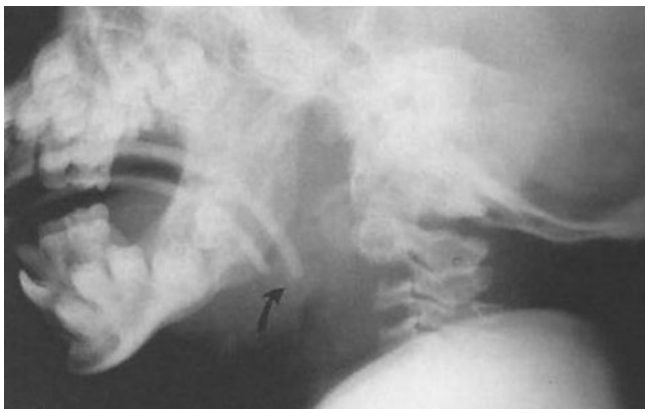


Figure 2.22 Lateral neck radiograph of a 2-year-old with Hurler syndrome showing abnormal upper cervical vertebrae, a high larynx and the epiglottis being depressed by a Guedel airway.

centers by the most experienced members of the department. The airway could be more easily maintained by using a nasopharyngeal tube. If a laryngeal mask airway (LMA) is used it should not be inserted as far as usual to avoid epiglottic obstruction of the glottis. Fiberoptic bronchoscopy and videolaryngoscopy may now simplify the task or, if intubation is not essential, a nasopharyngeal tube or LMA can be used but requires careful positioning.

KEY POINTS: UNRAVELING MYSTERIES AND CHALLENGES

- Malignant hyperthermia was described in 1962 after a 20-year-old man with a family history of anesthetic deaths survived a high fever during anesthesia
- Massive hyperkalemia after succinylcholine in a burn patient was described in 1960
- Anaphylaxis to anesthetic drugs, including propanidid and althesin, was described starting in the 1960s

Newer drugs in the development period (1950s to 1970s)

Halothane

Halothane (1956) played an important role, particularly in pediatric anesthesia where liver complications were exceedingly rare. After usurping cyclopropane it remained the most commonly used inhalational agent in children for many years until it lost out to sevoflurane. It could cause arrhythmias, especially when exposed to catecholamines. Laryngeal spasm sometimes occurred when the concentration was increased past 2% too quickly or during emergence. When sevoflurane was introduced and the vaporizer was turned full on to 8% and spasm did not occur, people tried putting halothane full on at 5% briefly until consciousness was lost – spasm did not occur. This negated the supposed faster induction with sevoflurane because the lower blood gas solubility was counterbalanced by the higher MAC of halothane when turned full on. The slower emergence from halothane was more peaceful in the recovery room than the restlessness with sevoflurane.

The cost of sevoflurane, when it was introduced, was 10 times that of halothane.

It was demonstrated by Gregory et al that halothane requirements (MAC) varied with age. Premature infants were very sensitive, and full-term neonates were more sensitive (required less) than older infants and children, who required more than adults. MAC decreased with advancing age [107]. This was then shown to apply to other inhalation agents such as isoflurane [108].

Methoxyflurane

Methoxyflurane (1960) is a halogenated ether with some of ether's properties but it is non-flammable. It has a slow onset and recovery. It is 25% metabolized to produce fluoride which can cause high-output renal failure in adults if given in excess (more than 2 MAC h) but in children the fluoride blood levels achieved are about half for the same exposure because more is taken up by bones and teeth (free dental prophylaxis) [109]. It can be a useful drug as a supplement in airway anesthesia and in neonatal anesthesia when given with a muscle relaxant and air because it provides good analgesia and using air prevents microatelectasis and diminished functional residual capacity (FRC) [18]. The latter avoids postoperative apnea in premature and small neonates, except in some babies who had apneic spells preoperatively.

Bupivacaine

Bupivacaine is a local anesthetic whose action lasted 4–6 h but could be extended, when used in the epidural space, by adrenalin, morphine, or clonidine. Unlike lidocaine, where convulsions (10 mg/kg) precede cardiac depression and arrest, with bupivacaine cardiac arrest was thought to occur before convulsions, and therefore the toxic dose of bupivacaine is more difficult to estimate. Maximum blood levels did not exceed 2 μg/mL with doses of 3 mg/kg given by the caudal or epidural routes [72]. Estela Melman from Mexico (Fig. 2.13A') reported no toxic effects seen when even 4 mg/kg were used. This drug was associated with a revival in interest in regional anesthesia and nerve blocks particularly in Brazil, Australia, France, and the UK, spreading to other countries as interest in its use in postoperative analgesia increased in the 1980s.

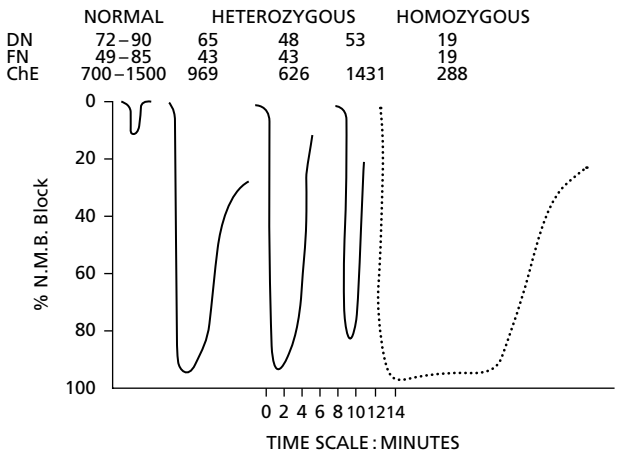


Figure 2.23 Electromyographic responses in patients with abnormal cholinesterase to 0.1 mg/kg succinylcholine with accompanying dibucaine (DN) and fluoride (FN) numbers and cholinesterase (ChE) levels.

Muscle relaxants

d-Tubocurarine, introduced by Griffith and Johnson in 1941 in Montreal [110], was a slow entrant to clinical anesthesia considering its muscle paralyzing effects had been demonstrated by Charles Waterton in 1815 when he brought back some Indian arrow poison (wourali) from South America. Having experienced two fatalities following injection into donkeys, Griffith and Johnson kept the next one alive after ventilating it for 4 h with a bellows inserted through a tracheostomy [111]. The drug was then used by Claude Bernard in physiological experiments and later by Embley in his studies on chloroform [5]. The action of d-tubocurarine lasted about 40–45 min (0.6 mg/kg) and had a gradual offset of action. Neonates were sensitive to it, requiring half the adult dose – 0.3 mg/kg.

It was later observed that infants and children with malignant liver, Wilms (kidney) and bone tumors exhibited resistance to d-tubocurarine. This resistance disappeared if the tumor was successfully treated with chemotherapy, removal or amputation [112].

Succinylcholine was structurally like two acetylcholine molecules attached together, which depolarized the receptors at the neuromuscular junction. The similarity of structure accounts for its vagal-like action on the heart. Normally paralysis lasted 4–5 min except when the patient had a genetic variant cholinesterase that did not metabolize it normally and thus prolonged its action. In heterozygotes this was about 15–20 min but in homozygotes paralysis might last 20–40 min and sometimes even longer [113] (Fig. 2.23). Patients, particularly homozygotes, were encouraged to carry an indicator of this hazard. Alternatively the dose could be reduced to 15–20% in homozygotes to produce the normal duration of action. This is an interesting example of pharmacogenetics.

Ketamine

Ketamine was a different type of drug – a dissociative anesthetic with which the airway and muscle tone were well maintained. It was used in burn anesthesia and for peripheral operations in less affluent countries where it could be administered intramuscularly by people with minimal training. It later became more important in low dose as an analgesic. As a sympathomimetic drug it was an effective bronchodilator.

Ketamine given to rats produced the first evidence of brain-specific neuroapoptosis [67]. Four years later the same group reported the finding that other anesthetics interacting with the γ-aminobutyric acid (GABA) receptor caused similar effects. This raised concerns that learning in babies and young children might be affected. Unfortunately ketamine later became a "street drug."

As other chapters of this book deal with the latest drugs and their use they will not be considered in this chapter.

KEY POINTS: NEWER DRUGS IN THE DEVELOPMENT PERIOD

- Halothane was introduced in 1956 and was the most commonly used agent in children for the next 50 years
- Gregory was the first to demonstrate that halothane MAC varied with age
- Methoxyflurane was a non-flammable anesthetic introduced in 1960
- d-Tubocurarine was the first muscle relaxant, introduced into clinical use in 1941

Adjuncts which were useful in difficult procedures

Hypothermia

Hypothermia was a topic researched during the early development of cardiac anesthesia because of the brain protection it provided. There was a subsequent period of research in the early 1970s when deep hypothermia for infant cardiac surgery developed (see section "Cardiac surgery").

Hypothermia has had other uses besides cardiac surgery. It is a useful adjunct to have when brain protection is desired, usually when large blood losses can occur such as during aneurysm surgery, removal of large hemangioma, liver trauma, and tumor resection such as that of intrapelvic sacrococcygeal teratoma [114]. The popularity of hypothermia has waxed and waned. Some people cite increased bleeding as a problem but it recovers on rewarming and can be counteracted locally by use of warm packs which speeds up coagulation.

Research on electrolytes showed that during surface cooling serum potassium decreases about 2 mmol/L between 37 and 27°C. If arrhythmias occur (usually between 28 and 29°C) administration of small increments of potassium chloride will abolish them – a useful piece of information when cooling. Hypokalemia is associated with a decrease in plasma insulin which results in commonly seen hyperglycemia [115].

Deliberate hypotension

Hypotensive anesthesia is another useful adjunct when bleeding can be a problem. Sodium nitroprusside was first made in 1888 and its cardiovascular effects were described by Johnson in 1927 [116]. It is a vascular smooth muscle relaxant with a very short action and is usually administered by infusion.

Vasodilators can be used to reduce bleeding when it was expected, or when it occurs unexpectedly and cannot be controlled, in cardiac surgery to reduce afterdrop in temperature postoperatively by adequate filling of the capacitance vessels before coming off cardiac bypass, and to reduce afterload postoperatively.

Phenoxybenzamine was an α-sympathetic blocker with a very long (up to 24 h) action which had the advantage in neurosurgery of not dilating cerebral vessels. It was also used successfully to treat neurogenic pulmonary edema which results from acute vasoconstriction and heart failure [117]. Otherwise a nitroprusside infusion was a good alternative. Unfortunately, like many other useful drugs used in anesthesia, phenoxybenzamine was removed from the market by its maker.

Janice Peeler, in Melbourne, used sodium nitroprusside induced hypotension for scoliosis surgery, initially for insertion of Harrington rods, for over 30 years from 1972. Blood loss, commonly 3–4 units, was reduced to about 1, but importantly operating time decreased when it was introduced from about 3 to 1–1¼ h because the surgeons had a clearer view of the operating field.

Another acute situation was where endless bleeding was stopped in a neurosurgical tumor resection. The rate of bleeding prevented the surgeon finding the bleeding point. This was compressed with a swab until blood loss had been replaced and extra fluid was given. A small dose of sodium nitroprusside was given, the blood pressure decreased, and the surgeon could see and cauterize the bleeder when the pack was removed. The blood pressure normalized in 2–3 min. Massive transfusion was avoided, the patient recovered, and the stress on the surgeon and anesthesiologist was removed.

Sodium nitroprusside has also been useful in reducing blood loss in ruptured liver and in liver tumor resections in children where significant blood loss can occur [118]. It is also useful in controlling rising blood pressure in pheochromocytoma surgery and to stop dysrhythmias by lowering blood pressure.

Other vasodilators have been used such as nitroglycerine, trimethaphan, and phentolamine [119].

Vasodilators are safer in children with unobstructed vessels than in older people with atherosclerotic vascular disease who are more prone to develop ischemia.

Pain management

Pain management became more rational in the 1980s, partly due to the work of Anand and colleagues who demonstrated that babies feel pain [120], though Robson of Toronto recognized this years before [57]. Applying basic pharmacological principles that an intravenous infusion will give a more constant blood level of analgesic than painful intramuscular injections, which were often given after pain had begun to return, was another factor. It is hard to believe that in earlier years it was thought that babies did not feel or respond to pain and, if they did, they would not remember it anyway.

Much interest was generated in the use of regional anesthesia and nerve blocks. Caudals and epidurals gained popularity, sometimes with infusions to prolong the block. Nerve blocks could be done quickly and effectively [38] but the techniques have largely been replaced with ultrasound-guided methods.

Pain management and regional anesthesia are covered elsewhere in this text (see Chapters 20 and 37) and in books on the subject [121].

Improved pain management required extra training of staff and more staff to supervise its administration. The extra costs of staff and equipment inhibited the development of pain teams initially in many places where funds were short but they are now well accepted, especially in more affluent countries. Dilip Pawar, when he was chair of the WFSA Pain Committee, developed simplified protocols for teaching improved pain management systems in some less developed countries in Asia.

Children also suffer chronic pain associated with cancer and conditions such as complex regional pain syndrome (CRPS) II [122]. This tends to be managed by separate pain specialists but anesthesiologists played an important part in its development and doing blocks which helped, such as sympathetic nerve blocks in CRPS [123].

Outpatient anesthesia and non-operating room anesthesia

Out of the operating room anesthesia and shorter stay were among the big changes in anesthetic practice in the later years of the twentieth century.

In the earlier years the radiology department might have been the only venue where anesthesiologists worked outside the operating suite. Neuroradiology before computed tomography (CT) and magnetic resonance imaging (MRI) consisted of cerebral angiograms and pneumoencephalography [124]. In the latter, air was injected through a lumbar puncture, with the child sitting up, and allowed to rise in the subdural space. The air was then moved around the ventricles, with films being taken in each position, by laying the child supine, somersaulting, prone, and finally supine again. With all these changes in position attachments to multiple monitors was undesirable. The patient was anesthetized, intubated, and allowed to breathe spontaneously. Clinical assessment of the pulse could provide much valuable information and ventilation could be observed. Although there are problems associated with anesthesia for scans, especially MRI, with avoidance of magnetic objects and usually observing the patient from outside the scanner room and using non-magnetic monitors, they are not quite as extreme as pneumoencephalography.

Anesthesia in radiology departments and the development of day surgery units were the first moves out of the operating suite. Increasingly anesthesiologists have provided anesthesia or sedation for other procedures such as lumbar puncture, bone marrow aspiration, and many others to avoid patient discomfort and stress. They have also established safe guidelines for non-anesthetists to provide sedation for some procedures. A significant part of a department's workload can now be fulfilling these needs.

One can even be moved from the operating suite to neonatal units to operate on premature babies to avoid disruption of their stable environment caused by transfer.

Pediatric anesthesia societies and meetings

Communication in pediatric anesthesia was enhanced by courses and meetings that allowed interchange of ideas [70]. One example was 2-day meetings begun in Los Angeles by Digby Leigh. These were run for many years by Wayne Herbert. Alan Conn began similar annual weekend courses at HSC in Toronto which alternated between anesthesia and intensive care. He had an impressive group of speakers for the first one in 1964 including Digby Leigh, Jackson Rees, and Bob Cope from England, Robert Smith from Boston, Tony Davenport from Montreal, and Tom McCaughey from Winnipeg.

In 1970, following the Asian Australasian Congress in Canberra, a Centenary Meeting was held at the Royal Children's Hospital (RCH) in Melbourne. After Kester Brown became Director there in 1974 he instituted meetings every 3–4 years from 1975 until 2000 which brought most of the Australian pediatric anesthetists together, forming a very cohesive little group which gradually grew. Visiting overseas lecturers came from many countries. In 1988, two eminent pediatric anesthetists stopped at each of Kuala Lumpur, Singapore, Bangkok, Manila, Hong Kong, and one to Colombo, Brisbane, and Perth on the way to the Australian Society and Melbourne Paediatric Anaesthetic conferences. This was a big exposure for pediatric anesthesia in the region. In 1995 the Royal Children's Hospital celebrated its 125th anniversary. That year an anesthesiologist from each continent was invited as a guest speaker, recognizing the spread of expertise around the world. Estela Melman spoke on fetal surgery in Mexico and how repair of cleft lip left no scar. A case of separation of conjoined twins was presented from Chile. In the ensuing discussion it was found that members of the audience had been involved in 27 cases including ten in Japan and five in Capetown. We should never underestimate the experience of colleagues in other countries.

World and other large congresses usually have pediatric anesthesia sessions. Special world Pediatric Meetings were held during World Congresses in Manila in 1984 (organized by David Steward and Seizo Iwai) and in Washington, and following the World Congresses in Amsterdam, Melbourne, and Halifax, Nova Scotia.

The Association of Paediatric Anaesthetists in Britain began regular annual meetings in 1974. Later they also held joint meetings with some national societies, the first being in Helsinki in 1981.

The American Academy of Pediatrics established an anesthetic section in the 1960s. Alan Conn and Leonard Bachmann were initial organizers. Its membership was confined to full-time specialist pediatric anesthesiologists. In the United States, the Society for Pediatric Anesthesia started later, in 1987, and was open to all anesthesiologists interested in children's anesthesia.

As the specialty has grown there has been a proliferation of regional and national societies. The Asian Society was set up

Figure 2.24 Touring together – Great Ocean Road, Victoria, Australia. Making international friendships. From left: Brian Anderson (New Zealand), Susan Jones (UK), Adrian Bosenberg (South Africa), Peter Booker (UK), Seizo "Jake" Iwai (Japan).

by Agnes Ng in Singapore. Other major contributors in the region have been Rebecca Jacobs (Vellore, India), Dilip Pawar (Delhi), Angelina Gapay (Philippines), and Masao Yamashita in Japan (Fig. 2.13).

Pediatric anesthesiologists' tours following or between conferences have given groups of pediatric anesthetists the opportunity to meet, spend time, and make lasting friendships while they travel together. These have occurred in Finland, Australia (Fig. 2.24), Canada, and South Africa.

Visiting other departments (Fig. 2.25) and meeting colleagues in these ways has built up a vibrant and friendly subspecialty – pediatric anesthesia.

Pediatric Anesthesia journal

The beginning of *Pediatric Anesthesia* as a specialty international journal in 1980 brought papers together which previously had been scattered through other journals. It encouraged more

Figure 2.25 The author, Kester Brown, visiting Bangkok Children's Hospital, 1988, with department head, Anchall Attachoo.

Figure 2.26 The first meeting of the Editorial Board and Committee of *Pediatric Anesthesia* in Rotterdam, 1989. From left, sitting: Gerry Black (Belfast), Edward Sumner (London), Gordon Bush (Liverpool – Editor), Claude St Maurice (Paris). Standing front: Isabel Murat, –, Mario Govaerts (Belgium), –, Etsuro Motoyama (USA), Jerrold Lerman (Canada), Kester Brown (Australia), Peter Morris (UK). Standing, back row: Krister Nillson (Sweden), –, Raafat Hanallah (USA), –, Olli Meretoja (Finland), –, Paolo Busoni (Italy), Karl Rondio (Poland), Nishan Goudsouzian (USA).

Figure 2.27 Archie Brain – inventor of the laryngeal mask airway.

specialists to contribute. Gordon Bush from Liverpool was the first editor followed by Ted Sumner (London), Neil Morton (Glasgow), and Andrew Davidson (Melbourne), all of whom helped it to become a high-quality, well-recognized journal worldwide. The first Editorial Board and Committee met in Rotterdam in 1989 (Fig. 2.26).

Training in pediatric anesthesiology

The development of organized pediatric anesthesiology was accompanied by the initiation of pediatric anesthesiology fellowship programs in the 1970s and 1980s based primarily in the prominent children's hospitals in North America, the UK, and Australia including Boston Children's Hospital, the Children's Hospital of Philadelphia, the Hospital for Sick Children in Toronto, Great Ormond Street Hospital, the University of California, San Francisco, and the Royal Children's Hospital in Melbourne. The early fellowships were served after residency or registrar training, were 6–12 months in duration, and were devoted primarily to exposure to and mastery of specialized pediatric anesthesia cases, especially neonatal anesthesia. In the United States training evolved to become a 12-month fellowship certified by the Accreditation Council on Graduate Medical Education in 1997. In 2013 the American Board of Anesthesiology offered its first Pediatric Anesthesiology certifying examination. See Chapter 3 for more information about education and training.

Conclusion

We will conclude with some highlights. Probably the most important development to enhance safety was the pulse oximeter, introduced in the mid-1980s. Capnography, introduced several years later, also provides much useful information. The laryngeal mask airway (LMA) introduced by Archie Brain in the late 1980s (Fig. 2.27) had a major influence on anesthetic practice. The most important factor in raising the standards of anesthesia and reducing morbidity and mortality is the improvement in the training of anesthesiologists. Ralph Waters, of Madison, Wisconsin, was the first professor of anesthesia in the United States and trained many of the early influential leaders in the specialty including Digby Leigh who initiated training programs and whose influence spread far beyond his native Canada.

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 3

Education in Pediatric Anesthesiology: Practice in the Present with the Future in Mind

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> If you want to learn something, read about it. If you want to understand something, write about it. If you want to master something, teach it.
>
> *Yogi Bhajan* [1]

Introduction

Reflect for a moment on a powerful, positive learning experience you have had. Perhaps you were the learner, or perhaps you were in a teaching role. What were the elements that created such a learning moment? What factors were attributable to individual performance such as the attitudes, beliefs, or communication style of the teacher, the learner, or other people involved? How much of the impact of that experience is attributable to the situation or to factors invisible to you in the moment? When you reflect on positive learning experiences, what features stand out? What are the common threads?

Powerful, positive education in pediatric anesthesiology does not occur by chance alone, but is a deliberate, examined practice. It is necessary not only for the provision of the safe perioperative care of children, but for fostering a discipline imbued with a culture of inquiry, respect, and the pursuit of excellence.

This chapter explores tenets of education in pediatric anesthesiology: identification of the need (the "Why"); grounding the practice in theory (the "How"); and elements of successful execution (the "What").

Why pediatric anesthesiology education? The needs assessment

Educating anesthesiologists about pediatric patients is essential if children are to receive the most effective and efficient anesthesia care. This important concept was a major impetus for the development of accredited subspecialty educational programs in pediatric anesthesiology [2]. What justifies the existence of a special subspecialty of anesthesia patient care devoted to children and the need for education specially focused on this clinical care area?

The need for expertise in pediatric anesthesiology

Pediatric population data alone are a compelling justification (Box 3.1). The Federal Census Bureau has recorded that as of 2015, the US population under 18 years of age included 73,683,825 children. This number represents 23% of the 2015 US population [3]. While recent trends indicate a small decrease in the total number of births and the birth rate, in 2015 there were 3,978,497 births in the US [4]. An appreciable portion of these newborns present with clinically significant morbidity necessitating surgical and non-surgical diagnostic and therapeutic procedures which can only be safely accomplished under the care of a skilled pediatric anesthesiologist. Approximately 1 in 33 babies born in the USA has a birth defect. A baby with a congenital anomaly is born every 4½ minutes in the USA, which means that 120,000 babies are affected by birth defects each year [5]. While some defects may be minor abnormalities, others may significantly affect the infant's physiology.

Approximately 40,000 babies are born every year with congenital heart disease, the most common birth defect requiring intervention in the first year of life [6]. Twenty-five percent of these babies have high acuity cardiac defects needing anesthesia care for surgery or diagnostic procedures. Some of the other significant pathophysiological birth defects include more than 7000 babies born each year with cleft lip and/or palate defects [7] and approximately 6000 babies born each year with Down syndrome [8]. Birth anomalies are the

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

Box 3.1: Births in the United States: data for 2015 [3,4]

- Number of births: 3,978,497
- Birth rate: 12.5 per 1000 population
- Fertility rate: 62.9 births per 1000 women aged 15–44 years
- Percent born low birthweight (less than 2500 g): 8.0%
- Percent preterm births (infants delivered at less than 37 weeks of gestation): 9.57%
- Percent unmarried: 43.9%

Box 3.2: The 10 leading causes of infant death (under 1 year of age) (2014) (23,215 deaths from all causes) [9,10]

1. Congenital malformations, deformations and chromosomal abnormalities (congenital malformations)
2. Disorders related to short gestation and low birthweight, not elsewhere classified (low birthweight)
3. Newborn affected by maternal complications of pregnancy (maternal complications)
4. Sudden infant death syndrome (SIDS)
5. Accidents (unintentional injuries)
6. Newborn affected by complications of placenta, cord, and membranes (cord and placental complications)
7. Bacterial sepsis of newborn
8. Respiratory distress of newborn
9. Diseases of the circulatory system
10. Neonatal hemorrhage

leading cause of all infant deaths and predispose newborns to a greater chance of acute illness and long-term disability than babies without birth defects (Box 3.2) [9,10].

On a yearly basis, approximately 9.2 million children (0–19 years of age) are treated in emergency departments for unintentional injury. More than 12,000/year (approximately 1 every hour) die as a result of their injury [11]. A clinically significant number of these children will need diagnosis and therapy requiring pediatric anesthesia patient care.

Availability of expert pediatric anesthesiology care

The number of children needing anesthesia patient care is large yet the distribution of pediatric patients in hospitals is quite uneven. There are more than 5500 hospitals in the US [12]. There are only approximately 250 children's hospitals in the US, with fewer than 50 as freestanding [13]. Current data about the pediatric surgical volume and acuity are lacking. In 2009, more than 216,000 pediatric procedures were projected with as many as 40% of inpatient surgical procedures being performed in adult hospitals [14]. The full range of resources specifically geared to pediatric patients, i.e. pharmaceuticals, equipment, and knowledgeable, skilled, and psychologically savvy physicians and paraprofessionals, is intuitively more plentiful in hospitals that care exclusively for children and their families.

In a 2005 report in the Newsletter of the American Society of Anesthesiologists (ASA), Hackel and Gregory highlighted that pediatric patients and their anesthesia patient care needs are clearly different from those of the adult population [15]. Recognition and acceptance of this resulted in the development of special practice guidelines for pediatric anesthesia patient care, published in 1999–2004 by the ASA, American Academy of Pediatrics (AAP), and the Society for Pediatric Anesthesia (SPA) [16–18]. Yet many community hospitals, with less than the full complement of pediatric anesthesiology resources, are faced with a need to care for children. The American College of Surgeons in 2017 instituted a Children's Surgery Verification Quality Improvement Program, similar to their existing Trauma Verification Program, whereby institutions performing children's surgery are designated Level I, II, or III [19]. Level I cares for the most complex pediatric patients, and Level II less complex pediatric patients; both of these levels require that Board Certified Pediatric Anesthesiologists be on staff and available to care for patients aged 2 years or less. Level III centers care for ASA I–II patients >6 months old with simple pediatric procedures, and require an anesthesiologist with pediatric experience be available for patients 2 years and under.

In all pediatric patient care settings, pediatricians, pediatric surgeons, and pediatric subspecialists want anesthesiologists who are knowledgeable and skillful in pediatric anesthesia patient care. As the public has become more informed about pediatric healthcare, with understandable health information easily accessed on publicly available Internet websites, parents have also requested, and in some instances demanded, anesthesia patient care for their children provided by anesthesiologists knowledgeable and skillful in pediatric practice. "Data from other areas of medicine support this demand and show that fewer complications arise the more often practitioners perform a procedure" [20].

Building the case for education in pediatric anesthesiology

The intuitive assumption is that provision of expert pediatric anesthesia patient care requires sufficient manpower (anesthesiologists with pediatric anesthesiology expertise) and sufficient sophistication (fully educated and certified as pediatric anesthesiologists) to care for all of the children (all acuity, patient care scenarios).

In 1999, the American Academy of Pediatrics Section on Anesthesiology published Guidelines for the Pediatric Perioperative Anesthesia Environment, providing a foundation for pediatric anesthesia patient care [17]. This was preceded in 1997 by a publication that made the case for the establishment of a standardized curriculum for pediatric anesthesiology [2]. The Accreditation Council for Graduate Medical Education (ACGME) through its Anesthesiology Residency Review Committee established requirements for standardized education in pediatric anesthesiology that have guided pediatric anesthesiology education for more than a decade. In 2012, the American Board of Anesthesiology (ABA) approved a certification process to recognize clinicians with special expertise in this subspecialty [21]. In the first 3 years (2013–2015) of the ABA pediatric anesthesiology examination, 2734 candidates were certified.

In 2012, the Pediatric Anesthesia Leadership Council, in conjunction with the Pediatric Anesthesia Program Directors' Association in the US, organized a Second Year Advanced Fellowship Network. Recognizing the increasing need for extended subspecialty training in pediatric

anesthesia subspecialties and for further training in leadership and academic disciplines, the network included 12-month voluntary non-ACGME program requirements and curricula in Cardiac, Pain, Education, Research, and Quality and Outcomes fellowship training [22]. In 2015, 24 of 53 (45%) of the US ACGME Pediatric Anesthesia Fellowship programs offered one or more advanced fellowships in this network. Approximately 15–20% of ACGME fellows pursued additional training in these programs from 2012 to 2017 [23]. As of this writing, these same groups were leading an effort to explore lengthening the duration of the ACGME Pediatric Anesthesia Fellowship to 2 years, and enabling the programs to offer extended formalized training in these and other areas. The rationale for this effort is to better prepare leaders in pediatric anesthesiology who will also take on significant roles in hospital, health system, and academic leadership, in an increasingly complex and challenging healthcare environment.

The "How" of pediatric anesthesiology education: theory and strategy

With the need for subspecialty education of pediatric anesthesiologists clearly identified, the question arises: How do we educate anesthesiologists to capably care with confidence and skill for the sickest children? And how do we prepare these well-trained practitioners to pass on their expertise as skilled physician educators of the rising crop of pediatric anesthesiologists? Answers to these questions come from identifying key elements of the "how" of educating expert pediatric anesthesiologists, and what grounded theories and systems exist to support excellence in the education of these specialty physicians.

The medical educator: preparing the doctor to teach

It is taught early in medical school that the root of the word from which "doctor" arises is the Latin *docere*, "to teach." However, most medical schools lack formalized curricula to educate rising physicians on theories of education and provide little opportunity for teaching, let alone coaching toward teaching excellence. Education in pediatric anesthesia for medical students, residents, and fellows occurs primarily in academic settings, wherein the physician must embrace (regardless of comfort level) the role of teacher. Many academic physicians report that they feel ill-equipped for this role, having never received formal training in education. With increasing recognition of the importance of interdisciplinary teams, even in non-academic environments, the pediatric anesthesiologist must be facile at assessing receptivity of surrounding practitioners of varying levels of sophistication, and at conveying complex and nuanced information in readily-understood ways. In addition, a skilled physician teacher must be able to provide information that may challenge the beliefs of the learner, whether it be a nurse, colleague, or patient, in a manner that preserves the integrity of the intended audience. These tasks can be challenging even for experienced educators. For those with no formal grounding in education theory or practice they may seem potentially daunting.

Learners of pediatric anesthesiology are sophisticated and resourceful. A rapidly increasing scope of medical information needed for mastery of the subject is available in easily-searchable electronic formats [24,25]. With such sophisticated learners, it is no longer enough to presume that the authority of being a physician confers expertise in the educational domain.

Many institutions have responded to the lack of formal training for physicians in education by developing teaching academies or teaching scholar programs, which expose physicians to a variety of educational theories and practice, allow for education project development, and provide mentoring and support for physician educators as they develop teaching aptitude [26,27]. There are also an increasing number of masters programs in medical education, which provide in-depth exposure and build expertise in education theory and program development for practicing physicians.

In addition to these structured programs, it is also important for educators in pediatric anesthesiology to remember the value of modeling professionalism in their demeanor with patients, colleagues, and trainees alike [28]. Learners are savvy observers of their surroundings, and their behaviors will be shaped by the actions of those around them. Modeling effective teamwork, communication, expertise, leadership, and patient ownership, among several other professionalism domains, is likely to have a lasting effect on learners, even outside of a formalized curriculum [29].

Learning theory

Learning can be conceptualized as a change in thinking or behavior based on evaluated experience. Several theories attempt to shed light on how learning occurs. From the stimulus-response of operant conditioning [30], to the theory of multiple intelligences [31] (still being refined), there are virtually hundreds of ways to understand how we learn. Postgraduate medical education in pediatric anesthesiology engages a highly specialized subset of learners and embeds them in a unique learning environment with specific outcome needs. As a result, certain learning theories may prove more germane than others to this context.

Experiential education

To some, residency and fellowship represent an apprenticeship, wherein learners partner with both institutions and experts to build the knowledge base and hone the skills to prepare them for independent practice. This is experiential education in one of its purest forms. The philosophy of experiential education is well described in a 1938 treatise by John Dewey, wherein he describes the fundamental need for learning by *doing*. Dewey [32] is among the constructivist learning theorists, and like contemporaries Leo Vygotsky and Jean Piaget, believed that learning is an active and contextualized process of building rather than acquiring knowledge [33]. Understanding and learning are built on the existing scaffold of the learners' psyches, informed by previous experiences and viewed through subjective lenses. Dewey describes the "educative experience" as powerful, embracing all the senses to build multifaceted knowledge, with far greater likelihood to engrain memory and impart

meaning than cognitive preparation alone. In evaluated experiential education, simply *doing* is not enough, however – the *doing* of residency and fellowship specialty training in pediatric anesthesiology is an examined one, with preparation and active reflection as necessary complements to the development of psychomotor skills.

The adult experiential learner

The learner of pediatric anesthesiology is an incredibly sophisticated one, having been successful in traditional educational models relying on both cognitive and psychomotor skills throughout undergraduate education and medical school, while having accumulated a life of experiences. By the time they reach residency these learners are skilled, curious, and questioning, but most of all they already carry with them a minimum of two decades of life experience that will inform how they engage in learning [34]. Adult learners play many roles in their lives that will influence their learning style. They themselves may already be, among other roles, parents, teachers, scientists, writers, or businesspeople. They may come from varied social backgrounds which may contextualize the same event very differently for them depending on the individual. Adult learners are highly motivated, self-directed, results-oriented, and tend to be more intrinsically motivated than their younger counterparts [35]. They should be involved with the planning and evaluation of their instruction, and will often actively engage in processes to improve their own education built around their own insights.

Learning and performance orientation

The learner's approach to novel experiences also influences how events are interpreted and integrated to form new understanding. This has been described as "learning" versus "performance" orientation [36]. In learning orientation, when the student encounters a challenging novel task (such as intubating a neonate or generating a perioperative plan for a medically complicated child), she embraces it as an opportunity to build mastery, even if early attempts are unsuccessful. This relies on the belief that the student holds within herself the necessary skills or motivation to eventually achieve mastery. In performance orientation, when the student encounters a challenging task at which she was not successful, the inclination is to blame extrinsic factors. While this also represents a degree of confidence (perhaps beyond a skill level that is justified), it dangerously presumes that the student bears minimal responsibility for the events (i.e. lack of preparedness is blamed on equipment failure; negative patient outcome is blamed on non-compliance or poor baseline status). From a lifelong learning perspective, the safe and expert practicing pediatric anesthesiologist should favor learning over performance orientation, with a robust sense of accountability and intellectual curiosity. As educators in pediatric anesthesiology, it is important for us to encourage learning over performance orientation, to build confidence and skill while identifying factors attributable to the student.

Strategies for educating in pediatric anesthesiology

Grounding educational practice in theory is important, and several strategies exist to guide teachers of pediatric anesthesiology on how to approach the task. While there are a practically limitless number of methodologies that may help shape how we educate pediatric anesthesiologists, there are a few highly practical ones.

The intraoperative learning environment

The intraoperative arena is a unique learning environment, wherein even the most skilled pediatric anesthesiologist must work to balance the potentially competing priorities of patient care and protection, education of the anesthesia learner, and the flow of the operating room. While many of the psychomotor and affective skills of crisis resource management for high-stakes rare events are best learned in high-fidelity simulation, often the development of skills in frequently-occurring events (such as routine airway management, intravenous catheterization, or speaking with families) is mastered in the course of clinical care. Varying levels of proficiency and comfort of front-line clinician learners may dictate their need, interest, and readiness to learn. Providing graded autonomy while maintaining appropriate supervision is key to supporting the growth of the rising pediatric anesthesiologist. Powerful anesthesiology education involves the support of practice with evidence or literature, maintenance of personal clinical expertise, providing rationales for clinical decision making, and embedding teaching in a relevant context [37]. Anesthesiology learners may also be struggling to develop their own sense of competency, and messages of support of their development, as well as simply making teaching a priority, are well received.

Deliberate practice

Deliberate practice is described as the repeated rehearsal of specific tasks to achieve mastery, under the guidance of a mentor with directed feedback [38,39]. It is suggested that those who engage in deliberate practice, strategically striving to be better on a regular basis, will continue to build skill and develop expertise. Those who engage in their profession in a rote manner will quickly reach a plateau in performance well below that of a top performer. Many of the "tasks" of pediatric anesthesiology are challenging even to those who have achieved consultancy status, and mastery of these skills is paramount in the discipline. We owe it to our patients to be at our very best, dedicated to continuing to improve, in every stage of training and well into our practice as attendings. Active coaching of pediatric anesthesiologist learners also forces the teacher ("coach") into an active role of examined practice, which can serve as a form of learning for teachers themselves.

Facilitated reflection and feedback

Facilitating performance feedback is not only critical to practice improvement, it is longed for by learners. While there are multiple barriers to providing feedback (investment of time, comfort with difficult conversations, fear of retaliation in teaching evaluations even if feedback is constructively critical), engaging in reflective conversations with learners about their performance, while sensitive in nature, is crucial to their learning. Feedback may be *formative*, designed to be integrated in the moment for learner growth, or *summative*, evaluation after completion of observed performance. Feedback takes many forms, but increasing evidence supports creation of an entire culture of feedback. This includes not only making it part of the daily routine for all providers and the creation of a safe environment for feedback, but also a transition in attitudes about

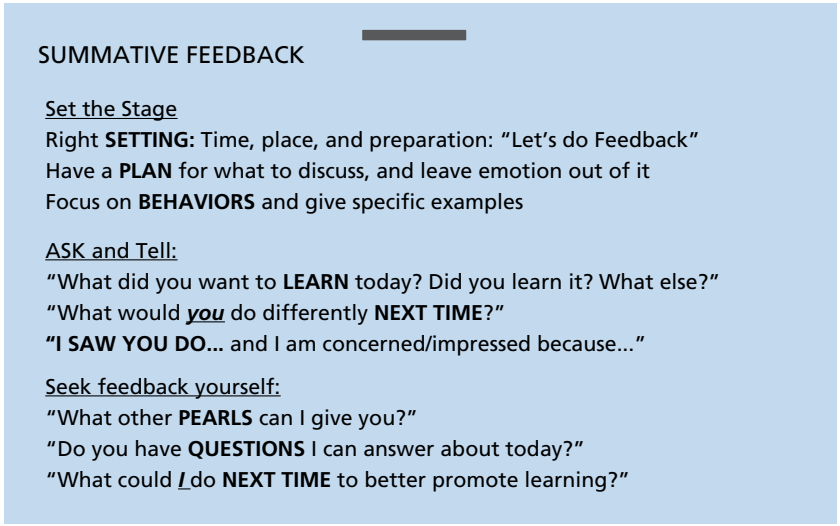

Figure 3.1 An example of a feedback-related cognitive aid. This image is laminated and provided to all staff anesthesiologists as well as anesthesiology fellows for use in real time during end-of-day discussions.

feedback: evidence supports the use of facilitated reflection as more effective than corrective comments [40,41]. In other words, during the modern feedback session the learner should be talking more than the teacher.

There are several tools and strategies useful for providing feedback. The "R2C2" model describes a four-phase approach: building **R**elationship, exploring **R**eactions, exploring **C**ontent, and **C**oaching for performance change [42]. Alternatively, the Pendleton Model uses a different four-step technique, designed to solicit learners' insights on their own performance [43]. In step one, the learner states the positives of his or her performance; in the second step, the educator identifies positives of the learner's performance. In step three, the learner identifies areas in need of improvement, and in the final fourth step the educator notes areas for the learner's development. Another approach, the "reflective feedback" conversation, invites learners to reflect on their own practice and identify areas in need of development. This strategy relies heavily on learner ownership and investment in improvement. Figure 3.1 shows one example of a cognitive aid used for providing feedback in a reflective model. Multiple other methods also exist, but regardless of the approach to feedback, several themes remain (Box 3.3).

Box 3.3: Suggestions on giving feedback

- Feedback should be routine and viewed as part of the daily work
- Learners should be clear on the standard by which they are judged
- Feedback should be directed at specific behaviors, not generalities
- Only a few, directly observed behaviors should be commented on
- Feedback should be given soon after observations, but in a setting where learner integrity is preserved
- Seek the learner's perceptions as feedback evolves
- Provide strategies for implementation of practice change

Adapted from Cantillon and Sargeant [43].

Curriculum development

Development of educational programs, while sometimes serendipitous or borne of necessity, should be a deliberate practice in itself. In the same way that physician educators are often not exposed systematically to teaching strategies or educational theory, often those responsible for developing education programs or curricula may feel ill-equipped to do so. Different structures may provide guidance for these efforts, in which there are several consistent themes about how to approach curriculum development. An effective curriculum must be collaborative and contextualized. It will be more relevant and successful if stakeholders (learners, educators, administrators) contribute to its construction.

Guidelines for developing medical curricula can be complex, but several approachable texts make the task less daunting [44]. Major phases of curriculum development should include the following:

1. *Planning*: Perform a "needs assessment" – identify the problem, contextualize it to the target learner.
2. *Development:* Outline goals (ideals) and objectives (measurable targets), and identify educational strategies (content, methods, materials).
3. *Implementation:* Execute the proposed curriculum.
4. *Evaluation:* An ongoing process, to refine the program for greater efficacy.

With strategies that include learners in each stage, curricula will be more adaptive and relevant. Having concrete, measurable learner outcomes after engagement with the curriculum will also increase effectiveness.

The "What:" pediatric anesthesiology education in practice

Having discussed the rationale and some methods of pediatric anesthesiology education, germane questions remain, such as:

- What are the necessary essentials for implementation of pediatric anesthesiology educational programs, including accredited core anesthesiology residency and the advanced subspecialty fellowship in pediatric anesthesiology?
- What is the role of pediatric anesthesiology in the education of non-anesthesiology patient care providers?
- What are effective methods of evaluation for learners, teachers, and programs?
- What is the role of faculty education in the development of any high-quality educational program?

These questions, among others, will here be partly addressed by outlining existing strategies and programs; understanding the responses to these complex questions may allow the reader advance the goal of excellence in specific educational programs.

Core residency education in anesthesiology in the United States

The relatively recent development of Pediatric Anesthesiology as a certified subspecialty of the ABA has altered expectations for core resident education in pediatric anesthesiology. In the few years since certification became available, the number of pediatric anesthesiology fellows in the nation has doubled to over 200 per year. As a consequence, many practices, even those with primarily adult patient populations, employ at least one fellowship-trained pediatric anesthesiologist for care of pediatric patients.

The downstream impact of this has been some national disagreement about what a core anesthesiology resident "should" learn about pediatric anesthesiology, and whether or not the current fellowship training model meets the goals for creating the workforce for the future [2,21]. It can be anticipated that in the next decade there will be more clarity on these issues. In the meantime, the ACGME and the ABA have helped guide the minimum pediatric educational experience by setting standards that all residency educators should be aware of. These two organizations have traditionally taken different approaches to their guidelines. The ACGME defines the experience using an apprenticeship model defined by duration (a minimum of 2 months of pediatric anesthesiology rotations during the Clinical Anesthesiology CA-1 to CA-3 years and a maximum of 6 months during the same interval) and case mix (minimum number of patient experiences by differing age groupings). In some institutions, this exposure may be augmented with either pediatric residency rotations or a complete pediatric internship year (postgraduate year 1) prior to the start of the CA-1 year. Alternatively, the ABA defines the expected education in terms of topics that should be mastered in order to achieve Primary Certification in Anesthesiology (Box 3.4). Educators should be aware of both of these guidelines, and have an obligation to ensure that core anesthesiology residents are adequately prepared for primary anesthesiology board certification and the practice of anesthesiology as it pertains to the subspecialty of pediatric anesthesiology.

Box 3.4: Pediatric topics for primary certification in anesthesiology (adapted from the American Board of Anesthesiology)

- Apparatus
- Premedication
- Agents and techniques
- Fluid therapy, blood replacement, and glucose requirements
- Problems in intubation and extubation
- Neonatal physiology
- Congenital heart and major vascular disease
- Emergencies in the newborn
- Pediatric medical problems with anesthetic implications
- Anesthetic implications for common non-neonatal pediatric subspecialty surgery

Fellowship education in anesthesiology

If the purpose of resident education in pediatric anesthesiology is to prepare the learner for a broad career in anesthesiology that may include the care of children, the next logical question is, "For whom is fellowship training in pediatric anesthesiology warranted?" What is the purpose and value of extended education in pediatric anesthesiology? This may not be self-evident, bearing in mind the considerable opportunity cost that learners cope with by delaying full, unrestricted licensure and employment by at least 12 months. In addition, there is a potential financial risk of an ultimately lower salary should the learner choose a career at an academic or free-standing children's center compared to the private sector jobs for which they are eligible upon successful completion of core anesthesiology residency training.

First, there is no question that both the breadth and depth of cases mastered at graduation are greater for fellowship-trained pediatric anesthesiologists. In many institutions pediatric cases are divided into "resident cases" and "fellow cases," either implicitly or sometimes explicitly. A 1-kg, 1-day-old neonate, for example, with a congenital heart defect and trachea-esophageal fistula who is scheduled for thoracotomy for tracheal repair is unlikely to be cared for by a core resident in anesthesiology in most circumstances. Furthermore, many residents would consider this case to be out of the scope of any practice they would anticipate joining, and thus are not surprised to see this patient cared for by expert pediatric anesthesiologists (including fellows).

Clinical exposure

While this guiding principle of "relevance to practice" is helpful, the ACGME has also outlined program requirements for pediatric anesthesiology fellowships, including a list of "index cases" required of each fellow for graduation (Table 3.1) [45]. Any center considering expanding or creating fellowship positions in pediatric anesthesiology must have adequate case volumes in each of these categories in order to ensure the appropriate clinical experience among graduates. This must be accomplished without negatively impacting core anesthesiology resident education and clinical experiences. Similarly, the ABA has created a subspecialty certification examination in pediatric anesthesiology with a detailed content outline (see abbreviated version in Box 3.5). Completion of an ACGME-accredited 12-month pediatric anesthesiology fellowship program is now prerequisite to sitting for this examination.

Developing the academic pediatric anesthesiologist

Anesthesiology is one of the few medical fields in which being an outstanding resident does not necessarily translate into expert function as an attending anesthesiologist. This can be attributed to the differences in roles between front-line providers in the operating room and faculty members who engage in such activities as managing multiple anesthetizing locations, teaching educational conferences, and serving on hospital committees. For this reason, perhaps more importantly than the *clinical* experience of subspecialty training, one of the major goals of fellowship is the development of academic skills prerequisite for a successful career as an expert pediatric anesthesiologist. This includes scholarly expertise

Table 3.1 Pediatric anesthesiology fellowship case minimums

Category	Minimum number
Total number of patients	240
Age of patient	
Neonates	15
1–11 month olds	40
1–2 year olds	40
3–11 year olds	75
12–17 year olds	30
ASA physical statement	
ASA 1	25
ASA 2	42
ASA 3	50
ASA 4	20
Procedures	
Arterial cannulation	30
Central venous cannulation	12
Epidural/caudal	10
Flexible fiberoptic technique	4
General anesthetic	200
Peripheral nerve block	11
Type of surgery	
Airway surgery (excluding T&A)	7
Cardiac with cardiopulmonary bypass	15
Cardiac without cardiopulmonary bypass	5
Craniofacial surgery (excluding cleft lip/palate)	3
Intra-abdominal (excluding hernia)	12
Intracranial (excluding shunts)	9
Intrathoracic, non-cardiac	5
Major orthopedic surgery	5
Other non-operative	10
Other operative	55
Total neonate emergency	3
Pain management	
Consultations and PCA	17

ASA, American Society of Anesthesiologists; PCA, patient-controlled analgesia; T&A, tonsillectomy and adenoidectomy.
Source: Reproduced with permission of the Accreditation Council for Graduate Medical Education. Please visit ACGME website for the most recent edition.

Box 3.5: Content outline for pediatric subspecialty certification

Basic science
- Anatomy
- Physics and anesthesia equipment
- Anesthetic pharmacology

Organ-based basic and clinical sciences
- Respiratory system
- Cardiovascular system
- Central and peripheral nervous systems
- Gastrointestinal system
- Renal/urinary systems
- Endocrine/metabolic systems
- Hematology/oncology
- Genetics

Clinical subspecialties
- Fetal
- Neonatal
- Painful disease states
- Otolaryngology
- Plastic and oral-maxillary facial surgery
- Ophthalmology
- Orthopedic surgery
- Trauma and burns

Clinical science of anesthesia
- Evaluation and preoperative preparation of the pediatric patient
- General considerations of the perioperative period
- Regional anesthesia and analgesia
- General anesthesia
- Complications of anesthesia
- Special techniques and situations
- Postoperative period
- Monitored anesthesia care and sedation
- Acute and chronic pain management

Special problems or issues
- Special surgical procedures
- Professional issues
- Principles of biostatistics and study design

Source: Adapted from The American Board of Anesthesiology. Please visit the ABA website for the most recent version.

(e.g. original research or educational workshop development) and skills for leadership outside the operating room, fostering of an understanding of practice management, and educational mentorship. For example, a program may pair fellows with faculty members for recurring resident didactic teaching sessions. The faculty member role in this setting is to silently observe the fellow as teacher, then to provide meaningful feedback about teaching style and efficacy to the fellow following the session. With this approach, over the course of the year the fellows not only master the topic they choose to present but also begin to think of teaching as a skill unique from the rest of their practice and one about which they often have had no prior training.

As noted above, for those physicians who are interested in mastery of an even more focused clinical field within pediatric anesthesiology, select centers offer advanced fellowships in pediatric cardiothoracic anesthesiology, pediatric acute pain, pediatric regional anesthesiology, and more. Documentation of successful completion of one of these advanced fellowship programs is increasingly mandated for those anticipating, for example, a career caring for children with congenital heart disease undergoing cardiothoracic surgery at major centers. From a programmatic standpoint, advanced second-year pediatric anesthesiology fellowship programs share an important similarity: they are often tracks to faculty positions at large centers. In fact, several large centers in recent years have decided to hire only faculty with such advanced training. Medical educators should bear this in mind and should develop these programs with an emphasis on academics and scholarly work in addition to clinical mastery, building on the academic foundation initiated during the general pediatric anesthesiology fellowship training. With the exception of select pediatric pain fellowships that have paired with adult pain programs, there are no board certification examinations yet in any of these advanced subspecialties.

Oversight of educational programs

For any ACGME-accredited educational program (including resident and fellow programs) there are considerable regulatory and administrative expectations that change on a regular

basis. To avoid misinformation, review of the most accurate information available about specific requirements for fellowship is accomplished via the ACGME website (www.ACGME.org). Program directors and coordinators should be aware of both common program requirements (that apply to all programs) and specialty-specific program requirements. On this site there is also a "Program Directors Virtual Handbook" as well as a section called "Resources for New Program Directors." Program directors are encouraged to review this information to ensure compliance with existing regulations and provide feedback on proposed changes to regulations. Directors of non-ACGME fellowship programs may also find the resources helpful.

In addition to the ACGME, every teaching hospital has a Graduate Medical Education office, directed by a Designated Institutional Official (DIO). The DIO is a physician who takes accountability for the management of all GME programs in the hospital and is a useful resource for troubleshooting educational program issues as they arise. Both ACGME-accredited and non-ACGME accredited programs benefit from the umbrella of the GME office and the DIO. Establishing relationships with the DIO and the GME team is paramount to the success of educational programs.

Education of non-anesthesia providers

Pediatric anesthesiology education extends well beyond the "accredited training program." Many pediatric anesthesiologists are likely aware that for every anesthesiology trainee, there is one or more non-anesthesia provider who rotates to the operating room for "anesthesia experience." Some of these learners seek basic or advanced airway management education. Others come to practice vascular access skills in immobile and insensate children. Others may use anesthetic drugs in practice and seek experience with dosing and titration. There is a wide variation in level of experience of the learners, including but not limited to non-anesthesiology residents and fellows, attending physicians, medical students, sedation nurses and physicians, student nurse anesthetists and anesthesiology assistants, transport paramedics, and pre-hospital providers.

Key to the success of any program with rotating learners of varying experience and educational goals is the thoughtful formulation of specific learning objectives for each individual or group of learners. Care must also be taken to avoid altering or potentially diminishing the educational experience of anesthesiology trainees in the planning of education for non-anesthesia learners. It is imperative to ensure also that all patients receive safe anesthetic care. Having non-anesthesia providers in the operating room requires intense supervision to prevent unintended patient harm.

There are potential vast differences in baseline knowledge, skills, and perceptions of self-confidence among non-anesthesiology learners. Because of the limited resource of patient encounter opportunities compared with the seemingly unlimited supply of learners, larger institutions may find it helpful to create curricula or programs to optimize learning for visitors to the operating room, rather than encouraging sporadic opportunistic visitation.

One example of such a program is the Pediatric Airway Skills Education (PASE) curriculum at The Children's Hospital of Philadelphia (CHOP), with standardized prerequisites to visiting the operating room. This multi-modal educational program includes online learning modules focused on: (1) pediatric airway anatomy and assessment; (2) pediatric manual ventilation and adjuncts; and (3) endotracheal intubation and resources for failed intubation. Following completion of the online modules, learners attend Part 4 – a 1-hour, facilitated, hands-on training session with simulation equipment to practice mask ventilation, oral and nasopharyngeal airway insertion, endotracheal intubation, and laryngeal mask airway insertion. This is similar to the American Heart Association approach to the various advanced life support learning programs. Online learning occurs at the learner's own pace and upon successful acquisition of the content, skills competence is assessed. This approach enables learners to invest in their own education, limits patient contact to those who are prepared for it, and focuses the role of the teacher at building on previously acquired knowledge and skills.

Evaluation in pediatric anesthesiology education

Evaluation is a crucial foundation to any educational endeavor, offering insight through critical reflection and identifying opportunity for improvement. In pediatric anesthesiology, evaluation of the learner, teacher, and program can together create educational experiences of excellence.

Evaluating the learner

There have been major changes to the way that learners are evaluated over the past decade. Educators in pediatric anesthesiology must be aware of both the rationale and the implementation of these new evaluation systems. Gone are the Likert scale-associated "ACGME Core Competencies" wherein "Medical Knowledge" was assessed on a 1-to-5 scale. What has replaced them is a tool similar to that used by pediatricians for generations: the ACGME milestones [46,47].

Each specialty and subspecialty has developed unique milestones in conjunction with the ACGME and the ABA. The milestones expectations for anesthesiology residents on the pediatric anesthesiology rotation will be different from those for the pediatric anesthesiology fellow. The pediatric anesthesiology fellowship milestones are available online [48].

The concept of the milestones is that an intern can be outstanding but is expected to function differently from an outstanding fellow. Using the old 5-point Likert scale, should both receive a score of 5? Each metric in the milestone system represents a continuum of knowledge, skills, and attitudes. Trainees are rated based on their actual performance on these scales, and anchors are put in place to guide expectations. For example, for pediatric anesthesiology the target for graduation is a milestone score of 4. Five is considered aspirational and some faculty may not function at a level of 5 for all milestones. Fellows are expected to enter fellowship with approximately a 1 on the fellowship-specific milestones. This may represent a psychological burden for both faculty and trainees, since an outstanding fellow may receive "low scores" at the start of the year, and this is different from previous evaluation systems. While the system is clearly imperfect, it is far more helpful than the old evaluation system at guiding the development of the learner. Increasingly non-ACGME

programs have begun using similar systems and the medical educator is bound to encounter these systems in practice.

Borrowing from the mounting corporate literature, 360-degree evaluation has become an important component of evaluation (and is now mandated by the ACGME). Depending on the setting and the relevant stakeholders, this may take many forms; the common theme is that attending physicians are not the only, or the best, judges of how trainees interact with nurses, staff, children, parents, or others. Tools for 360-degree evaluation such as the one shown in Figure 3.2 can serve as enormous, otherwise untapped, sources of data about learners.

In addition to board certification examinations, there is a growing demand from both the public and regulatory agencies such as the ACGME for "Entrustable Professional Activities" (EPAs). The concept of the EPA is very simple: how do we know that *Resident X* is able to perform *Skill Y* without direct supervision? [49,50]. Not long ago, autonomy was granted based on postgraduate training year alone. In the modern era, it is clear that this is inadequate due to the variability of learning acquisition for different tasks. How do we know, for example, if a resident is competent to place a jugular central venous line? Can we confirm not only that she has performed enough lines (quantity), but that she has done them correctly and without complications (quality)? In the EPA model, this procedure would be tracked, and after successful completion of a requisite number with appropriate performance (both of which need to be agreed by educators and conveyed to learners) the resident is considered eligible to perform the procedure with indirect supervision only. Anticipate increasing discussion about the role of EPAs in anesthesiology education in the coming decade; this area is ripe for research on validated tools at this time.

Evaluating the teacher

What is a good teacher? How does the medical educator evaluate teaching efficacy? If a student does not learn, is it the fault of the teacher or the student – or both? Questions like these haunt medical educators, who often think of teaching as their life's work. It can be daunting to effectively evaluate learners. But the meaningful evaluation of teachers has an added challenge: the evaluator is usually also the student, leading to a complex interaction of interests.

Consider two teachers: a pleasant person who always brings food to lectures and is rated very highly by students, and a faculty member who corrects every action (with explanations of her rationale) in the operating room. The latter may suffer from poor "teaching scores" when students react to corrective statements, but may in fact be teaching at a far higher quality than the former. Perhaps a more accurate method of assessing the teacher would be regular third-party observation, however this poses logistical and interpretive challenges, and risks a Hawthorne effect on the educational interaction, wherein the act of observing influences the behavior observed.

Consider another example of two teachers: one teaches a very mundane but often misunderstood concept, and another teaches a very eccentric and rarely used technique. Both are potentially valuable; however, most faculty would likely argue the former is higher value than the latter, while residents may give lower teaching scores to the former teacher. This example demonstrates two important concepts. First, it is not always clear whether it is the teacher or the subject matter that is being evaluated. Second, in many cases there is a discrepancy between what the learner *wants* to learn and what the teacher *knows the learner needs*.

Within academic medicine there exists significant motivation to evaluate teaching effectiveness, and although no system is perfect, relying exclusively on learner-driven teaching evaluations is potentially perilous. Teaching evaluations may be more reflective of how the learner feels about the educator ("likeability" and character traits of the teacher) than actual teaching effectiveness, and may even penalize teaching that challenges the learner's assumptions about his or her own performance or aptitude [51]. There exists concern among faculty at academic institutions of "reciprocity bias," wherein learners are predisposed to evaluate the teacher as they feel the teacher will evaluate them. Despite their imperfections, teaching evaluations play a significant high-stakes role in advancement and promotion of academic physician educators. This should prompt the academy to consider complementary data on teaching effectiveness.

In defining good teaching, more remote learner outcomes should be examined to know if educational efforts have made a lasting difference, rather than relying on how a learner feels about the educational experience in the teaching–learning moment [51]. In addition, data from educational outreach activities such as peer education, conference or institutional workshops, lectures and grand rounds presentations, to name a few, should also be considered.

Evaluating the program

Many books have been written by business professionals about the evaluation of programs [52,53]. The medical education community has begun to realize the value of such a strategy and thus structured evaluation has become a routine part of the maintenance of teaching programs. At a minimum, this takes the shape of the ACGME-mandated Program Evaluation Committee (PEC) meeting.

The PEC is made up of a cross-section of faculty members and at least one trainee; it may also include other staff as the program director deems appropriate. The PEC must be chaired by the program director and is required to meet at least once per year. Sources of information to be gathered prior to the meeting may include faculty evaluations, fellow evaluations, alumni surveys, ancillary staff input, lecture evaluations, curriculum assessment, and board certification pass rate for graduates. The PEC is required to suggest changes each year for program improvement; the program director is charged with implementing and assessing improvements over time. Details about the PEC function can be found on the ACGME program requirements website for the educational program in question [45]. In addition to the minimum-required annual PEC review, some programs utilize other measures of program efficacy. The PEC may meet more frequently, or data may be gathered in an ongoing fashion for continuous program improvement. At CHOP for example, regular fellow debriefing sessions are utilized to proactively gather real-time data about concerns, suggestions for improvement, and other relevant outcomes. The PEC meetings facilitate structured annual changes.

Parent Survey of Pediatric Anesthesiology Fellow

Fellow Name: _____

Dear Parent,

Training future pediatric anesthesiologists is an important part of our mission at The Children's Hospital of Philadelphia. Today, your child was cared for by a team that included a "fellow" physician – one who has completed training in anesthesiology but has chosen to continue further training as a pediatric anesthesiologist.

We need your help to make sure our fellows are the best doctors they can be. Please take a moment to provide us with feedback, and return this form to your recovery room nurse or to the locked "FELLOW EVALUATION BOX" in the PACU/recovery room. Your answers are anonymous and will not affect the care your child receives today or in the future.

Thank you!

When you think about your interactions today with the fellow physician who cared for your child, did he/she:

1. Introduce him/herself and explain his/her role clearly?
☐ Needs improvement ☐ Met my expectations ☐ Exceeded my expectations

2. Listen attentively to your concerns and questions?
☐ Needs improvement ☐ Met my expectations ☐ Exceeded my expectations

3. Respect your child, your family, and your culture?
☐ Needs improvement ☐ Met my expectations ☐ Exceeded my expectations

4. Examine your child before surgery, using appropriate respect and gentleness?
☐ Needs improvement ☐ Met my expectations ☐ Exceeded my expectations

5. Explain a clear plan of care for the day using language that you understood?
☐ Needs improvement ☐ Met my expectations ☐ Exceeded my expectations

6. Appear knowledgeable about medical issues?
☐ Needs improvement ☐ Met my expectations ☐ Exceeded my expectations

7. Follow-up with my child in the recovery room (PACU) to be sure he/she was comfortable?
☐ Needs improvement ☐ Met my expectations ☐ Exceeded my expectations

8. Ask me whether I had concerns after surgery and prior to my discharge?
☐ Needs improvement ☐ Met my expectations ☐ Exceeded my expectations

Overall, in thinking about the care provided to your child by a pediatric anesthesiology fellow today, would you be comfortable having this doctor care for your child again? *(please check one)*

☐ YES ☐ NO

Please add any additional comments (or explanations to answers above) you would like us to know in the future when we review the results of this survey with your pediatric anesthesiology fellow.

_____

_____

_____

_____

Please return to "FELLOW EVALUATION BOX" in Purple PACU

Revised 11/2014

Figure 3.2 Parent evaluation form for pediatric anesthesiology fellows. A similarly structured, yet different in content, form is used for allied health professional evaluation of pediatric anesthesiology fellows.

Mid-year changes are employed when needed to guarantee that educational goals are met.

An often-overlooked, yet important, aspect of program evaluation is succession planning. In the ideal setting, the program director has a co-leader and shadow in an associate program director, and the associate program director may also have an identified successor. These individuals should understand the issues and share in the program director tasks. Annual program requirements and other administrative tasks should be clearly delineated so that, in the event of unplanned or planned change in program director, the program can continue to run without interruption. Too often, "local champions" are responsible for running programs; the result is that if the champion disappears there is no one in the organization with the full knowledge of how to maintain the program in its current state, let alone

which changes need to be made as part of the ongoing program improvement process.

Continuing education in pediatric anesthesiology

In addition to the various graduate medical education programs that involve pediatric anesthesiology, anesthesiology departments (and educators) must be thoughtful about continuing education for faculty and staff. In addition to formal "Continuing Medical Education" (CME) courses that are often offered locally or are available nationally through organizations such as the Society for Pediatric Anesthesia (www.pedsanesthesia.org), there is a renewed focus on internal faculty development programs. These programs should be based on a local needs assessment and may cover topics as diverse as technical skills (for example, a refresher on defibrillator use or other rarely used skills), workshops in medical education techniques, professionalism education series, and burnout prevention strategies [54]. The ABA Maintenance of Certification Program for Pediatric Anesthesiology includes required activities for lifelong learning for both the base anesthesiology certification and the pediatric anesthesia subspecialty boards. These occur over a 10-year cycle requiring substantial CME credits, periodic review questions, of which 50% are on pediatric anesthesia topics, and evidence of significant quality improvement activities [55]. Many anesthesiologists have significant professional educational needs that are distinct from those of medical trainees, yet the stigma associated with admitting a knowledge gap among experienced faculty members inhibits appropriately directed educational efforts. It is the role of the educational leaders of the department to find a means to perform needs assessments and to provide meaningful educational experiences for all community members.

Conclusion

Education in pediatric anesthesiology is itself a model of deliberate practice, an opportunity for developing expertise through curricular reiteration, grounded in philosophy with practical application in design. Regardless of strategy, the paramount goals are to establish a culture of support for learning and find a way for both education and clinical work to serve the same master: the provision of expert anesthesiology care for children, both now and for the future.

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CHAPTER 4

An Introduction to the Ethical Design, Conduct, and Analysis of Pediatric Clinical Trials

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Introduction

Pharmacology and physiology, drug behavior, and organ function are the fundamental underpinnings of perioperative anesthetic practice. At our core, anesthesiologists are physiologists and pharmacologists; we titrate drugs against an individual patient's response to achieve a desired therapeutic goal. Understanding the pharmacokinetics (uptake, distribution, elimination, and sensitivity of a drug's effects in an individual patient) and pharmacodynamics (clinical effects of the drug on effector sites; hemodynamic, respiratory, renal, and central nervous system function) of the drugs we administer is essential for the safe provision of anesthesia. But more fundamentally, how can one determine if a therapy will be effective in the first place? Or if given a choice of therapies, which one is best? Further, although anesthesiologists titrate drugs to an individual patient's response, how do they know the population kinetics on which to determine how much drug to administer to produce the average or typical response? Or, over what period of time should a drug be administered and be expected to last? Equally important, how are outcomes determined or tested, and over what period of time?

Historically, most studies involving anesthetic drugs and techniques looked at the perioperative period as the time frame for outcome. However, what if the effects of these drugs or techniques only reveal themselves weeks or years later? At one time, this would have been considered preposterous. However, we now know from long-term studies where follow-up was years rather than days that the consequences of how an anesthetic was delivered can have profound effects years later [1]. Studies examining the effect of variations in perioperative anesthetic management of adults with coronary artery disease and newborn infants undergoing anesthesia have revealed significant effects years after the anesthetic was provided [1,2].

The randomized, double-blind, placebo-controlled trial (RCT) is the "gold standard" for determining the efficacy and safety of therapeutics. No other study design can provide better evidence for cause and effect between an intervention and an outcome. Unfortunately, when children are participants, ethically acceptable RCTs are more difficult to design and there are numerous impediments to practical implementation. When an RCT is not feasible, clinicians must rely on weaker forms of evidence from other trial designs such as pragmatic clinical trials, clinical trials without placebo controls, cohort studies, case–control studies, and even anecdote. While all of these are valuable, their results are less convincing due to the potential for confounding and bias.

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

No matter what the specifics of the study design, performing a clinical trial is challenging, often expensive and, when done to Good Clinical Practice (GCP) standards, challenging and expensive to conduct. Clinical trials strain resources and patience and are often viewed by investigators as an ordeal to overcome rather than as a welcomed ally.

New therapies approved for adults rapidly assume the mantle of the "standard of care" for pediatric patients, increasing the barrier to conducting an RCT and encouraging off-label prescribing which is rampant in pediatric practice [3,4]. Psychologically, this creates a very narrow window of time during which investigators are willing to conduct clinical trials of new therapies for children. When either clinicians or patients accept a therapy as effective, they do not want to participate in a study with the risk of enrolling into a placebo or control arm. However, using drugs off-label in children exposes them to ineffective care and untoward side-effects. Children who receive off-label drugs during an inpatient hospitalization have nearly double the likelihood of having an adverse drug reaction [5,6]. It is well established that children can have unique responses to drugs (e.g. weight gain, decreased growth), require different dosages and delivery methods, and often fail to show a therapeutic response even when the therapy provided is very effective for identical problems in adults (e.g. the use of triptans for migraine headaches or selective serotonin reuptake inhibitors (SSRIs) for depression) [7].

Given that it is not possible to predict whether children, from neonates to adolescents, will respond to a given drug in the same way as adults, RCTs remain essential. The alternative to evidence of safety and efficacy is perpetual uncertainty with acceptance of unproven therapies. In this chapter, we will provide an introduction to clinical trials and discuss the special problems of performing them in infants, children, and adolescents.

What is a clinical trial?

A clinical trial is a planned experiment that involves assigning subjects to an intervention with the objective of evaluating the effect of the intervention on the participants. Usually, the objective is to determine the efficacy and safety of the intervention (Fig. 4.1). Although vital, for the purposes of this chapter, we will not discuss clinical trials that involve a single group, such as pharmacokinetic studies. The intervention need not be limited to drugs, biological agents, or devices, but could include diets (e.g. preoperative fasting interval), a method or processes of delivering care, or any other procedure that can be manipulated by the investigator. At a defined point in time, the outcomes between one or more groups of subjects who receive the test intervention are compared with those of one or more parallel comparable populations of subjects in a control group.

Common impediments

Nothing can be more frustrating for investigators than to realize that there is a clinical question that requires an RCT for a definitive answer but only then to realize that it is not possible to address the question because of organizational, design, or execution issues. This can be true not just for investigator-initiated single-center trials; obstacles can also impede industry- or government-sponsored multicenter trials. Common impediments in all trials include inadequate planning, protocol development issues, and lack of available subjects or funding. Furthermore, almost all clinical trial investigators, both in industry and in academia, have unrealistic or overly ambitious timelines for study completion. Indeed, data from the National Institutes of Health (NIH) indicate that 85% of clinical trials fail to complete on time.

Overly ambitious objectives or rushed timelines can result multiple revisions to a protocol, an inability to get contracts between trial sponsors and centers finalized, and investigational review board (IRB, also referred to as research ethics committee or REC) approval delays [8,9]. (A sponsor or sponsoring agency is the institution, organization, or foundation that provides the fiscal and often the administrative and scientific support for a given clinical trial or project.) Inappropriate subject selection and incomplete data collection due to inadequate instructions or collection forms can result in unnecessary protocol deviations that compromise the fidelity of the study or in unanticipated adverse events that can compromise the entire study. Unrealistic or overly ambitious timetables may also raise doubts in the minds of the investigators about their ability to participate, forcing them to opt out rather than taking part in the trial. These factors result in approximately 30% of sites in multicenter studies failing to enroll even a single subject. Alternatively, some investigators who are frustrated by the time required to perform a proper trial may begin an inadequately designed trial before all the necessary procedures and support systems have been adequately tested and developed. This not only endangers the trial but, worse, exposes subjects to unnecessary risks of a trial that produces unusable data.

Getting started

To avoid many of these pitfalls, an organized stepwise approach, involving teamwork and an understanding of

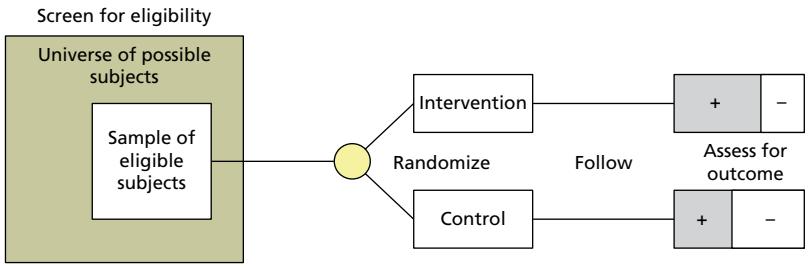

Figure 4.1 A clinical trial is a planned experiment that involves administration or implementation of an intervention to a sample group of subjects who are representative of the general population and is intended to determine the efficacy and safety of the intervention.

clinical trials methodology, is necessary [10–12]. More than ever, clinical research is a collaborative venture between clinicians, research methodologists, statisticians, study coordinators, IRBs, and study participants.

Defining the research question

Research begins with the research question that derives from a clinical problem. The research question is a general formulation and addresses the global question of interest such as "Does this drug or medical procedure or device work?" This overarching research question is unfocused and first needs to be formulated into a PICOT (Population, Intervention, Comparison, Outcome, Timeline) question [13]. The population refers to those patients intended to be recruited for the trial based on age group and other inclusion and exclusion criteria. The intervention needs to be defined precisely: dose or doses, interval between doses, and duration of administration. Comparison means the group against whom the intervention will be compared. The outcome of interest involves the plan for assessing whether or not the intervention works. The measures – morbidity, mortality, change in physiological variable, scale, or test, etc. – to be used need to be specified ahead of time. Finally, the timeline at which the comparison will be made must be agreed upon. In our experience, it can take considerable time and negotiation amongst the various investigators or between investigators and the sponsor to arrive at mutually agreed upon definitions for the PICOT question. Nevertheless, the time it takes to do this is vital for the success of a trial. The efforts expended upfront will avoid disappointment and potential failure later on.

There is often confusion about the meaning of three related but distinctly different terms – objectives, endpoints, and hypotheses. The study *objectives* serve as a statement of the general purpose of the clinical trial. In general, they are written in the form "to determine the …" and this is followed by the thing to be determined such as "the efficacy of the study drug for the treatment of … or "the pharmacokinetics of oral study drug …" An example may help. Assume that a clinical trial will test a new antihypertensive drug and the primary objective could be to determine the efficacy of the study drug for the treatment of moderate-to-severe hypertension in adults 18–65 years of age (P and I in PICOT). The primary objective serves as the basis for the sample size calculation while the secondary objectives are often exploratory (inadequate sample size to definitely address the objective).

The study *endpoints* convert each objective into an explicit operational definition that clearly defines how the objective will be measured and when it will be measured. The endpoints specify the comparison groups, the time points at which the comparison will be made, and the exact measurements or evaluation that will be used for the comparison (C, O, and T in PICOT). In our antihypertensive example, the primary endpoint might be the difference in the change in noninvasively measured systolic (or diastolic) blood pressure in mmHg after 4 weeks of treatment compared to baseline in the study drug group compared to the placebo control group. Lastly, there is frequent confusion about where to place the study *hypotheses*. They are often mistakenly included with the study objectives but in reality belong in the protocol statistical method section. The hypotheses are expressed in statistical terms as a null hypothesis and as an alternative hypothesis.

After development of the objectives and endpoints, the next question in any clinical trial is simply: "Is it worth the effort to mount a trial in the first place?" The answer to this question is predicated on the following questions: What is already known about the research question? Is this question worth the time and effort to answer? If the results were available today how would it change clinical practice? Is it ethically permissible to conduct this study in humans? and, finally, is it feasible to answer this research question with a clinical trial or would an alternative approach be better?

Choice of control group

The choice of the test and control treatments is the obvious and most important next step in designing a clinical trial [14]. The groups must differ from one another and investigators and subjects must be willing to enroll into both. The principle of equipoise is one approach for determining whether or not it is ethically permissible to conduct a comparative trial [15]. When low-quality evidence accumulates suggesting that one treatment may be superior to another, investigators may be reluctant to participate in the trial because they are unwilling to randomize their patients. However, even when the investigator is convinced that the experimental intervention will be superior to the alternative, provided that there is genuine uncertainty within the clinical community based on the available evidence, then the research question is in a state of equipoise and it is ethical to proceed. There is a long history of unexpected results in clinical trials, often with the placebo group having a survival advantage compared to what was perceived as the preferred treatment [16]. In 50% of the Children's Oncology Group clinical trials, the new study drug fails to outperform the standard treatment arm, emphasizing that frequently we are in a state of true equipoise [17].

By the time pediatric clinical trials begin, data from adults frequently suggest that the drug is active and effective, at least to some extent, for the proposed indication. In this situation, true equipoise might not exist. The requirement for true equipoise can be quite constraining and a number of alternative formulations have been proposed to substitute for it [18–20]. Many ethicists contend that in this situation, the decision about whether or not it is ethical to conduct the trial hinges on the risks associated with assignment to the control group (theoretically the less advantageous arm of the study). When the potential harms are minor and temporary then it may still be ethical to conduct the trial [21]. For example, a trial of a drug to replace acetaminophen for tension headache or a new treatment for allergic rhinitis could be ethically conducted because in neither situation would subjects suffer undue harm from assignment to a placebo.

The control group may be historical or concurrent, and assignment to groups may be via a randomized or nonrandomized process. While it is tempting to simply use an historical control to compare to a study intervention, the practice should be avoided. Considerable experience has shown that trials using historical controls are much more likely to conclude that a new therapy is effective than those using concurrent controls [22]. Choices for concurrent controls include placebo,

different doses of the same intervention (dose-ranging or dose–response studies), an established intervention/treatment (active control), or a combination of all of the above. The International Conference on Harmonization (ICH) "Choice of Control Group and Related Issues in Clinical Trials" document provides an extensive discussion of the advantages and disadvantages of each of these options [14].

The use of placebo controls remains a contentious and controversial topic [19,23,24]. The US Food and Drug Administration (FDA) has a clear mandate from Congress to only approve drugs, biologics, and devices that have proven to be safe and effective. In making their determinations, it is obvious that the FDA's clear preference is for placebo-controlled trials. Since many drugs that worked in adults have failed to establish efficacy in pediatric clinical trials (e.g. triptans [25] and antidepressants [26]), the FDA's preferences have considerable basis. Active controlled trials that seek to demonstrate equivalence suffer from the conundrum that if no difference is found between the two intervention arms, then it is possible that neither worked or both worked. As many as 40% of clinical trials for drugs for the treatment of depression, pain, and hypertension (amongst other conditions) fail to demonstrate superiority to placebo, contributing to the reluctance of the FDA to rely on active-controlled trials [23]. Placebo provides assay sensitivity – the ability to distinguish an active drug from an inactive one. Placebos also allow an accurate estimation of the magnitude of effect and help distinguish low-frequency adverse events caused by the intervention from background. Clinical trials of antidepressants in children firmly established that suicidality was a major concern, something that would not have been possible without a placebo control.

While a more complete discussion of this issue is beyond the scope of this chapter, in general, it is ethically permissible to use a placebo control in the following circumstances: whenever there is no proven treatment for the condition or disease, if the available treatments work poorly or have undue toxicities, if the participant has failed to respond to existing alternative therapies, or if there will be no undue discomfort or serious or permanent morbidity as a consequence.

Receipt of placebo is not usually equivalent to the absence of treatment. Frequently subjects receive standard care plus or minus the study intervention. There are two methods that can be built into a clinical trial to provide a margin of safety. First is the option for early escape – the study ends when the subject reaches an endpoint rather than after a fixed duration; the second is the use of immediate rescue treatment [14,27]. For example, in placebo-controlled pain studies, intravenous (IV) patient-controlled analgesia (PCA) morphine has been used as a rescue if the placebo (or study drug or procedure) is ineffective. The use of the rescue, the time to rescue, and the difference in the amount of rescue treatment have been used in some trials as the study endpoints rather than pain scores [27–29]. Finally, for many clinical trials involving anesthetic agents, it is not possible to use a placebo control but it often is for adjuvant therapies. As a result, trials of many anesthetic drugs focus on pharmacodynamics rather than efficacy. For example, trials of a muscle relaxant focus on dose–response, the time of onset, and duration of effect rather than on comparisons in efficacy between agents.

Ensuring validity: randomization and allocation concealment

Clinical trials rely on two processes to ensure their validity: masking (or blinding) of allocation assignment, and randomization [30]. Masking has two components: concealment of the allocation assignment at the time of randomization, and prevention of discovery of the assignment during the trial. The term masking is preferred to "blinding" because blinding has the potential for confusion, particularly when used in conjunction with a trial where loss of vision is the outcome measure or in a trial involving patients who have lost their vision. Indeed, the common phrase that "the investigators were blinded …" provokes comical imagery. It does not really mean that the investigators were actually "blinded," rather, it means that the allocation to treatment groups was masked. Randomization assures that all confounding variables, known and unknown, are distributed at random and hopefully equally between the two groups. A variety of techniques can be used to generate the treatment assignment including use of a table of random numbers or computer-generated sequences [31–33].

Simple random assignment can result in large imbalances in the number of subjects between the two groups in a trial. There are alternative techniques that ensure that the randomization sequence keeps the number of subjects in both groups relatively equal, both for the study as a whole and, for multicenter trials, within centers [34]. The most frequent approach is to randomize subjects in blocks such as groups of two, four, or six subjects, to ensure that the number of subjects is equal within each block. For example, if the block size is two, then subjects are randomized to treatments A and B in the order AB or BA. However, if the treatment assignment is discoverable (e.g. the masking is incomplete), then knowledge of the first subject assignment in each block could permit prediction of what the next subject's assignment would be. Using a larger block size increases the number of possible treatment assignment combinations and makes it harder to predict the subject's assignment. Another method used to ensure balance between the study groups is the use of permuted block sizes. In this technique, two different size blocks are used at random, making it very difficult to predict treatment allocation. For example, some blocks would consist of four subjects and some would include six. Without knowledge of the block size, it becomes impossible to predict the next subject's treatment group assignment.

The treatment group allocation process must not only be random but the outcome must be concealed, which is the first part of masking. If the investigator knows the group assignment for the next subject, this can affect their willingness to enroll the subject, can bias the consent process, or could lead to measures to manipulate procedures to influence the assignment. There are reports of studies where investigators have held sealed envelopes up to bright lights or found other measures to defeat the randomization schedule to choose the subject's group assignment.

To prevent discovery of the treatment assignment, the statistician should not reveal either the randomization schedule or the block size to any member of the investigative team. In a single-center trial, someone other than the investigator should generate and maintain the randomization sequence. If the study is a drug trial, having a pharmacist not otherwise associated with the trial prepare the study drug for administration is

a very effective way of concealing assignment. When the outcome measure is subjective, the subject, the investigator, and the statistician should ideally all be masked to the subject's treatment assignment. Concealment of treatment assignment after start of the intervention limits expectation bias on the part of the subject and biased assessments by the investigator. If the outcome measure is unbiased, for example death, then it may be less important to maintain masking. Since concealment is key to a valid study, an assessment should be made and included in any publication of the extent to which the masking was preserved during the clinical trial [35].

In comparing two active treatments, it may not be possible to disguise the drugs because of method of administration, size, or color of the drug. Using a double dummy approach where both active treatments have matching placebos can be an effective alternative. Each subject takes one of the two active treatments and a placebo to match the other treatment. For many anesthesia and pain studies, it may be quite difficult to mask the treatment if it involves a volatile anesthetic whose concentration must be monitored or if the intervention is invasive (e.g. an epidural nerve block). When treatment assignment cannot be concealed from the investigator, it may still be possible to prevent the subject from discovering their treatment assignment and to have someone other than the investigator perform the assessments of outcome to minimize bias.

Outcomes measures

Meaningful clinical trial outcomes include clinical events that change an individual's health in some discrete and meaningful way (to them), e.g. prevention of death, prolongation of life, prevention of morbidity, change in quality of life, or an improved economic endpoint [36]. All other outcomes, such as change in a physiological variable or a biological measure, are considered surrogate endpoints [37–39]. Surrogate endpoints are frequently used in place of clinical events because they are easier to measure and the variable measured is believed to be correlated to the clinical outcome of interest. Surrogates may be easier to assess but unless proven to predict the outcome of interest, i.e. they have been validated, they are poor substitutes for patient-relevant outcomes [40,41]. In the Cardiac Arrhythmia Suppression Trial (CAST), those patients receiving encainide or flecainide had less ventricular ectopy (surrogate outcome) but nearly three times the number of deaths as the placebo group [16].

In a hypothetical clinical trial designed to determine which of several different anesthetics had the best outcome for children with upper respiratory infection, hemoglobin-oxygen saturation <94% would be considered a surrogate measure of adverse respiratory outcome compared to pneumonia requiring hospitalization, brain injury, or death. However, the relationship of hemoglobin-oxygen saturation <94% to death, morbidity, quality of life, or cost is very tenuous. Therefore, it is always better to select an outcome directly related to something that matters to the patient or the healthcare system (cost).

Sample size and power

Even experienced investigators must consult with a biostatistician early in the protocol development process. David Sackett, one of the founders of evidence-based medicine, sagely advised that "If you don't start looking for a biostatistician co-principal investigator the same day that you start formulating your study question, you are a fool, and deserve neither funding nor a valid answer" [12]. A key decision in any clinical trial is to determine the number of patients needed to detect a clinically important difference in outcome with specified type I and II error protection [10,42]. A type I error is the probability of rejecting the null hypothesis when it is true (false-positive result) and is usually designated in most formulas by the Greek letter alpha (α). The null hypothesis postulates no underlying difference in the population or groups being compared with the factor, trait, characteristic, or condition of interest. In clinical trials this means that the true underlying effect of the test treatment, as expressed by a specified outcome measure, is no more or less than that for the control treatment. A type II error is the probability of accepting the null hypothesis as true when it is false (false-negative result) and is usually designated in most formulas by the Greek letter beta (β) with power defined as 1-β. Power in this context is the probability of rejecting the null hypothesis when it is false. Thus, calculations based on type I and II error and power will determine the number of patients needed in a trial and will often determine a trial's feasibility, cost, and the number of study sites needed to perform the study.

Power is typically set at 0.8 and occasionally at 0.9; this means that if a real difference exists of the magnitude specified, the trial has an 80% (or 90%) chance of detecting that difference. The variables in the power calculation include the magnitude of the clinically important difference, the number of events observed, and the variability (standard deviation). The greater the difference or the number of events anticipated, the fewer the number of subjects required. The greater the variability in outcome of interest (i.e. the wider the standard deviation), the greater the number of subjects required in a trial. Unfortunately, few treatments have as dramatic an effect as most investigators presuppose. Indeed, a 25% effect is actually quite large. Overestimating the efficacy of the new treatment will result in an underpowered trial which has an impact on the ethics of conducting the trial. An underpowered trial cannot achieve its stated objectives and exposes participants to unnecessary risk without prospect for answering the research objectives [43,44].

The variables that enter into the power calculation are amongst the most manipulated and debated elements in a study design. Often, when the number of subjects needed is large, event rates are adjusted or the magnitude of the anticipated effect is exaggerated. With or without these manipulations, in worse-case situations, if the number needed to study is so large, it may preclude conduct of the study. On the other hand, if the sample size is manipulated by altering the pretrial assumptions regarding the number of anticipated outcome events or the standard deviation, the results of the study may become inconsequential or invalid. Many have called for a re-evaluation of the methods used to estimate sample size, preferring the use of the width of confidence intervals or effect sizes rather than simply performing power calculations. This further underlines the importance of collaborating closely with a biostatistician during the initial planning phases of a trial [43,44].

Deciding on the number of subjects needed for a trial requires an active interaction between the investigators, study

sponsor, and the study biostatistician with input from the regulatory agencies who will review the study results. Although it is beyond the scope of this chapter to discuss the details of how one calculates for type I and II errors or estimates the required sample size, we have referenced several good reviews and textbooks that will provide an overview [45–47]. Interestingly, the choice of type I and II error protection is somewhat arbitrary. At first blush, the study team may want a trial that prevents both types of error. In reality, this may not be possible and the final decision as to which factor should take precedence may depend on the medical and practical implications of the two kinds of errors. Thus, relatively high error rates ($\alpha = 0.10$ and $\beta = 0.2$) are usually used for preliminary trials that are likely to be replicated. On the other hand, smaller error rates ($\alpha = 0.01$ and $\beta = 0.05$) are used when replication is unlikely.

Pilot studies

Investigators often classify underpowered clinical trials as "pilot studies." This is a misuse of the term and intent of a pilot study. Pilot studies are intended to refine the research question, or to establish the feasibility of executing the proposed study design. This can include assessing the ease of recruitment and retention of subjects, the clarity of the inclusion/exclusion criteria, the feasibility of the study procedures, refining the data collection forms, ensuring that the study management procedures are optimized, and study capacity issues [48–50]. For new drugs, pilot studies (phase I studies) obtain pharmacokinetic data and early safety data needed to plan later phase trials. The analysis of pilot studies should be primarily descriptive with a sample size determined not by a power calculation but by other pragmatic factors need to achieve the study objectives. Some contend that the pilot studies can be used to assist in formal power calculations. However, given the small sample size, the standard deviations, point estimates, and confidence interval widths will typically be quite large, making this a fraught exercise.

Single-center versus multicenter

Anesthesiologists (the authors included) have most frequently resorted to single-center trials because they are relatively easy to mount and carry out. The research personnel are all located within the same institution, know each other, and can achieve a higher degree of uniformity in the execution of the study procedures and data collection. Perhaps most importantly, single-center trials are significantly less expensive and more efficient to perform because the bureaucratic structure required to design, execute, and supervise a multicenter trial is unnecessary. The publication and academic promotion issues that are so critical for academic investigators are more clear-cut and without conflict.

Publication and the recognition investigators receive for publication are amongst the most important driving forces creating resistance to participation in multicenter pediatric clinical trials; it is also one of the least publicly discussed issues. Promotion, at most academic institutions, is based on the number, quality, and originality of, and authorship position in published papers. In single-center trials, the investigator's name will be listed and he/she may even be the first or senior author, the most prized position for academic promotion. In multicenter trials, pharmaceutical sponsors often base authorship on recruitment success and not on intellectual contribution. Indeed, most investigators are often only listed in the footnotes of the journal article within the membership of the study group. Furthermore, if the study is an industry-sponsored trial, authorship is often considered "tainted." Some have advocated abandoning authorship for contributorship, where each individual's role in the research is listed at the end of the publication rather than perpetuating the current inaccurate system [51]. Academic centers and promotion committees would need to agree to reward contributions listed rather than just authorship for this model to take hold.

While most academicians prefer the single-center model, there are serious limitations to this model. It may be difficult, if not impossible, to recruit enough participants in a timely fashion if only one center is involved. Further, when all the subjects come from within the same geographic area and are treated by a small group of clinicians, the results may have internal validity but may lack external validity, making them less generalizable to other practice settings [52]. Medical care has fortunately also reduced the number of poor outcomes, making differences in discrete clinical events that much harder to detect. For example, survival for childhood cancer has improved dramatically. Similarly, death related to anesthesia has dropped precipitously over the past 30 years. As a result of these successes, the size of the expected differences in outcome between two treatment groups has grown smaller. Since power is based on the number of events, not the number of subjects, better outcomes overall have translated into the need for clinical trials with larger and larger sample sizes.

Collaborating on large, simple trials, with multiple sites participating is the logical approach to addressing the limitations of the single-center trial [53]. To ensure the validity of a multicenter trial, all sites need to use a common protocol, the data collection tools need to facilitate accurate recording and transmission of data, and an administrative and organizational structure to coordinate all activities. To make this all happen can be very expensive [54]. The NIH has been creating a mechanism to facilitate multicenter trials through networks such as the Clinical Translational Science Award centers (CTSA), and various subspecialty component groups focusing on rare diseases and at-risk populations have done so as well (e.g. cystic fibrosis, sickle cell disease, Marfan syndrome, etc.). Additionally, multicenter data management software has made computerization and standardization of data entry much easier. Before embarking on a clinical trial, it is important for the investigator to check for these institutional resources because they can be invaluable (and often free) in setting up a clinical trial.

Funding

All clinical trials cost money, lots of money. Where the money comes from and how much there is to spend are two of the key stumbling blocks in all clinical trials. Ideally, funding should come from a mix of private and public sources, including the government, the drug and device industry, and health insurance companies. Unfortunately, this ideal is rarely met and much of the funding comes from the government, private

grants, and the pharmaceutical industry. The NIH, the primary healthcare research funding agency of the US government, rarely funds perioperative anesthetic research. Indeed, there is no specific institute within the NIH for anesthesiology. Further, the NIH cannot possibly bear the full burden of anesthesia-based research because of its priorities to primarily fund basic science research. Also, until very recently, industry was also unwilling to mount pediatric clinical trials because the pediatric market was viewed as too small to justify the return on investment, particularly because, as we will discuss shortly, most drugs used in pediatrics are used off-label anyway.

There is no easy answer to the lack of funding conundrum in pediatric perioperative anesthetic and analgesic trials. Despite the difficulties, it is essential to try. Giving up without a significant effort only assures failure. It has been our experience that if the project is worth doing, funding will be found either from traditional sources like the government and industry or from not so traditional sources like private and public foundations or local philanthropists. Often overlooked, there are anesthesia-specific foundations and societies that fund both novice and well-established investigators. These include the Foundation for Anesthesia Education Research (FAER), the Anesthesia Patient Safety Foundation (APSF), the International Anesthesia Research Society (IARS), and the subspecialty anesthesia societies, such as the Society for Pediatric Anesthesia (SPA). Additionally, many public foundations, such as the Mayday Fund and the Bill and Melinda Gates Foundation, provide research funding for pediatric clinical trials, particularly pain trials.

Another funding source that is closer to home, and one that is often poorly mined by anesthesiologists, requires raising funds from within the community in which the trial will take place. Within every locality there are philanthropists, corporations, and community organizations that can be recruited to support anesthetic research, education, and patient care. Although hospitals in general and children's hospitals in particular are very good at this, anesthesia departments are notoriously poor at it.

Developing and raising money for research endowments or endowed chairs specifically designed to provide seed money for young and established investigators is essential for clinical trials and for our specialty. Finally, regardless of how one obtains funding, the funding source(s) must always be disclosed to the IRB, the institutional conflict of interest office, and the public when patients are being recruited to enter into the trial and when the data and conclusions generated by the trial are presented in public forums or published in the lay or scientific press.

Phases of testing a new drug

A considerable proportion of anesthesia research involves testing of drugs. All US studies involving investigational new drugs require an Investigational New Drug (IND) application issued by the US FDA before testing can move from animals to humans. The first stage of testing a new drug is called phase I (Fig. 4.2). Phase I trials generate preliminary information on the absorption, distribution, metabolism, elimination, and safety of a drug. Phase I studies typically involve 20–80 subjects and are usually first conducted in healthy adult human volunteers. However, some phase I trials, for example chemotherapeutics targeted to pediatric cancer, may need to be conducted in children. In contrast to phase I studies in adults, pediatric participants must have the target disease or condition. Phase I studies are rarely if ever done with a comparison group; if one is included, it is typically the study drug at a different dose.

After phase I studies have established the basic pharmacology and safety profile for the new drug, testing proceeds to phase II. Phase II trials can be further subdivided into two basic types [55]. Phase IIa are generally smaller pilot clinical trials to explore efficacy (and safety) in selected populations with the disease or condition to be treated, diagnosed, or prevented. Phase IIb are well-controlled trials to evaluate efficacy (and safety) in subjects with the disease or condition to be treated, diagnosed, or prevented. These clinical trials usually represent a more rigorous demonstration of a medicine's

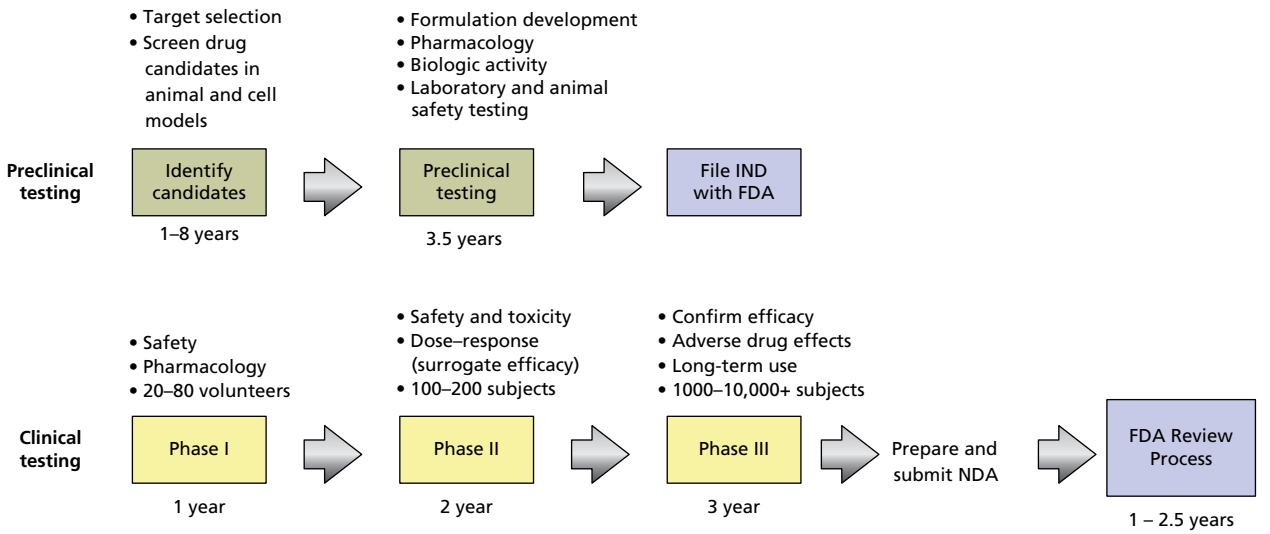

Figure 4.2 All studies investigating new drugs go through a process of preclinical testing in animals, several phases of human clinical trials, and culminate in a new drug application and approval by the FDA. The process takes years, with failure possible all along the way. FDA, US Food and Drug Administration; IND, Investigational New Drug; NDA, New Drug Application.

efficacy. These trials explore the efficacy in individuals with the disease or condition of interest, usually using surrogate measures of efficacy (e.g. decrease in blood pressure or reduction in tumor size rather than mortality). These are well-controlled trials designed to provide preliminary evidence of efficacy, explore the useful dosage range of the drug, and supplement the data about the safety profile of the drug. They often include additional pharmacokinetic testing during repeat dosing and at the anticipated therapeutic dose. Phase II trials frequently involve a few hundred individuals.

Phase I and II studies frequently explore the relationship between the dose administered and the physiological response. Typically, five or six doses are needed to establish the complete range of responses – ranging from the highest no-response dose, the lowest dose with a meaningful response, and up to the dose beyond which either no further effect or undue side-effects are seen. When only two or three doses are studied, then the trial is more appropriately termed a dose-ranging trial. Given the expected intra-individual variation, dose-ranging trials generally require dosages that are a factor of 3–4 to clearly distinguish one dose from the other. Failure to establish the correct dose prior to conducting efficacy studies can result in failed efficacy trials or unnecessary toxicity. At the end of phase II testing, preliminary evidence of efficacy and safety has either been established sufficiently to proceed to confirmatory trials or development ends. For chemotherapeutic drugs, it is also necessary to identify the maximal tolerated dose (MTD). Based on dose–response studies, the dosage for confirmatory trials of efficacy is selected. At the end of phase II testing, the sponsor and the FDA meet to establish the endpoints to be used for the phase III or pivotal trials.

Phase III trials, or confirmatory trials, are the final stage of new drug development and are designed to enable drug approval and labeling by the FDA. The drug label, distributed as a package insert, is the document approved by the FDA and furnished by the manufacturer of a drug for use when dispensing the drug. It lists a summary of the basic information about the pharmacology of the drug, its approved uses (conditions, populations, recommended dosage), contraindications, and potential side-effects. Phase III trials are usually large, randomized, controlled clinical trials designed to confirm both the efficacy and safety of the drug. It is a given that all drugs provide a trade-off between their benefits and their side-effects. The results must be generalizable to the wider population. Surrogate measures of efficacy are no longer sufficient to support a labeling indication. For a cancer chemotherapy drug, improved survival would need to be established rather than simply reduction in tumor size. A new pain medication would need to not only demonstrate a statistically significant difference in pain score between groups, the difference would need to be large enough to be considered clinically important.

When the sponsor believes that they have established the efficacy and safety of the drug for a specific indication, they submit a New Drug Application (NDA) to the FDA to label and market the drug to the public. Of every 1000 drugs that enter preclinical testing, only 100 drugs enter phase I testing in humans, approximately 70 go on to phase II testing, and 30–40 make it into phase III testing. Only about 12–15 result in an NDA submission and, of those, only nine or 10 are approved (see Fig. 4.2).

Once a drug is approved, the sponsor must continue to conduct postmarket surveillance. Many serious adverse drug effects and interactions are only discovered after a drug has been approved for use and released into the marketplace. In reality this should not be surprising since at the time of initial approval most newly approved drugs have only been tested in 1000–5000 people. Although to investigators and sponsors this is a considerable number of people, in reality it is too small to detect rare but potentially important side-effects. Most rare but serious side-effects occur in less than 1:10,000 individuals. Obviously, adverse drug effects this infrequent will not be reliably detected at the time of drug approval if less than 5000 people were exposed to the drug. This underscores the importance of postmarketing surveillance and explains the headline-making news accompanying the withdrawal of an approved drug, a process that occurs in approximately 1.5–5% of all newly approved drugs, depending on the epoch [56].

Some of the recently withdrawn drugs include: oxymorphone, a long-acting μ_1-receptor agonist removed for higher than expected abuse potential; rofecoxib, a COX-II inhibitor removed because of an increased risk of myocardial infarction; rapacuronium, a short-acting muscle relaxant, removed because of severe or fatal bronchospasm; hydromorphone extended-release, removed because of the risk of accidental overdose; and ximelagatran, removed because of hepatotoxicity. Rare cases of idiosyncratic hepatotoxicity and increased risk of myocardial infarction may be difficult to detect in phase III trials.

None of the risks associated with these drugs was detected during initial testing and the risks came to light from postmarketing surveillance rather than as the result of phase IV trials. However, when common patterns emerge, the FDA and its European counterpart the European Medicines Agency (EMA) can impose additional requirements for the approval of all new drugs. For example, as the result of several drugs (e.g. astemizole, terfenadine, and cisapride) being withdrawn due to cardiac arrhythmias in the 1990s, all new drugs are now tested for possible effects on prolonging the QTc interval.

To ensure and evaluate the long-term safety and efficacy of the newly approved drug following FDA approval and drug licensure, the FDA may require phase IV trials [57]. The pharmaceutical sponsor may also choose to explore additional indications for the drug or to study the drug in wider populations than studied in the phase III trials. Unfortunately, many phase IV studies do not have sound scientific designs and are funded by the pharmaceutical sponsor as seeding trials to increase interest in the drug and to generate sales.

Timing of pediatric clinical trials

Ideally, all new therapeutic interventions would be rigorously tested before introduction into clinical practice. The reality is far different, with clinical adoption of new therapies far outstripping a solid evidence base on which to make these therapeutic judgments. As stated previously, there is often a very narrow window of time during which it is feasible to test a new therapy, particularly for children. After introduction into practice, interventions approved for adults become "standard of care" for children, even without the benefit of adequate evidence of their efficacy or safety in children. Indeed, this is one

of the ongoing conundrums of small case reports, case series, and other forms of uncontrolled trials that flood the medical literature. The recent mandate to conduct clinical trials in children has clearly demonstrated that trials are not only feasible but also essential. Children have been shown to experience unique adverse effects (e.g. growth impairment and suicidality), require different dosage levels or formulations, and may fail to respond to a drug in the same way that adults do, even when the disease is the same (e.g. triptans for migraine headache and SSRIs for depression) [7,58]. Clearly, the adage that "children are not small adults" has been proven true over and over again. Therefore, the ideal time to start pediatric trials is before or just after a new treatment is first approved, before preconceived notions regarding its merit develop. Unfortunately, this is rarely the case because, as we will describe, the planning, organization, and structure of a proper trial take a fair amount of time, patience, discipline, and money – qualities that many investigators unfortunately lack.

Anesthetic and pharmacological research in pediatrics

Although most children cannot swallow pills, few drugs are available in liquid formulations [59]. While pharmacies can make extemporaneous formulations, these must be used without information about bio-availability or palatability. Changes in formulation and route of administration affect uptake, distribution, and ultimately efficacy in unpredictable ways. Inadequate information exposes children to age-specific adverse reactions, ineffective treatment due to inappropriate dosing, and lack of access to new drugs because physicians tend to prescribe less effective known medications. Additionally, insurance companies and other third-party payers may refuse payment for off-label use of medications. Indeed, in the past, so little pharmacokinetic and pharmacodynamic testing was performed in children that by 1968 they were termed "therapeutic orphans" [60].

To remedy the lack of appropriate labeling in children and in pediatric subpopulations (newborns, infants, school age, and adolescents), the US Congress enacted the FDA Modernization and Accountability Act (FDAMA) of 1997, its successor, the Best Pharmaceuticals for Children Act (BPCA, 2002) and the Pediatric Research Equity Act (PREA, 2003). Taken together, these laws were intended to promote standards and requirements for the use and labeling of drugs in children. The FDAMA and BPCA offered pharmaceutical companies incentives to study pediatric indications for approved drugs while the PREA required that all new drugs and biologics, all new formulations and indications for approved drugs be tested and studied in children. The PREA and BPCA were reauthorized into a single law as part of the FDA Amendments Act (FDAAA, 2007). These programs have been tremendously successful, with labeling changes to more than 750 pharmaceutical package inserts to date [61–64].

Despite the major advances in labeling drugs for children made since 1997, most of the drugs used in infants, children, and adolescents during the perioperative period are still administered off-label, that is, they have not been thoroughly tested for efficacy or safety in pediatric trials. One of the main reasons for this is that most anesthetic and pain management drugs are older and had no patent life or exclusivity remaining at the time the FDAMA was signed into law. However, some drugs, including desflurane, ondansetron, midazolam, milrinone, oxycodone, tramadol, and sevoflurane, have been studied under the FDAMA or BPCA. Looking forward, all new drugs must be studied under the PREA. Unfortunately, off-label administration of older medications to pediatric patients often goes beyond the indications on the approved label and by routes of administration neither tested nor approved even in adults. It is hard to extrapolate the data available from the relatively healthy adult participants in most phase III trials to chronically ill adults, the aged, pregnant women, infants, children, adolescents, and both adult and pediatric critically ill patients without consideration of the maturation of drug-metabolizing enzymes or alterations in sites of action over the normal course of aging. To deal with the issue of older drugs, the BPCA included funding for off-patent drugs under a partnership between the NIH and the FDA. These studies are currently being managed through a large grant by the Duke Clinical Research Institute (DCRI) via the Pediatric Trials Network (PTN).

Ethical aspects of clinical trials

Overview

There is a long history of shame involving human research, from the Nazi war crimes in which lethal medical experiments were conducted on Jews and other subjugated people, to the Tuskegee syphilis study, which was conducted by the US Public Health Service from 1932 to 1972, in which minority men with syphilis were enrolled to study natural disease progression without being informed that they had the disease and without being treated after penicillin became available.

In the United States, the Belmont Report written by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research identified beneficence, respect for persons, and justice as the essential ethical principles that should underpin research involving human subjects. These principles are not merely ideals; they have been translated into the federal research regulations known as the Common Rule (45 CFR 46) and into the FDA research regulations (21 CFR 50 and 56). An excellent review has proposed that there are seven requirements for ensuring the ethical conduct of clinical research, referring back to the fundamental principles articulated in the Belmont Report. Despite considerable progress, the death of Jesse Gelsinger in a gene transfer trial at the University of Pennsylvania in 1999 served to increase the attention on compliance with federal regulations, conflicts of interest in research, and clinical trials oversight by institutions. For more information concerning federal regulations, we refer the reader to the FDA website [65].

Investigational review board review and approval

All institutions in the United States who receive federal funding for research must have a Federal Wide Assurance (FWA) issued by the Office for Human Research Protections (OHRP). The FWA is the institution's assurance to the government that it will follow the federal regulations guiding human research. Worldwide, the Declaration of Helsinki

first adopted by the World Medical Association in 1964 and amended repeatedly (most recently in 2008) serves as an important expression of clinical research ethics worldwide. The Declaration is important for international trials but does not supersede American law and federal regulations. The FDA has recently adopted the International Conference on Harmonisation Guidelines on Good Clinical Practice to supplant the Declaration [66]. Other organizations with important clinical research ethics statements include the Council of International Organization and Medical Sciences (CIOMS) guidelines on the ethical conduct of clinical trials and the World Health Organization (WHO) operational guidelines for ethics committees that review biomedical research. Some organizations have produced more specific guidelines for pediatric clinical trials, including the EMA. All these organizations share a common ethical perspective, namely, that the well-being of the individual research subject must take precedence over all other interests.

A fundamental principle of all clinical research mandated by US federal regulations (as well as by the CIOMS, WHO, EMA, and the Declaration of Helsinki internationally) is the requirement for independent review and approval by a research ethics committee prior to initiation of any research protocol involving human subjects. In the United States these ethics committees are known as institutional review boards (IRBs) and consist of five or more individuals with diverse backgrounds in clinical research, medicine, law, research ethics, biostatistics, nursing, and, when children are involved, pediatrics [67]. To ensure independence and outside perspectives, at least one member of the IRB must be unaffiliated with the institution in which the research takes place and at least one member must be a non-scientific person, who preferentially is representative of the community surrounding the trial site's institution. Research that is no more than minimal risk (Box 4.1) can be expedited with just the review of the chair of the IRB. Most clinical trials are greater than minimal risk and require review by the convened board of the IRB. IRBs generally have a very formal application process that requires extensive documentation of the elements of the trial. Assembling and preparing this documentation is laborious, time consuming, and expensive, with many IRBs charging a fee for submission that can run into thousands of dollars. This cost and the cost of preparing the documentation for submission are often overlooked in trial design and implementation.

Typically, the documentation required by the IRB includes copies of the protocol, the informed consent form and assent documents, copies of any advertisements and brochures that will be used to recruit study participants, study data collection instruments, the investigational drug Investigators' Brochure, funding sources, and revelation of any conflicts of interest by the study investigators. Increasingly, many IRBs also require a detailed plan for data management, genetic specimen security, and for how protection of subject privacy and confidentiality of data will be maintained. Finally, many institutions require documentation confirming that participating investigators have taken and passed institutionally mandated courses (through national programs such as the online CITI Program, Miami FL, https://support.citiprogram.org) in research ethics, patient safety, billing, and confidentiality protection.

For multicenter research studies, a "central" IRB offers many potential time-saving, organizational efficiencies, and cost advantages [68]. A central IRB acts on behalf of a local IRB by reviewing and approving a trial proposal. Its organizational composition and process of review are identical to a local IRB. However, unlike a local IRB, the central IRB can simultaneously serve as the IRB of record for numerous sites. Central IRBs can be located either in an academic center or, as is most common, in one of many for-profit centers. Although the cost of submission and processing is often higher than a local institution's IRB, it is both much cheaper in the short and long term because of its center-by-center cost and much more time efficient. Some have even advocated that the ethical oversight is superior when just one IRB takes responsibility for the trial [69]. Indeed, nothing is more expensive in a trial than not being able to start and enroll patients while awaiting IRB approval. Because of this, central IRBs are a favored review oversight method of the pharmaceutical industry. To facilitate government funded research, the NIH is also now requiring a single IRB (sIRB) for all of its new multicenter trials. In addition, a new provision has been added to the Common Rule at 45 CFR §46.114 which requires use of a single IRB for all cooperative research conducted at US institutions. This new regulatory requirement took effect as of 20 January 2018 [70].

Regardless of how a proposal is reviewed, the process often takes 3 months or more. For many investigators and sponsors, this delay becomes a source of friction and frustration. Although this is understandable, it can be made significantly more onerous if the IRB submission itself is inadequate or poorly conceived and written. It is our experience that delays

Box 4.1: Waiver or alteration of consent for minimal risk research

To approve such a waiver or alteration, the IRB must find and document that:

- the research involves no more than minimal risk to the subjects
- the waiver or alteration will not adversely affect the rights and welfare of the subjects
- the research could not practically be carried out without the waiver or alteration
- whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Source: US Department of Health and Human Services Regulations: 45 CFR 46.116(d)

Examples of minimal risk research not requiring informed consent from patient, parent, or guardian:

- retrospective medical record review of anesthetic techniques for several hundred patients, where the process of finding patients and obtaining consent would prevent the study from being done
- retrospective medical record review of hundreds or thousands of anesthetics for complications, e.g. laryngospasm
- research from already existing large databases, i.e. state Medicaid databases, University Health Consortium, U.S. Agency for Healthcare Research and Quality Kids' Inpatient Database (KID), Child Health Corporation of America (CHCA) Database
- research involving only materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). Examples: excess waste blood or urine for a novel biomarker assay technique; height and weight data from a large population of children to determine incidence of obesity in a given population presenting for anesthesia.

in IRB approval are often prolonged by sponsor or investigator revisions, amendments, and the rush to complete the submission. Our mantra in protocol development and submission is to "measure twice and cut once." The trial planning process should ensure that there is sufficient time for both the initial IRB review as well the review of the IRB's requested modifications to the application, protocol, and consent documents. Finally, contracting issues also take time and are more frequently the rate-limiting step in getting a trial started. Again, it is our experience that it is far better and more efficient to do these in tandem than sequentially.

Special considerations when children are participants

The principle of respect for persons, which encompasses the right of the individual to self-determination, requires that investigators obtain the informed consent of participants prior to enrolling them in a clinical trial. Since children cannot legally give their consent and may be unable to comprehend the information about the trial, they are considered a vulnerable population in clinical research. Subpart D of both the Common Rule (45 CFR 46) and the FDA research regulations (21 CFR 50 and 56) contain additional protections for children. Extraordinary risk of harm is permissible when those risks are outweighed by the prospect for direct benefit, such as in an oncology trial. When the research offers no prospect of direct benefit, Subpart D limits the amount of risk to which the child can be exposed. It also delineates the requirements for parental permission and child assent. There are four ascending categories of risk/benefit that have corresponding increased levels of scrutiny (Box 4.2) (45 CFR 46 and 21 CFR 50: Subpart D).

Informed consent is not simply a document that requires a signature; it is a process that involves detailed ongoing explanations regarding the purpose of the trial, the nature of the procedures, the risks and potential benefits, and the alternatives to the research intervention and procedures. Components of the informed consent process include an assessment by the physician of the competence and decision-making capacity of the subject, disclosure, and the assurance, as much as is possible, that the individual has the freedom to choose the medical alternatives without coercion or manipulation. Further, subjects must be told explicitly that they can withdraw their consent and discontinue trial participation at any time without affecting the quality of their care and by whom and where it is provided. Since children cannot legally or developmentally provide consent, the child's parents or guardians serve as surrogate decision makers and provide permission for their child to participate. Just as in clinical care, there is an expectation that parents will make their decision for research participation based on the best interests of their child. Studies that have greater than minimal risk (see Box 4.2) without prospect for direct benefit to the child must be approved under the provisions of the Common Rule (45 CFR §46.406 or §407) or the FDA's Protection of Human Subjects (21 CFR §50.53 or §54). These regulations require an added protection: the need to get the permission of both parents (when it is practical to do so).

The assent of the child is required whenever the child is deemed capable of comprehending the required information [71,72]. Assent must be active and affirmative; failure to disagree does not constitute assent. In contradistinction to the requirements for consent, assent does not require the child to make a risk/benefit assessment. The assent process should disclose the purpose of the research, the nature of the procedures, and the right to withdraw assent at any time. Obtaining the assent of child participants requires an awareness of the child's cognitive abilities and the investigator's ability to describe the therapy, procedure, and trial objectives in terms that the child or adolescent can understand in age-appropriate language. In general, children less than 7 years of age are thought to be incapable of decision-making capacity and of providing assent. Children between 7 and 14 are in a gray zone and IRBs are quite variable in their requirements. In practice, we try to obtain assent for research trials in all mentally competent children older than 7 years of age. Above age 14, assent is required by most all IRBs in developmentally capable children. When assent is required, the requirement for documentation will be determined by the local IRB. Some require a separate written assent form and others just documentation of assent on the consent form [73,74].

Box 4.2: Federal classification for pediatric research

§46.404 and §50.51: Research not involving greater than minimal risk

- IRB determines minimal risk
- Adequate provisions are made for soliciting assent from the child and consent from the parent or guardian
- In the State of Maryland, even this level of study must be of direct benefit to the patient

§46.405 and §50.52: Research involving greater than minimal risk but presenting the prospect of direct benefit to the child

- IRB justifies the risk by anticipated benefit to the child
- The anticipated benefit-to-risk ratio is at least as favorable as the current available alternative therapy
- Adequate provisions are made for soliciting assent from the child and consent from the parent or guardian

§46.406 and §50.53: Research involving greater than minimal risk and no prospect of direct benefit to the child but likely to yield generalizable knowledge about the disorder or condition

- IRB determines that the risk represents a minor increase over minimal risk
- The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations
- The intervention or procedure is likely to yield generalizable knowledge which is of vital importance for understanding or amelioration of the subject's disorder or condition
- Adequate provisions are made for soliciting assent from the child and consent from the parent or guardian

§46.407 and §50.54: Research not otherwise approvable that presents an opportunity to understand, prevent or alleviate problems affecting the health and welfare of children

Level of acceptable risk

Perhaps the unique aspect of pediatrics clinical research concerns the limits of acceptable risk. The definitions of minimal risk and a minor increase over minimal risk are key to

understanding when research is approvable. When a clinical trial has risks that are no greater than minimal, any child can take part (§46.404 and §50.51). However, if the risks are more than a minor increase above minimal, then the trial is not possible unless there is a prospect for direct benefit to the child (§46.405 and §50.52) that "is at least as favorable to the subjects as that presented by available alternative approaches." The definition of minimal risk is inherently confusing because embedded in it are two separate standards: the routine examination standard and the daily life standard. While the risks of routine examination are essentially trivial, the risks of daily life are considerable [75]. Almost all IRBs will consider a clinical trial involving administration of an investigational drug, no matter how innocuous, to be at least a minor increase above minimal risk.

The risk of death or serious injury in childhood is not zero. The risk of death from a car ride (adult driver) varies from 0.06 to 0.6 per million car trips depending on the age of the driver, the time of day, and road conditions. The daily cumulative likelihood of death, predominantly from car accidents and drowning, is 1.5 per million children per day. The likelihood of hospitalization and an emergency department visit varies between 1.0–2.1 and 6.4–64 per million children per day depending on the age of the child [75]. American Society of Anesthesiologists physical status I or II children undergoing general anesthesia currently have an estimated risk of death of approximately 4–5 per million (1:200,000). Thus, riding in a car, which is part of the risks of daily life, would be considered minimal risk, whereas receiving a general anesthetic, which is riskier, is at least a minor increase above minimal risk. Different IRBs and ethicists will come to different conclusions about the level of risk associated with some procedures. In 2016, the FDA Pediatric Advisory Committee could not come to a consensus regarding the risks of general anesthesia for procedures, such as MRI. The committee was divided seven (minor increase) to nine (more than a minor increase) [76]. To avoid the possibility of exposing children to too high a level of risk, some within the research ethics community believe that there should be just a single standard for risk and generally they favor risks closer to the routine examination standard [77]. Adoption of this unified standard would have a chilling effect on pediatric research. Part of the discrepancy between various IRBs in their decision making is due to the difference in their threshold for these two definitions.

Benefits

Benefits in clinical research can be direct, indirect, or both. Research offers a prospect for direct benefit when there is a reasonable and plausible expectation, based on prior research, preclinical data, or other basis, that participants will receive a meaningful clinical benefit [77]. Clinical trials that have greater than a minor increase above minimal risk are only permissible if they offer a prospect for direct benefit. As long as the prospects for benefit outweigh the risks and are at least as good as the alternatives available outside the research, the IRB can approve the research (§46.405 and §50.52).

If the research or a component of the research is purely for research purposes and is not for the participants' direct benefit, the IRB can only approve the research if the risks are limited to a minor increase above minimal risk (§46.406 or §50.53). Since the definition of minimal risk is controversial, it should be expected that the definition of minor increase is controversial too. Rid et al have proposed a rubric for assessing risk which requires that all the probabilities for all negligible, small, moderate, significant, major, severe, and catastrophic harms be defined for each intervention and then compared to the risks of daily life [78]. Investigators know much more about the procedures proposed than the IRB. It is their responsibility to provide the IRB with as much data as possible about the probability and magnitude of all possible harms from the procedure or intervention to assist the IRB in making its determination.

Coercion and undue inducements

Recruiting subjects can create or cross a very real line between persuasion and coercion. Coercion of subjects can include manipulating or misusing information, or instilling fear that non-participation will result in withdrawal of or inferior medical care. Many institutions consider it coercive to be both the principal investigator and also the individual's primary physician. Coercion is a threat and should be distinguished from undue inducement, a reward so generous that subjects ignore their better judgment and assume risks that they would not otherwise be willing to endure.

Undue inducement means payment or rewards so excessive that it makes it hard for subjects with limited means (economically vulnerable subjects) to decline participation. Examples of inducements can include indirect benefits of participation such as increased access to care or excessive financial remuneration. Indirect benefits of participation such as access to clinical experts, reduced waiting time for clinic visits, door-to-door transportation, and free care including study drugs during and after the trial can be quite persuasive incentives. The provision of free care and drugs and shortened wait times can be very powerful incentives indeed to participate. There can be a fine line between fair subject payment and undue inducement. Reasonable compensation is ethical and provides all individuals the opportunity to take part in research without experiencing financial hardship. There is no evidence that moderate payment negatively affects subjects' judgment [79,80]. The object in designing a budget should be to try to make payment neutral so that it offsets the costs and burdens of participation.

Payments can be broken down into four components: reimbursement for expenses, compensation for time and effort, gifts of appreciation, and incentives [80,81]. Incentives are almost universally forbidden by IRBs. Appreciation gifts to subjects should be of nominal value. If participation imposes no travel or other burdens, then it may be inappropriate to include any payment. When subjects must return to the hospital or clinic for follow-up, payment of travel costs (reimbursement) and lost work time of the parents (compensation) is absolutely fair and expected. When the child participant has to complete procedures, such as diaries, or must forego leisure activities, it is fair to compensate them for their time and effort as well as their parents [82,83]. Payments to children need to be age appropriate; children less than 9 years generally do not understand the relationship between the amount of effort and size of payment and should be paid with a fixed-size payment.

Operational planning and trial execution

As with any large-scale project, a clinical trial has several stages that must be managed for the trial to be run and completed successfully. Each has specific features and timelines for completion and each is associated with pitfalls that, if not dealt with, will lead to failure and frustration. For most clinical trials, the stages include initial design, feasibility assessment, protocol development, data management and document preparation, subject recruitment/screening and enrollment, study treatment and follow-up, close-out and study termination, and an optional post-trial follow-up (Fig. 4.3). Once the enrollment and follow-up are complete, the data must be checked to ensure that they are accurate (data cleaning) and only then can analysis commence. Obviously, there is overlap across each of these stages.

Initial design stage

The initial design stage specifies the rationale, purpose, and objectives of the clinical trial. A literature review is essential to identify pertinent background information about the target disease or condition and the proposed study intervention. Pharmaceutical trials compile this information in an Investigators' Brochure but it is up to the investigators to establish what is already known about the safety and efficacy of the intervention. Although confirmation of previous results has some value, it is usually a waste of time and resources to repeat work that has been done previously. Exposing subjects to risk when the answer to the research question is known is also unethical [78].

In our experience, the best approach is to start by creating a synopsis or concept protocol. This is a 2–4-page document that outlines the PICOT questions for the trial as well as the method of assignment to the various study arms and the methods for concealing treatment allocation. The primary and secondary endpoints should be formalized, the required sample size estimated, and the statistical plan for the analysis of the primary endpoint specified. Only when all members of the protocol development team have agreed on the synopsis should the study planning proceed. As the details of the concept protocol are being finalized, the details of the recruitment plan should also be considered to determine how many sites would be needed for the study. A preliminary timetable for the trial, the organizational structure, subject safety, and plans to ensure data integrity, quality, and security all need to be developed and implemented. Finally, it is at this point that funding proposals are sought, written, and submitted.

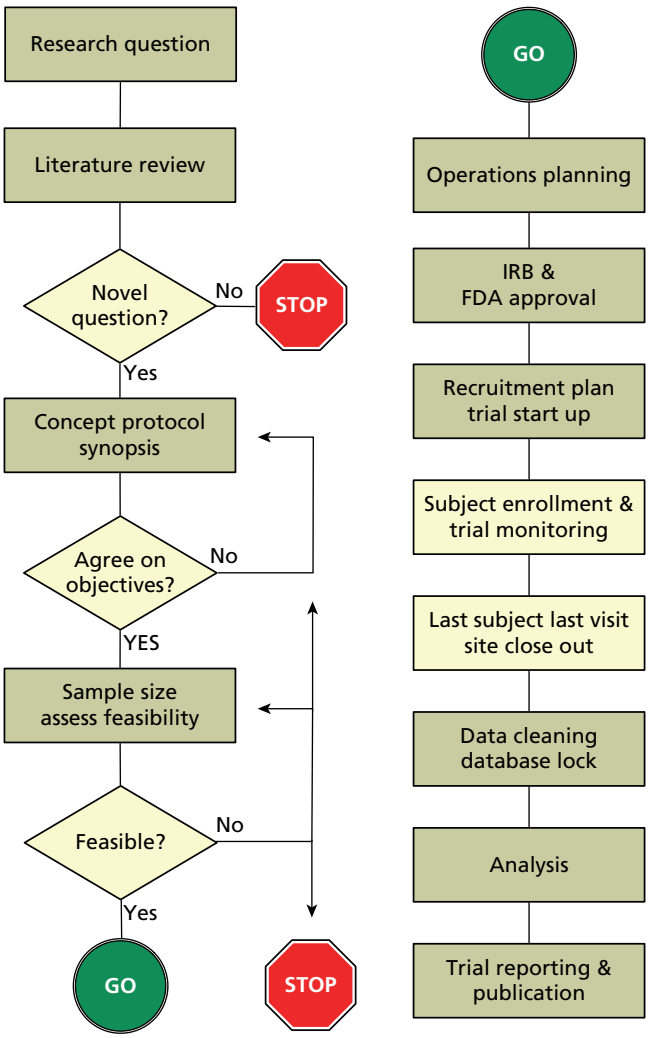

Figure 4.3 The primary stages of a clinical trial. Each major phase shown as a diamond has components shown as rectangles that are shared across the clinical trial. FDA, US Food and Drug Administration; IRB, investigational review board.

Feasibility and recruitment planning

With the protocol synopsis in hand, the principal investigators next need to assess whether the plans are operationally feasible. A realistic appraisal of the likely number of available subjects will determine whether or not the study can be conducted at a single site or whether other institutions will be needed to increase the pool of available subjects. Starting a clinical trial is a time-consuming process and unless the proposed study is feasible, it should not be started. Most ethicists consider underpowered or unfeasible studies unethical and many IRBs will not approve a study that has no hope of being completed [84].

If it has not already been done, it is at this moment of protocol planning that the principal and co-investigators must include and obtain the advice of experienced study clinical coordinators for managing many study-associated activities. Having a study coordinator assist in project planning can help ensure that pre-established work scope, study protocol, and regulatory requirements will be feasible and pragmatic. Study coordinators often assist in the recruitment of subjects and are often delegated to ensure the study team adheres to the study protocol. They can serve as the principal administrative liaison between the study's administrative coordinating center and the local site. Finally, the study coordinator often oversees and coordinates the provision of administrative and staff services to the site investigators and maintains record-keeping systems, regulatory binders, and procedures.

Recruitment planning requires the input and planning of each study site and is often a collaborative effort between the study investigator and coordinator. The first step is to review the potential available population, keeping in mind the inclusion and exclusion criteria. If it appears that there will be

insufficient numbers of potential participants, then the options are to loosen the inclusion/exclusion criteria to increase the available pool of subjects, increase the number of sites participating, or plan for an advertising campaign to widen the potential audience (see Fig. 4.3). In general, investigators greatly overestimate their ability to enroll subjects and the majority of trials fail to complete enrollment on time. In our experience of coordinating multicenter trials, a quarter to a third of sites fail to enroll even a single subject while the best 25% of the sites enroll 75–90% of the subjects. Since it is very difficult to predict which sites will successfully enroll subjects, it is usual to recruit more sites than would be expected to ensure study completion. During the actual recruitment process, the study coordinator should track all subjects from screening to completion. The 2010 CONSORT guidelines provide an excellent resource on how and why patients should be tracked through the recruitment process and include a recruitment table that should be provided in any randomized controlled trial for publication [85–87] (Fig. 4.4). The nature of the study will determine how, when, and by whom prospective subjects will be approached. For anesthesia and pain trials, this could include review of the operating room schedule, solicitation in surgeons' offices, or one or more publicity schemes, such as advertising in print or on the internet or radio.

Protocol development and operational planning

If the planned study appears feasible without modification, the next step is to flesh out the synopsis or concept into a complete protocol. It is at this stage that the nuts and bolts of the protocol are elaborated and put into writing ("cast in stone"). The objectives, endpoints, and inclusion and exclusion criteria will come from the study synopsis. However, many other items need to be specified, such as the time windows for screening and follow-up examinations, procedures for management of known or suspected complications related to the disease or therapy, and treatment algorithms for how the individual patient is to be monitored and treated if complications arise. The SPIRIT 2013 statement includes all of the elements that need to be specified in a clinical trial protocol [88–90]. Box 4.3 presents an example of a protocol table of contents for a clinical trial.

Most protocols provide very detailed scientific background sections but are left wanting when it comes to detailing the actual study procedures. The mark of a well-written protocol is that the study coordinator can read it and know which procedures to perform and when, and how to perform them for each study visit, the data manager can design the requisite case report forms, the biostatistician can perform the study analyses,

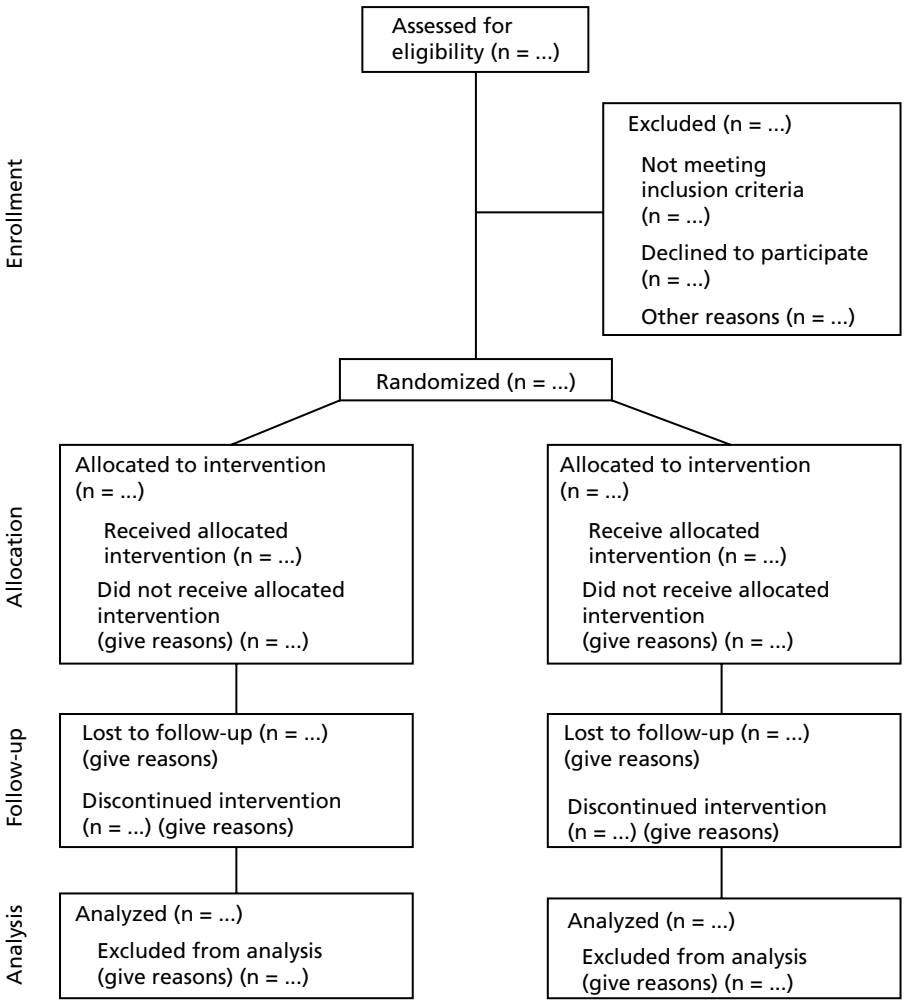

Figure 4.4 CONSORT 2010 flow diagram of the progress through the phases of a parallel randomized trial of two groups. *Source:* Reproduced with permission from Schulz et al [86], http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000251, licensed under CCBY.

Box 4.3: An example of a protocol table of contents for a clinical trial

1 Background information and rationale
- 1.1 Introduction
- 1.2 Name and description of investigational product or description of intervention
- 1.3 Findings from non-clinical and clinical studies
  - 1.3.1 Non-clinical studies
  - 1.3.2 Clinical studies
- 1.4 Selection of drugs and dosages
- 1.5 Compliance statement
- 1.6 Discussion of relevant literature and data

2 Study objectives
- 2.1 Primary objective
- 2.2 Secondary objectives

3 Investigational plan
- 3.1 General schema of study design (overview)
  - 3.1.1 Screening phase
  - 3.1.2 Treatment phase
  - 3.1.3 Follow-up phase (if applicable)
- 3.2 Randomization and blinding
- 3.3 Study duration, enrollment and number of sites
  - 3.3.1 Duration of study
  - 3.3.2 Total number of study sites/total number of subjects projected
- 3.4 Study population
  - 3.4.1 Inclusion criteria
  - 3.4.2 Exclusion criteria

4 Study procedures
- 4.1 Screening visit
- 4.2 Treatment phase
  - 4.2.1 Visit 1
  - 4.2.2 Visit 2 (etc.)
- 4.3 Follow-up phase
  - 4.4.1 Visit
- 4.5 Unscheduled visits
- 4.6 Concomitant medication
- 4.7 Rescue medication administration
- 4.8 Subject completion/withdrawal
  - 4.8.1 Early termination study visit

5 Study evaluations and measures
- 5.1 Screening and baseline evaluations (procedures and measurements)
  - 5.1.1 Physical exams
  - 5.1.2 Laboratory tests
  - 5.1.3 Other procedures
- 5.2 Efficacy evaluations
  - 5.2.1 Diagnostic tests, scales, measures, etc.
- 5.3 Pharmacokinetic evaluation (if applicable)
- 5.4 Safety evaluations/measurements

6 Statistical considerations
- 6.1 Primary endpoint
- 6.2 Secondary endpoints
- 6.3 Statistical methods
  - 6.3.1 Baseline data
  - 6.3.2 Efficacy analysis
  - 6.3.3 Safety analysis
- 6.4 Sample size and power
- 6.5 Interim analysis (if applicable)

7 Study medication (adapt for other interventions)
- 7.1 Description
  - 7.1.1 Packaging
  - 7.1.2 Labeling
  - 7.1.3 Dosing
  - 7.1.4 Treatment compliance and adherence
  - 7.1.5 Drug accountability

8 Safety management
- 8.1 Clinical adverse events
- 8.2 Adverse event reporting
- 8.3 Definition of an adverse event
- 8.4 Definition of a serious adverse event (saes)
- 8.5 IRB/IEC notification of SAEs
- 8.6 Investigator reporting of SAEs to sponsor
- 8.7 Medical emergencies

9 Study administration
- 9.1 Treatment assignment methods
  - 9.1.1 Randomization
  - 9.1.2 Blinding
  - 9.1.3 Unblinding
- 9.2 Data collection and management
- 9.3 Regulatory and ethical considerations
  - 9.3.1 Data and safety monitoring plan
  - 9.3.2 Risk assessment
  - 9.3.3 Potential benefits of trial participation
  - 9.3.4 Risk-benefit assessment
- 9.4 Informed consent/assent process
- 9.5 Payment to subjects/families
- 9.6 Confidentiality

10 Publication

11 References

and another group of investigators could replicate the clinical trial. The study procedures section should contain a visit schedule listing each and every measurement that is to be made during that encounter. Often, a simple bullet point list will do and usually a summary table is created as well. Having a complete list of visit-by-visit procedures is key to ensuring that all measurements are made as required at each time point. For clinical trials that take place in the operating room, the visits might be separated by minutes or hours rather than by days. To assist with this, the study evaluations and measures section should specify how each evaluation will be performed. Continuing with our previous example of a clinical trial of an antihypertensive drug, it is not enough to state that systolic blood pressure will be measured. Rather, the protocol must describe exactly how it will be measured (which arm, which device, whether the subject is to be seated, lying, or standing, after how minutes of rest, and how many measurements will be averaged).

When completed, the protocol becomes the blueprint for the study execution and, once put into place, its recipe must be followed to the letter if the trial is to be successful. Indeed, it is this "cast in stone" rigidity that so befuddles many clinicians and represents the fundamental difference between a clinical trial and routine clinical care [91]. In routine clinical care, physicians use their best judgment to make treatment decisions. On the other hand, in a clinical trial, the investigator's responsibility is strict adherence to the protocol, not to their own judgment, and this is absolutely essential to ensure the fidelity of the trial. For example, if a 6-year-old postoperative patient has an oxygen saturation of 92% in the postanesthesia care unit (PACU), some clinicians might decide to watch and wait, whereas others may prescribe and administer supplemental oxygen. However, if a study protocol treatment algorithm requires a subject to receive oxygen if their oxygen saturation decreases below 94%, then oxygen must be administered even if this is not the investigator's individual clinical practice. Put another way, if a study protocol requires that subjects eat green jello, the clinician/investigator must provide green jello, even if they would prefer red.

Data management and document preparation

When the protocol is finalized, the informed consent and assent forms and the case report forms (CRF), paper or electronic, can be developed. Data should be recorded first in the source document – the medical chart, anesthesia record, or data collection form – and then transferred to the CRFs. If data collection forms will be used, they should be tested for usability. The data management team should be organized and must develop the data storage, back-up, and security plans. In multicenter trials, the data team will produce the randomization and treatment allocation schedules and develop protocols for data transfer from each site to the data center. All clinical trials need a data quality control plan. If the study is conducted at a single site, the principal investigator will be responsible. For a multicenter trial, the overall study principal investigator, study sponsor or contract research organization (CRO) will be responsible for site monitoring and for reviewing performance and outcomes during the course of the trial. These procedures establish the plan for collecting, processing, and verifying study data accuracy and for on-site monitoring to ensure that the protocol is being adhered to and that the data forms actually are being completed correctly. Finally, the data monitoring group must develop guidelines for data security and access to study data by investigators within and outside the study and this access must be weighed by the rights of patients to privacy and confidentiality. The coordinating center may also be responsible for ancillary documents for the study staff to help ensure that the study procedures are followed precisely as well as to prepare any diaries or instructions for participants.

The Standards for Privacy of Individually Identifiable Health Information (the Privacy Rule) established, for the first time, a set of national standards for the protection of certain health information. The US Department of Health and Human Services (HHS) issued the Privacy Rule to implement the requirement of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). The Privacy Rule standards addressed the use and disclosure of individuals' health information (called "protected health information") by organizations subject to the Privacy Rule (called "covered entities"), as well as standards for individuals' rights to understand and control how their health information is used. Within HHS, the Office for Civil Rights (OCR) has responsibility for implementing and enforcing the Privacy Rule with respect to voluntary compliance activities and civil money penalties. The effect of the Privacy Rule on the conduct of clinical trials has not been major and largely involves expansion of the mandated confidentiality language in the informed consent document.

Informed consent document

The principal investigator is usually responsible for the development of the informed consent template document. However, for multicenter trials, the study sponsor usually provides a model consent form as a service to the site investigators. The consent form must follow the federal regulatory required elements of informed consent (45 CFR §46.116(a) and 21 CFR §50.25). The document should be written in plain language, with a target reading level of 6–8th grade (the average reading level for US adult trial participants). Approximately 12% of Americans have a below Basic health literacy proficiency and 22% are at the Basic level. Thus, if the informed consent form is written at greater than 8th-grade level, over a third of the participants will be unable to comprehend what they are reading [92].

Safety monitoring plan

All clinical trials require monitoring of unanticipated problems involving risks to subjects or others, including serious adverse events (SAEs). In multicenter studies, SAEs are usually reported promptly to the study sponsor. The sponsor is responsible for reporting these events to the regulatory agency overseeing the study. However, not all SAEs have to be reported to the IRB. Both the FDA and the OHRP have published guidelines on reporting of adverse events to the IRB. These require that unanticipated problems involving risks to subjects or others – events that are serious, related to the study intervention(s) and unexpected – require prompt reporting to the IRB. Regardless of the guidelines, investigators need to adhere to the policies in place at their local institution.

Safety monitoring should be tailored to the complexity of the study and the potential for harm to subjects. For a single-center study with a relatively low level of risk, the principal investigator's oversight should suffice. For a single-center trial with a moderate level of inherent risk, an internal data safety monitoring committee (DSMC) made up of the principal investigator and other knowledgeable individuals unassociated with the study would be advisable. Multicenter trials involving life-threatening conditions or interventions that have inherent risks should have an independent DSMC [93,94].

For all drug trials enrolling pediatric subjects, the American Academy of Pediatrics strongly recommends a DSMC for monitoring [95]. When the intervention has a track record of safety in adults and the condition of interest is not life-threatening, this level of oversight can be an unnecessary burden and can add substantially to the overhead costs of the study. Regardless of the oversight mechanism, meeting schedules and endpoints for interim analyses (if any) need to be defined and agreed upon. For trials involving life-threatening conditions, the protocol should contain stopping rules and procedures for early termination of the trial if serious unanticipated risks emerge. Only rarely should a trial be stopped for benefit and then only when one arm demonstrates a large margin of superiority [96,97].

Authorship and registration

Deciding exactly how the results of the study will be disseminated and by whom is a step often overlooked in the pretrial planning process. In our experience, failure to make this decision before embarking on a trial often leads to bad blood and ill will amongst the study investigators. As stated previously, for many investigators, authorship is essential for academic promotion. The order of authorship for study papers (and for ancillary studies) should be established and agreed upon by all investigators before starting a study. Ideally, a formal steering committee should be charged and entrusted with acting impartially on behalf of all the investigators early in a study design. The steering committee should establish procedures for review and approval of all publications and

presentations made by members of the investigative group before professional and lay scientific committees. At this stage it is also important to clarify trial roles. Some journals now request the exact role of each investigator at the time of publication. Finally, it is also important to establish safeguards that protect against premature disclosure of study results or the publication of the study results by a "minority" within the study group.

The final step within the protocol development stage is establishing the budget and staffing requirements for the trial. Does each prospective participating center have the manpower and skills to safely, effectively, and efficiently conduct the trial? Do they have enough potential participants to enroll in a timely manner? How will oversight be performed and by whom? How will study drugs be packaged, labeled, distributed, and safeguarded? How will the study be funded and by whom? Who will do all the regulatory work required for the trial? Funding and projected budgets are the keys to successful and unsuccessful trials. Inadequate funding, just like undercapitalization of a business, leads to failure. Indeed, it has been our experience that the real costs of conducting a study, including protocol development and site approval, are often underbudgeted, which often results in contract delays and misadventures.

Because many of the studies conducted by pediatric anesthesiologists involve drugs, and most if not all have invariably not been approved for use in children, approval by the FDA and its European counterpart the EMA may be required. It is beyond the scope of this chapter to discuss the process of obtaining an IND Application from the FDA but several useful sources are available at the FDA website (www.FDA.gov/CDER) including a guidance entitled Investigational New Drug Applications (INDs)— Determining Whether Human Research Studies Can Be Conducted Without an IND. Finally, all phase II, III, and IV trials require prospective registration in a national trial registry, such as www.clinicaltrials.gov in the United States. These registries are often funded by government entities and are designed to keep investigators from manipulating study endpoints by prespecifying the study objectives, intervention, subject population, sample size, and analysis plan of a trial before a trial is started. The databases are publicly available and are searchable. Most journals use and require trial registration for any trial submitted for publication.

Trial execution: treatment and follow-up

It is only after all the preliminary development, feasibility assessments, protocol development, and regulatory approval have been organized that the investigators are ready for subject recruitment and actually conducting the trial. For all multicenter trials there is usually an investigators' meeting held before the first subject is enrolled at which required training, standard operating procedures, and data management are finalized. For most perioperative pediatric anesthesia trials, the local investigator or their study coordinator recruits subjects from an in- and an outpatient operative list. The recruitment plan, including viewing and accessing these lists, should be included as part of the initial submission to the IRB. Advertising and liaisons with medical and lay societies that are so important in other adult and pediatric trials are often unnecessary. On the other hand, it is essential to inform the surgeons and the local referring pediatricians whose patients could be enrolled about the study and to get their tacit approval prior to recruiting subjects into the trial.

When it will be difficult to obtain consent and assent on the day of surgery, one approach is to screen the operative schedule and send letters to prospective study participants to inform them in general terms of the study objectives and procedures and to send a copy of the consent form to those who express an interest. Recruitment letters must be approved by the IRB prior to use and copies should be maintained in the study records. Without this prescreening and notification, there can be insufficient time to allow prospective participants to consider the risks, benefits, and alternatives to more complicated studies, making an informed decision difficult if not impossible. Thus, a successful recruitment plan often requires the investigator and study coordinator to screen and recruit in the surgeon's or pediatrician's office.

Before agreeing to take part in a clinical trial, both the investigator and the prospective participant need to understand that care provided during research is different from usual clinical care. The investigator's obligation is to adhere to the protocol and not to individualize care to the participant's need. It is not known whether or not the participant will benefit directly from their participation; to promise benefit is to presuppose the outcome from the trial. Failure to understand the difference between clinical care and research is termed "therapeutic misconception" [98–100]. The investigator must ensure that the prospective participant understands the difference so that expectations are aligned with reality. The data quality review, site monitoring visits, and meetings of the study steering committee, DSMC, and other study committees take place at regularly scheduled intervals. At these meetings, recruitment progress and projected time lines for completion of the study are reviewed to ensure that the study is meeting its goals.

Close-out and termination stage

Once the last subject has had their last visit and the final data queries issued by the data management team are resolved, sites can be closed. In practice, low-enrolling sites are closed well before this point so that there are sufficient monitoring resources to rapidly lock the study database. The site monitoring team will direct the disposition of equipment, supplies, drugs, and other stored materials. Once all data queries are resolved, the database can be locked, which means that no further changes will be made, even if small errors are discovered. As long as subject identifiers remain in the database used for analysis, the study must remain open and be approved by the IRB. For multicenter trials, most sites can submit a request for study closure once the sponsor has conducted the close-out visit.

The study statistician might or might not conduct the planned analyses blinded to treatment assignment. The statistician prepares results summarized in tables and figures. A formal study report is usually prepared and investigators and participants can be informed of the study's findings. The results of the study are submitted for publication and to regulatory agencies. Finally, if indicated, this is the time to plan for follow-up studies.

Other clinical research study designs

This chapter has focused on the prospective, randomized, blinded, placebo-controlled trial as the accepted highest standard of evidence to decide whether a therapeutic intervention (drug or other treatment) is efficacious in improving a specified outcome. Because of the complexity and cost of these trials, they are often not feasible, and other clinical research approaches are necessary to provide data to help determine effectiveness of an intervention, or to follow a cohort of patients with a particular condition to determine risk factors for particular outcomes. The principles of planning and conducting a randomized controlled trial are very useful when designing these types of clinical research; observational studies will be briefly described here. The reader is referred to several excellent reviews and texts summarizing the various approaches to clinical research [101–104].

Observational studies

Observational research studies include cohort, case–control, cross-sectional, and descriptive research. Depending on the nature of the study, the research could be exempt from the research regulations or require IRB approval. For research requiring IRB approval, informed consent is required unless the research qualifies for waiver of informed consent. For the research to be eligible for a waiver of consent, the research can be no more than minimal risk, it cannot violate the rights or welfare of the subjects, and it could not be practicable to conduct the research without the waiver. If the study involves additional research procedures – imaging studies, additional study visits, blood tests – it is unlikely to qualify for a waiver. If the study involves more than minimal risk, the study would be approvable only if the risks were limited to no more than a minor increase above minimal and would require two parents' signatures.

While observational studies are cheaper and faster to perform, they suffer from weaknesses. Compared to the clinical trials where assignment is based on randomization, there is no assurance that groups being compared were equivalent at baseline. Confounding variables that influence the outcome can be adjusted for but it cannot be assumed that all factors were accounted for. In addition, since blinding to treatment assignment is not present, bias can influence the investigator's assessments. It is therefore possible that differences in the populations at baseline are responsible for the differences in outcome rather than exposure to a risk factor(s). Compared to a clinical trial, it is not possible to establish, with certainty, cause and effect.

Cohort studies

A cohort study follows one or more groups of individuals over time. The groups or cohorts are defined by a risk factor or exposure – type of anesthetic, age, ASA physical status, anesthesiologist experience, etc. – rather than by treatment assignment and are then followed over time for outcome. Cohort studies can either be prospective – starting with an inception cohort in the present and followed forward in time – or retrospective where the inception cohort is defined in the past and followed up to the present or further into the future.

As an example, a cohort of neonates undergoing congenital complex open heart surgery could be divided by a risk factor of interest such as circulatory arrest versus no circulatory arrest. The cohort could be followed for a period of months to years, to assess neurodevelopmental outcome. The data collected would include demographic and clinical data, such as the details of the surgery and bypass, circulatory arrest, comorbid conditions and complications, monitoring and neuroimaging data, and anesthetic and sedative drug exposure. Outcome measures could involve information from the subject's usual clinical care or procedures performed only for the research, such as neuroimaging and neurodevelopmental outcome testing [105]. The usual method analysis of involves estimation of relative risks and their 95% confidence interval. Logistic regression can be used to simultaneously assess the association of two or more risk factors on outcome.

Just like a clinical trial, cohort studies should have defined objectives (e.g. low cerebral oxygen saturation as measured by near-infrared spectroscopy is associated with lower neurodevelopmental outcome scores at age 12 months) in a formal protocol. Cohort studies can identify possible risk factors and preliminary data that can be used to design a controlled trial of a therapeutic intervention (e.g. using a treatment algorithm for low cerebral oxygen saturation vs. standard care, and determining effect on neurodevelopmental outcome). All cohort studies should have a pre-defined analysis plan that can be as detailed as for a clinical trial [106] and the protocol should include all of the details required to meet reporting guidelines [107–109].

Another example of a prospective cohort study is the recently published APRICOT study, where 261 hospitals in 33 European countries prospectively collected very detailed adverse outcome data for a 2-week period and combined results for an analysis of over 31,000 anesthetics [110].

Case–control studies

Whereas a cohort study assigns subjects to groups based on the subject's exposure to a risk factor and then follows the subjects forward in time to identify the outcome, a case–control study starts with the outcome and moves backwards in time to identify risk factors. The choice of control group is key; an inappropriate choice can lead to spurious results [111]. Since the number of cases is usually limited, it is usual to assign more than one control to each case to increase the power of the study. Since the number of control subjects is chosen arbitrarily it is not possible to calculate relative risks. Instead, the method of analysis involves calculation of the odds ratio and its 95% confidence interval, which can approximate the relative risk when the frequency of the outcome is low.

Case–control studies can be performed rapidly but are one step further down the strength of evidence chain compared to cohort studies. However, when the strength of association is high and there is a strong physiological rationale, they can be persuasive. For example, the link between aspirin administration and Reye syndrome was established by a case–control study. A more recent example demonstrated that patients who developed bronchospasm were at a 3.3-fold risk of having received rapacuronium instead of vecuronium [112]. Notice that with a case–control study, the attribution of the risk factor to the outcome is the reverse of that for a cohort study; those

with the outcome of interest are at risk of having been exposed to the risk factor.

Database registries

In the last several decades there has been a large increase in the number of prospective single or multicenter databases relevant to pediatric anesthesia. These include adverse event registries, such as the Pediatric Perioperative Cardiac Arrest registry and Wake Up Safe registry [113,114]. Data from registries can be used to perform cohort studies and case–control studies or to provide benchmark data back to institutions.

Adverse events are identified, and along with the other data about the patient and the clinical scenario, are entered into the data collection forms. Causation for adverse events may be adjudicated by a panel of expert reviewers. Periodic analyses of these data have resulted in important new information about, for example, the higher risk of cardiac arrest in patients with congenital heart disease, the prevalence of medication errors, and the risk of hyperkalemic cardiac arrest with massive blood transfusion. Alternatively, a larger more comprehensive dataset can be collected about a population of interest with or without complications, e.g. Pediatric Regional Anesthesia Network, Congenital Cardiac Anesthesia Database [115,116]. With the considerable expense and complexity of prospective clinical trials, large databases may afford an opportunity for a "trial within a database," i.e. a hypothesis that an outcome is improved with vs. without a particular drug, allowing the data already collected to inform the study design, often at a much lower cost and with faster "enrollment" [117].

With the widespread adoption of electronic anesthesia records, automated digital data collection and submission to larger multicenter databases is possible. These "big data" sets can be analyzed for outcomes of interest, or to define the characteristics of a population, e.g. blood pressure ranges in anesthetized children [118].

Although the level of evidence for database research is not usually considered as high as for the prospective clinical trial, hypotheses can be generated for prospective studies, and the large number of patients often included in databases can at least partially overcome some of the weaknesses, such as incomplete data collection, incomplete set of variables, and not having an exact study hypothesis and primary outcome measure pre-specified when the database was designed. Additional discussion of database research is presented in Chapter 48.

Levels of evidence for clinical research studies

There are a number of schema to classify the quality or level of evidence and strength of recommendations when determining whether a particular drug or therapeutic intervention, or diagnostic test, is associated with a better outcome. One such approach is from the American Heart Association; it has been widely adopted and can provide a framework to understand the many other approaches to assessing levels of evidence, and the strength of recommendation for a particular treatment, drug, strategy, or diagnostic test [119]. The prospective, randomized, controlled trial is considered the highest level of evidence, and if there is more than one trial addressing a particular issue with the same result after a combined or meta-analysis, the evidence is considered strong for that particular intervention. Very few drugs or interventions in pediatric anesthesia have been subjected to a single, let alone multiple, randomized trials. One exception would be the recently published GAS trial comparing spinal vs. general anesthesia for infant inguinal hernia repair, and association with neurodevelopmental outcomes [120]. In this very well designed and adequately powered trial, outcomes at 2 years (the secondary outcome as the 5-year neurodevelopmental testing is primary) were almost identical, and as such a trial is unlikely to be repeated, this constitutes strong evidence for the neurodevelopmental equivalence of spinal vs. general anesthesia for a relatively short procedure. Most of the other clinical data in the field of anesthetic neurotoxicity are wholly or partly retrospective in nature, indicating a lower level of evidence for association of anesthetic exposure with lower neurodevelopmental outcomes.

Conclusion

The randomized, blinded, placebo-controlled clinical trial is the indispensable "gold standard" in determining the efficacy of therapeutics. Trials are time-consuming, maddeningly difficult, and often very expensive to perform, and can be frustrating from inception to execution to completion. However, the failure to properly perform a trial results in perpetual uncertainty. Performing a proper trial takes time to develop a protocol, create and test the data collection forms, obtain support and funding, and establish the structure for data intake and analysis. For complicated studies, it may be best to pilot the protocol before embarking on the trial. Once completed, the results of the trial must be published and made available to the public and regulatory agencies. Finally, above all else, all aspects of trial conduct must adhere to accepted ethical standards. Other study designs including prospective observational, retrospective cohort and case–control, and database research, can provide important data, although usually at a lower level of evidence than the prospective randomized controlled trial.

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 5
Development of the Cardiovascular System

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Introduction

Congenital heart disease (CHD) represents the most common birth defect, affecting approximately 1% of liveborns. The anomalies within this disease spectrum account for almost one-third of all major congenital malformations [1,2]. The etiology and mechanisms of congenital cardiovascular defects are incompletely understood [3]. Our current knowledge and understanding of the pathogenesis of CHD originates mostly from research in non-human species and progress in genomics, proteomics, transgenesis, imaging, and integrative systems biology [4].

Although cardiac anomalies have genetic and non-genetic causes, the multifactorial mode of inheritance of some defects is likely due to the interactions between several genes and modulating environmental factors [5–8]. Developmental mechanisms that may impact cardiac development include genetic and epigenetic molecular events, signaling pathways, cell migration, differentiation, proliferation, and death, and hemodynamic and contractile forces [9–15].

A segmental anatomical approach will be used in this chapter to describe the development of the cardiovascular system and demonstrate the relationships between abnormal development and specific congenital cardiac defects. It should be recognized, however, that cardiovascular development is a three-dimensional, spatiotemporal process with many elements occurring simultaneously.

Development of the cardiovascular system

Changing view of cardiac development

For many years the classic teaching in cardiac embryology was founded on the *segmental model*. It was theorized that the primordiums or earliest recognizable components of all the future cardiac segments were present in the linear heart tube [16]. The model assumed that the straight heart tube would eventually give rise to the atria, ventricles, bulbus cordis, and truncus arteriosus. Over the last several decades, however, many of these concepts have been challenged as more information has become available from scientific advancements (Fig. 5.1) [9]. Although early studies suggested that cells were added to the poles of the heart from the surrounding mesoderm [17–19], later investigations showed that cells are added to the heart after the initial stage of looping [20–22]. The current concept is that the primitive heart tube contains little more than the precursors for the left ventricle (LV) and that the precursor cells of the other cardiac components are added to both the venous and arterial poles from a second heart field outside the initial heart tube [16].

KEY POINTS: CHANGING VIEW OF CARDIAC DEVELOPMENT

- The classic concept in cardiac development that all cardiac chambers were derived from segments in the primordial heart tube has been challenged by ongoing research
- In the revised view of cardiac development it is considered that only precursors of the future left ventricle are present in the straight heart tube

Normal and abnormal cardiovascular development

During the first 2 weeks of development the human embryo relies on diffusion from the utero-placental circulation as it is lacking a heart and vascular system. At the end of the second week, the embryo is a bilaminar disk made up of the epiblast and the hypoblast (Fig. 5.2). In vertebrates, *the cardiovascular system is the first organ system to develop and function,* beginning during the third week of life. By the process of gastrulation,

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

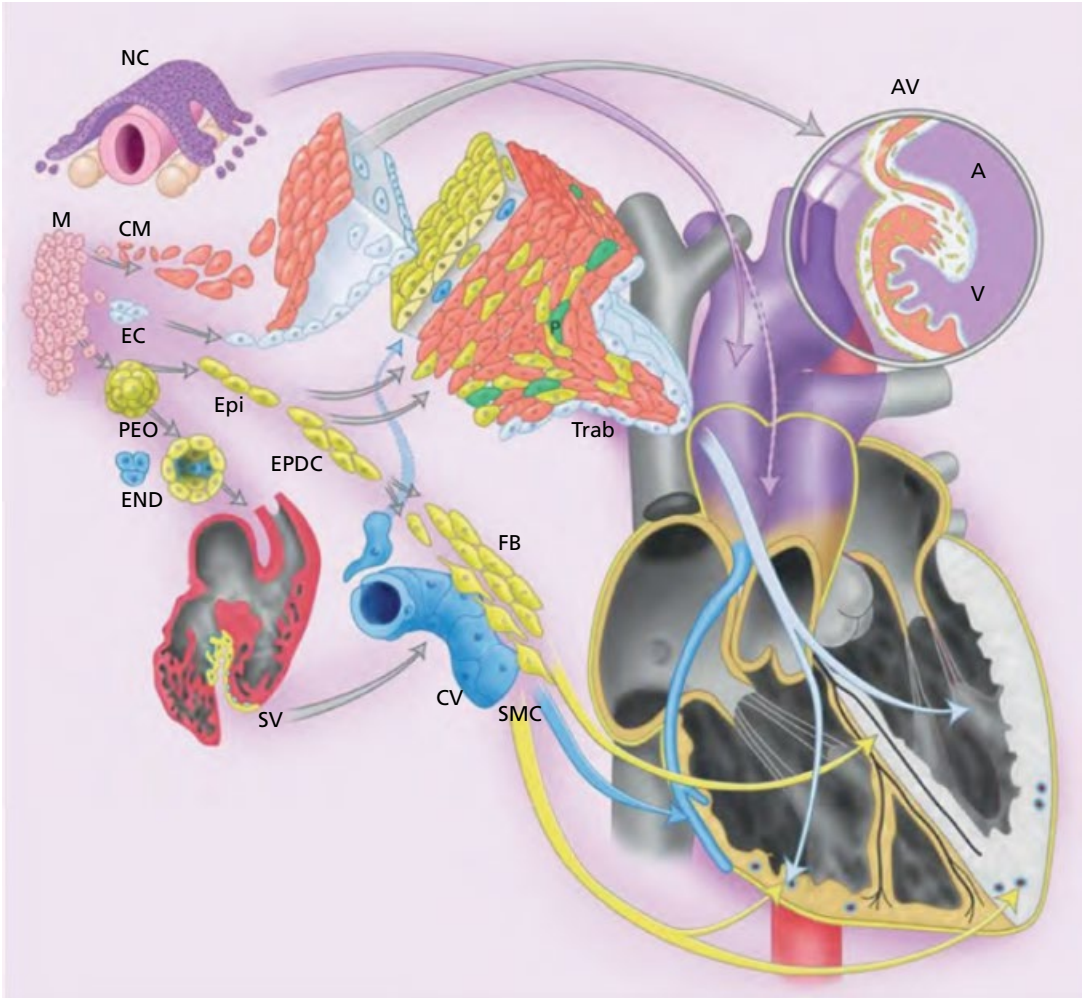

Figure 5.1 Cardiogenesis in a condensed form starts with mesoderm (pink) and neural crest (NC, purple) precursors. The primary and second heart field precursors are taken together. They develop into the cardiomyocyte (CM) line (dark pink), endocardium (EC, light blue), PEO-derived epicardium (Epi, yellow), and vascular endothelium (END, dark blue). The cardiomyocyte precursors give rise to the compact and trabeculated (Trab) myocardium of the ventricles (PHF-derived left ventricle, silver), SHF-derived right ventricle (gold), and atria (also SHF-derived, gold), including the interventricular septum (silver and gold), and part of the atrial septum (not depicted). The endocardium lining the myocardial wall at the inside gives rise to endocardial cushions, consisting of mixed cell populations (EC, NC, EPDC), and subsequently AV (inset) and semilunar valves. The cushions are also instrumental in septation processes (not depicted). The epicardium (Epi, yellow) covers the myocardial wall and develops into EPDC that differentiate into e.g. interstitial fibroblasts (FB) and coronary smooth muscle cells (SMC). EPDC probably are instrumental in induction of cardiomyocytes into peripheral Purkinje cells (P, dark green). Endothelial cells (dark blue) of the coronary system mostly arise from the sinus venosus/liver region (red), entering the subepicardial space and developing into the coronary microvascular network. At the arterial pole endothelial tubes invade the aortic wall to form the coronary ostia and become enveloped by EPDC-derived SMC to form the coronary arteries. Cardiac neural crest cells (purple) migrate around the pharynx, join the SHF, and find their way in the outflow tract and large arteries including semilunar valves, and probably also into the venous pole of the heart (not depicted). Finally, elements are depicted of the conduction system, e.g. sinus node, and bundle branches (black). A, atrium; AV, atrioventricular canal; CM, cardiomyocytes; CV, coronary vasculature; EC, endocardium; END, endothelium; EPDC, epicardial derived cells; FB, fibroblasts; M, mesoderm; NC, neural crest; P, Purkinje cell; PEO, proepicardal organ; SMC, smooth muscle cells; SV, sinus venosus; Trab, trabeculations; V, ventricle. *Source:* Reproduced from Poelmann and Gittenberger-de Groot [9] with permission of Elsevier.

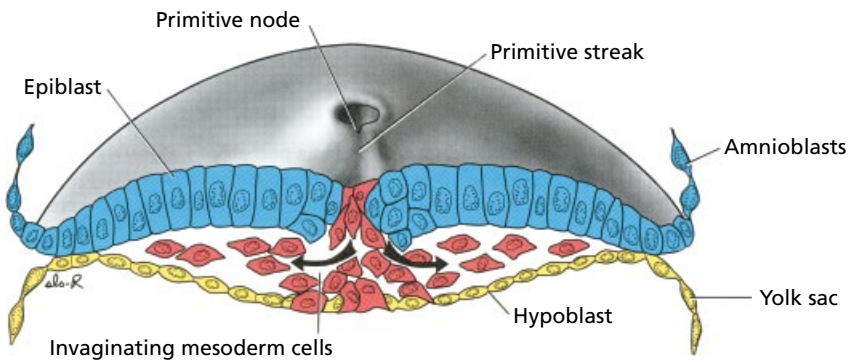

Figure 5.2 Formation of three cell layers. Cross-section through the cranial region of the primitive streak at 15 days showing invagination of epiblast cells. The first cells to move inward displace the hypoblast to create the definitive endoderm. Once definitive endoderm is established, inwardly moving epiblast forms mesoderm. *Source:* Reproduced from Sadler [33] with permission of Wolters Kluwer.

the embryo develops into a trilaminar disk, thereby establishing all three germ layers (ectoderm, mesoderm, and endoderm) [23].

Cardiogenic fields

After gastrulation, cardiac progenitor cells, located in the epiblast, migrate via the primitive streak laterally and cranially to the lateral plate mesoderm. The lateral plate mesoderm is split by the pericardial coelom into two layers: somatic (dorsal) mesoderm and splanchnic (ventral) mesoderm (Fig. 5.3). Cells in the somatic mesoderm will give rise to the pericardium, while cells in the splanchnic mesoderm form the bilateral *cardiogenic* or *heart fields* that will give rise to the myocardium [24]. The cardiogenic fields fuse in the midline to form the *cardiac crescent* (Fig. 5.4A and B). At least two distinct lineages of cells are present within the cardiac crescent: one referred to as the "*first (or primary) heart field*" (FHF), and the other as the "*second heart field*" (SHF) [12]. The FHF will give rise to the linear heart tube, and cells from the SHF will contribute at the inflow (venous) and outflow (arterial) poles during cardiac looping. As discussed later in the chapter, *the embryonic cells that contribute to cardiac development arise not only from the mesoderm in the heart fields but also from cardiac neural crest* [25] *and the proepicardium* [26].

KEY POINTS: CARDIOGENIC FIELDS

- Myocardial cells are derived from the bilateral cardiogenic or heart fields in the splanchnic mesoderm
- The cardiogenic fields merge to form a cardiac crescent, giving rise to two cell lineages, also known as first and second heart fields
- Cells contributing to cardiac development originate from heart field mesoderm, cardiac neural crest, and the proepicardium

Heart tube

The primitive heart tube is formed at the beginning of the fourth week of development. As the embryo folds, the lateral portions of the cardiac crescent come close together, forming the ventral aspect of the heart tube [27] (Fig. 5.4 C–G). The medial portions of the cardiac crescent form the dorsal part of the heart tube, suspended from the foregut by the dorsal mesocardium. The heart tube has two caudolateral inlets (venous pole) and one craniomedial outlet (arterial pole) [27,28]. It should be noted that the schematic drawings in embryology educational resources illustrating the presence of all cardiac segments in the primitive heart tube represent hypothetical constructions as most of the segments are added to the linear heart tube during the stages of cardiac looping [29].

The initial heart tube consists of an inner endocardial layer, a middle layer of cardiac jelly, and an outer myocardial layer. The *endocardium* is composed of a specialized endothelial cell type derived from the splanchnic mesoderm and develops simultaneously with the myocardium in the cardiac crescent. The *myocardium* is considered primitive or primary because the myocytes of the heart tube have few contractile elements, a poorly developed sarcoplasmic reticulum, a low density of gap junctions, and high automaticity [16].

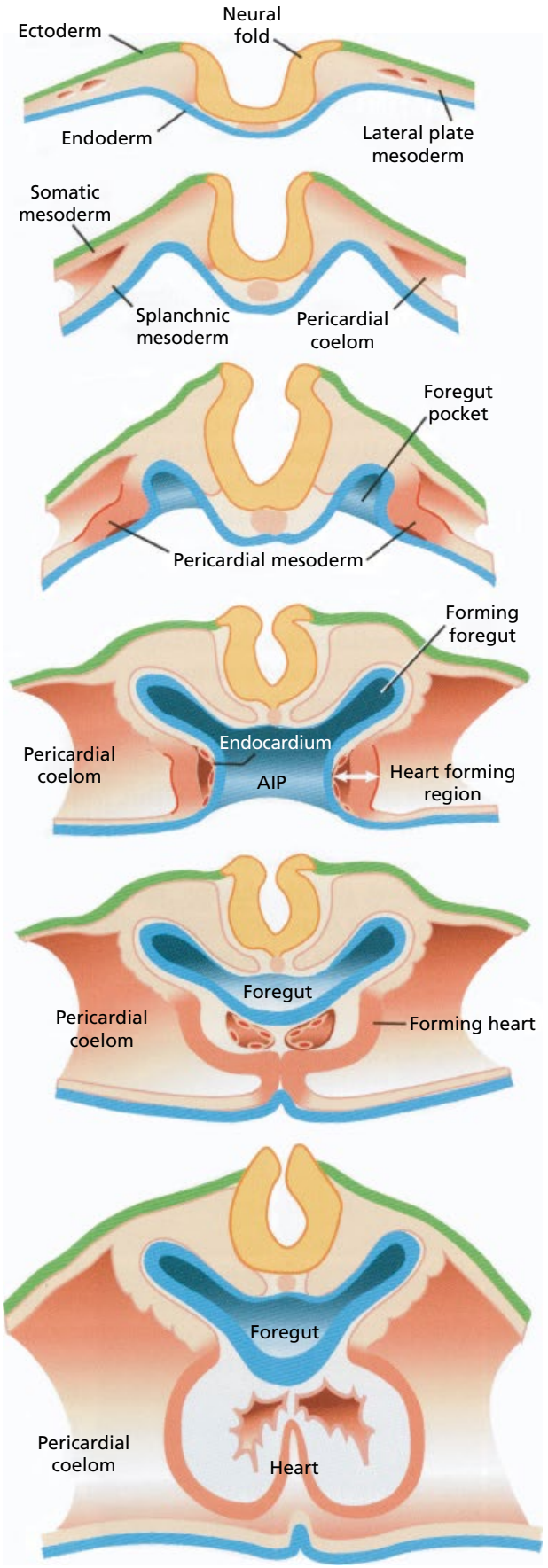

Figure 5.3 Diagrammatic representation of the formation of the heart, foregut pocket, and coelom in the chick embryo. *Source:* Reproduced from Kirby [34] with permission of Oxford University Press.

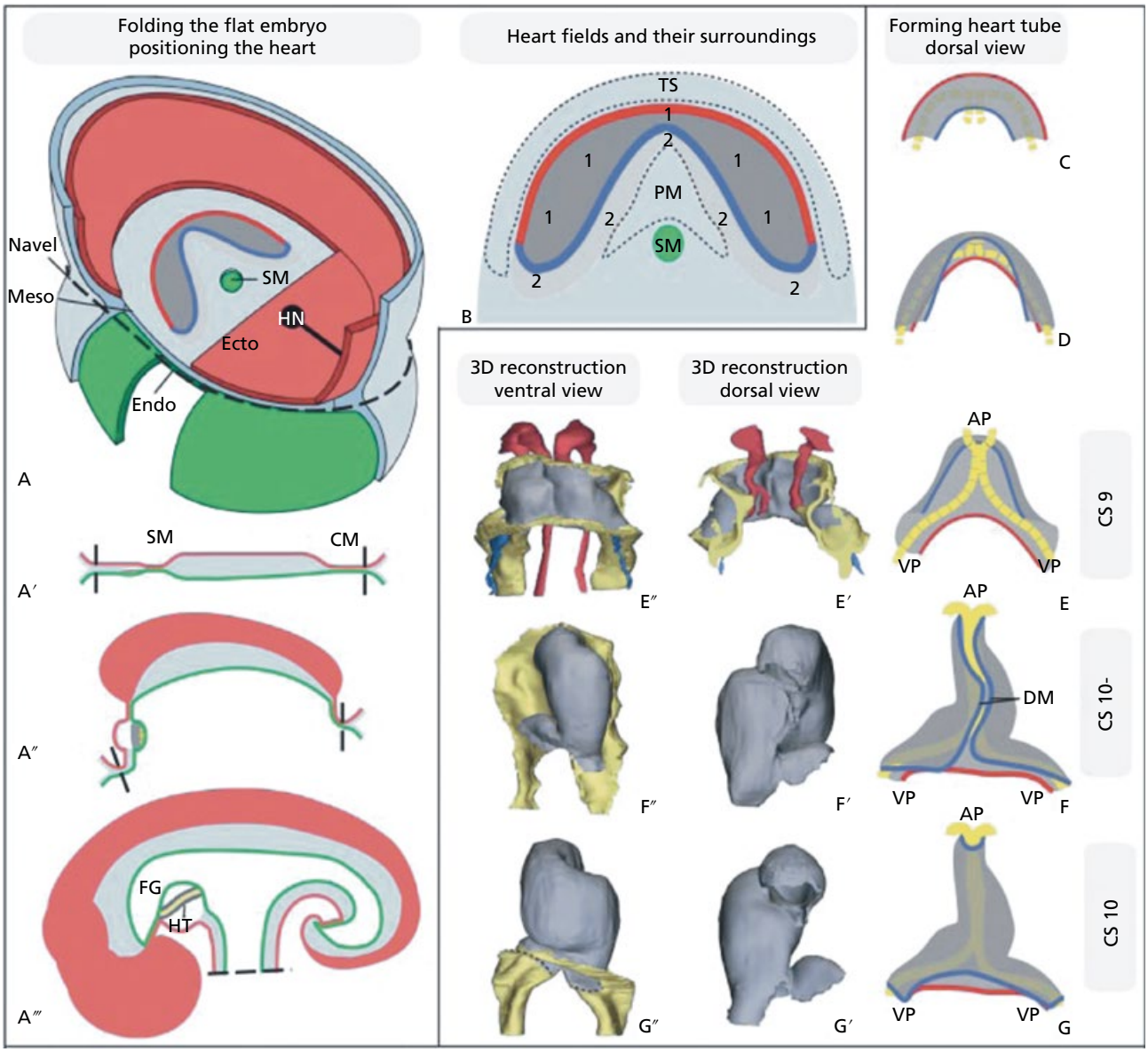

Figure 5.4 Folding of the embryo and formation of the heart tube. (A) The embryo starts as a flat disc containing the three germ layers, the ectoderm (Ecto), mesoderm (Meso), and endoderm (Endo). (A–A‴) With ongoing folding of the embryo the embryonic gut that runs from the stomatopharyngeal membrane (SM) to the cloacal membrane (CM) is formed. The heart (HT) becomes positioned ventrally to the foregut (FG), caudally to the head, and cranially to the umbilical cord and transverse septum (TS). HN, Hensen's node or primitive node. (B) Division of the heart-forming field into the first heart field (1), which will give rise to the linear heart tube, and the second heart field (2), which will remain in continuity with the first heart field during subsequent development and from which cardiomyocytes are added to the developing heart. In reality, the strict borders drawn here are gradual. PM, pharyngeal mesoderm. (C–G) Formation of the heart tube from a flat horseshoe-shaped cardiac crescent to a tube. Folding of the embryo brings the lateral portions of the cardiac crescent (red line) together to form the ventral part of the heart tube, while the medial portions of the cardiac crescent (blue line) will form the dorsal part of the heart tube, which is suspended from the foregut by the dorsal mesocardium (DM). After the DM closes and the suspension from the foregut is lost, cells of the second heart field can only be added to the heart via the arterial and venous poles (AP and VP). *Source:* Reproduced from Sylva et al [27] with permission of John Wiley and Sons.

Cardiac contractions begin around the third week of gestation in the human, and circulation through the embryo begins shortly thereafter. Given that the highest automaticity is found at the venous pole of the heart tube, a slow peristaltic contraction propels the blood from the venous to the arterial pole (unidirectional flow).

Abnormalities of heart tube formation

Failure of the heart tube to develop (*acardia*) results in fetal demise.

KEY POINTS: FORMATION OF THE HEART TUBE

- The primitive heart tube forms at the beginning of the fourth week of development
- Contractile activity commences and circulation through the embryo begins with formation of the heart tube
- Failure of the heart tube to develop results in fetal demise

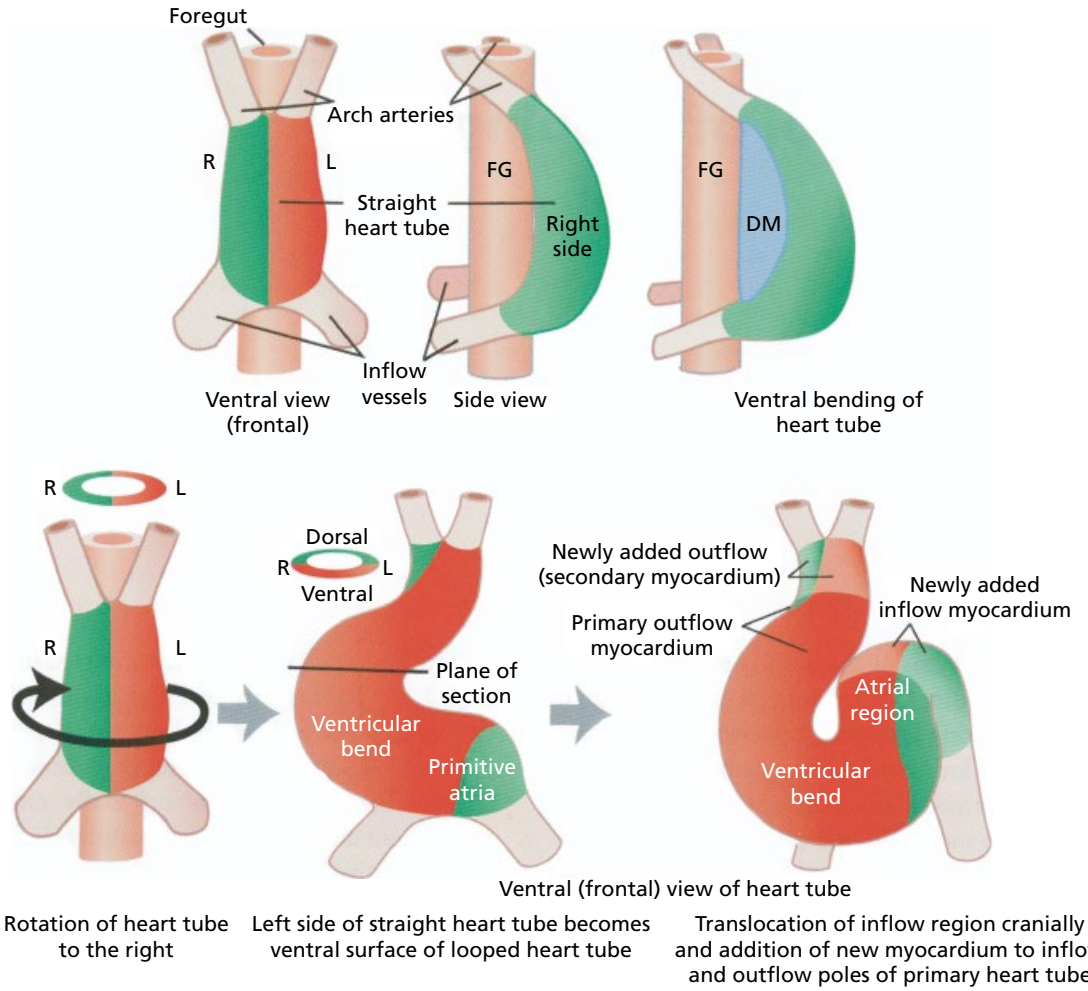

Figure 5.5 Steps in looping of the heart tube. The heart tube forms ventral to the foregut and is open to it at first. Then the heart tube is suspended at its nascent inner curvature from the ventral foregut by the dorsal mesocardium which quickly disappears. Ventral bending occurs first, followed by rotation to the right which brings the left side of the tube to the front and the inner curvature to the left side. Subsequent looping to form the S-shaped loop involves addition of cells at the inflow and outflow poles. DM, dorsal mesocardium; FG, foregut. *Source:* Reproduced from Kirby [34] with permission of Oxford University Press.

Cardiac looping

Cardiac loop formation brings the linear configuration of the primitive heart tube into the correct conformation for chamber specification, septation, and the creation of systemic and pulmonary pathways [29,30]. *The heart is not only the first organ to function, but it is also the first to develop a bilateral asymmetrical form through the process of looping*.

Cardiac looping begins with ventral bending and the loss of the dorsal mesocardium which, as described, suspends the heart tube from the foregut; this is followed by rotation to the right along a craniocaudal axis (*dextro- or D-looping*), bringing the left side of the tube to the front and the inner curvature to the left. These changes transform the straight heart tube into a C-shaped loop (Fig. 5.5) [29]. Subsequent conformational changes result in a two-dimensional, S-shaped loop. When looping is complete, the segments of the heart might be referred to (extremely variable between authors) as the sinus venosus, common atrium, atrioventricular canal (AVC), presumptive LV, presumptive right ventricle (RV), conus arteriosus, and truncus arteriosus (frequently referred to as the conotruncus) [31].

In the normal heart, cardiac looping to the right (*D-loop)* positions the RV towards the right side (Fig. 5.6, left panel) and leaves the heart lying predominantly in the left hemithorax with a leftward apex (*levocardia*). The normal heart is characterized by visceroatrial *situs solitus*, referring to the usual position of the thoraco-abdominal organs and the atria, as well as D-loop ventricles as described.

Abnormalities of cardiac looping

Abnormalities in left-right patterning are associated with cardiac malformations in both D- and L-loop hearts, as seen for example in heterotaxy syndromes, atrial isomerism, mirror image arrangements, and discordant connections [32].

Rotation of the heart tube around the craniocaudal axis to the left, instead of the right, results in a *levo-loop (L-loop)* heart (Fig. 5.6, right panel). In this setting, the RV is positioned towards the left side relative to the LV which is located towards the right.

Congenitally corrected transposition of the great arteries (CCTGA) results when the atria and outflow receive correct left-right signals but the ventricular segment loops abnormally to the left (L-loop ventricles), resulting in discordant atrioventricular (AV) and ventriculoarterial (VA) connections. This can be found within the context of visceroatrial situs

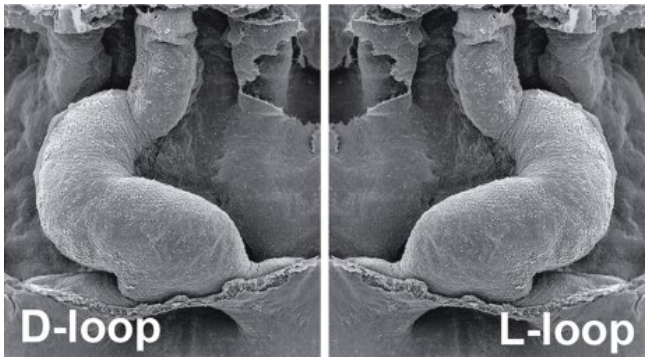

Figure 5.6 Handedness of the cardiac loop. Scanning electron micrographs of embryonic chick hearts, viewed from the front, showing the so-called D-loop (dextral-loop) and L-loop (levo-loop) configurations ("C-shaped" loops; HH-stage 12). *Source:* Reproduced from Männer [114] with permission of Elsevier.

solitus or in *situs inversus* where there is mirror-image reversal of organs such as the liver, stomach, and spleen.

In *dextrocardia* the heart lies predominantly in the right hemithorax, usually with a rightward pointing apex, while *mesocardia* refers to a midline heart with the apex pointing inferiorly or anteriorly. Mesocardia and dextrocardia can be associated with normal or abnormal arrangement of cardiac structures. *Atrial isomerism* refers to a bilaterally symmetrical pattern of the atrial appendages (i.e. bilateral left or right sidedness) and is usually associated with complex cardiac malformations [30]. *Mixed situs* occurs when some organs, or components thereof, have normal situs and others have situs inversus. This usually results in complex heart disease referred to as *heterotaxia* or *heterotaxy* syndromes.

KEY POINTS: CARDIAC LOOPING

- The heart is the first functional organ to develop in the embryo
- Looping represents a crucial process in cardiac morphogenesis that determines the shape of the heart and results in right-left asymmetry in the embryo
- Dextro- or D-looping refers to normal cardiac looping to the right; abnormal looping to the left results in levo- or L-looping

Cardiac septation

After looping of the heart tube cardiac septation occurs and consists of various processes that begin in the fourth week and continue into the seventh week of gestation [27]. These events divide the heart into four chambers and create separate systemic and pulmonary circulations [33].

Atrial septation

Atrial septation takes place in phases to maintain necessary atrial right-to-left shunting in the fetal heart. The *primary atrial septum*, known as the septum primum, emerges from the roof of the atrium and gradually extends inferiorly towards the endocardial cushions in the AV junction (Fig. 5.7) [34]. The leading edge is covered by a mesenchymal cap that is continuous with the dorsal mesenchymal protrusion. The communication between the leading edge of the septum primum and the AV cushions is known as the *primary atrial foramen* (ostium primum). This foramen closes when the septum primum becomes contiguous with the fused AV endocardial cushions. Communication between the left and right atria is maintained by the detachment of the septum primum from the roof of the atrial cavity to produce a secondary atrial foramen (ostium secundum) [35]. The *secondary atrial septum* (septum secundum) originates by folding of the dorsal wall between the primary atrial septum and the left leaflet of the sinoatrial valve. The foramen ovale arises because the septum secundum is crescent-shaped and does not form a complete partition of the atrial cavity. This structure acts as a one-way valve in fetal life, allowing the better-oxygenated blood from the inferior vena cava to course from the right atrium (RA) into the left atrium (LA).

The *venous pole* of the heart has two channels early in development, the left and right horns of the sinus venosus, which return blood from the embryo (via the cardinal, vitelline, and umbilical veins) to the sinus venosus and common atrium. The sinus venosus, including its right horn, and the sinoatrial junction become incorporated into the dorsal (back) wall of the RA (Fig. 5.8). The left horn of the sinus venosus is incorporated into the developing AV groove to become the coronary sinus. The dorsal (back) wall of the LA is also formed by incorporation of the pulmonary vein and its surrounding myocardium [34,36].

Defects in atrial septation

A *secundum atrial septal defect* (ASD) is the most common communication resulting in an atrial level shunt. The defect is located within the region of the fossa ovalis and in most cases is due to a deficiency of the septum primum [37].

A *patent foramen ovale* (PFO) represents failure of complete fusion of the septum primum and septum secundum. The foramen remains functionally closed if the flap valve is large enough and the LA pressure exceeds the RA pressure (probe-patent foramen).

An *ostium primum ASD* results from failure of the septum primum to fuse with the endocardial cushions. The defect extends from the inferior limbus of the fossa ovalis to the crest of the interventricular septum. This type of defect is part of the spectrum of AVC defects, also referred to as AV septal and endocardial cushion defects, and may occur in isolation or in association with other abnormalities of the AV junction.

A *sinus venosus ASD* occurs in the area derived from the embryological sinus venosus (posterior aspect of the RA) and represents an interatrial communication associated with anomalous entry of the right pulmonary veins to the heart [38]. The most common defect is the superior vena cava type located between the cardiac end of the superior vena cava and the right upper pulmonary vein. Less commonly, an inferior vena cava type can be found where the more caudal atrial wall is involved at the entrance of the right lower and/or middle pulmonary veins [37].

A *coronary sinus ASD* occurs when the tissue between the coronary sinus and the LA is either partially or completely absent (unroofed), resulting in a communication between the atria via the coronary sinus orifice.

A *common atrium* is caused by the absence of the septum primum, septum secundum, and atrial portion of the AVC septum, and is usually associated with heterotaxy syndrome [37].

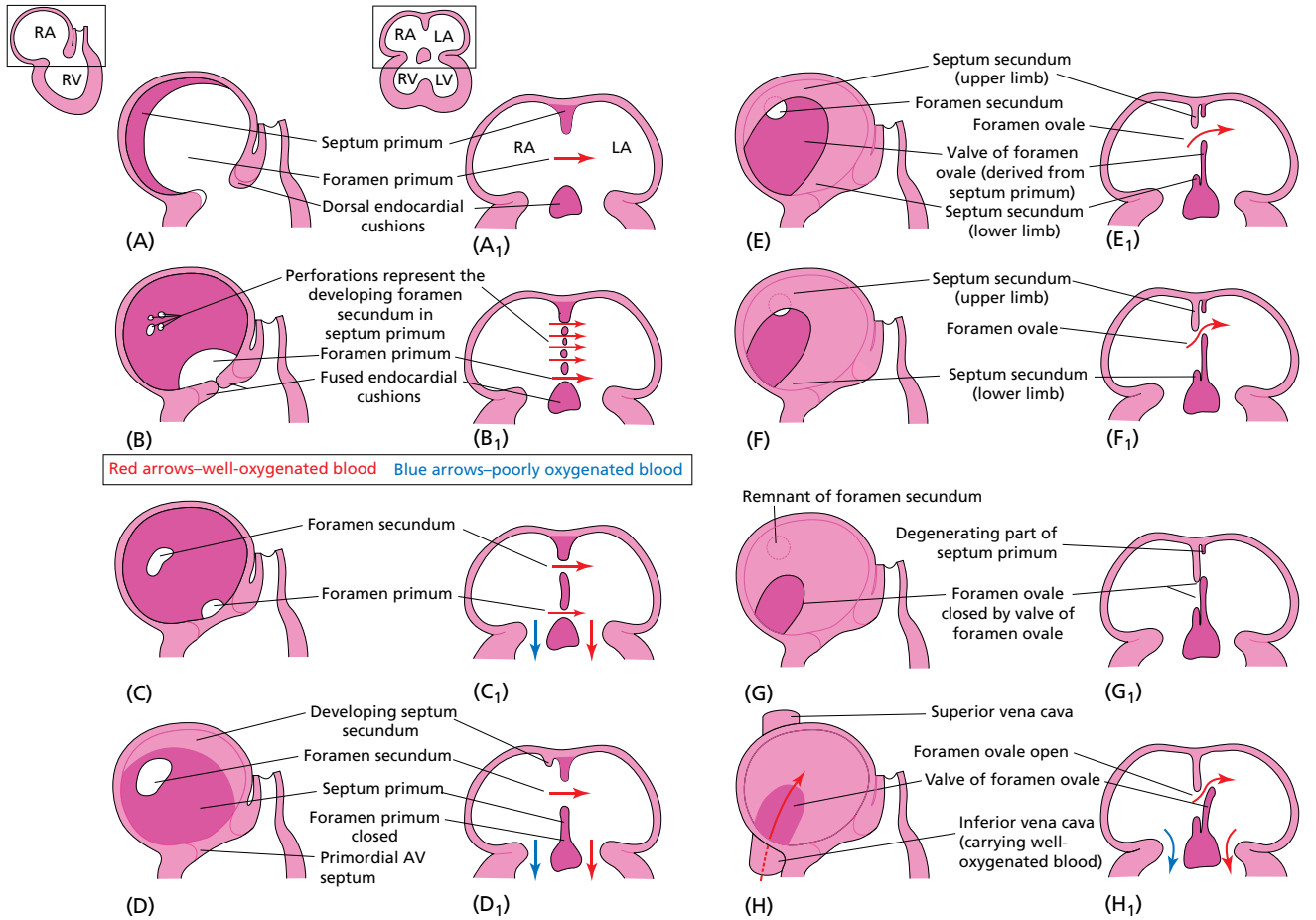

Figure 5.7 Atrial septation. Diagrammatic sketches illustrating progressive stages in partitioning of the primordial atrium. (A–H) Sketches of the developing interatrial septum as viewed from the right side. (A1–H1) Coronal sections of the developing interatrial septum. Note that as the septum secundum grows, it overlaps the opening in the septum primum, the foramen secundum. Observe the valve of the foramen ovale in G1 and H1. When pressure in the right atrium (RA) exceeds that in the left atrium (LA), blood passes from the right to the left side of the heart. When the pressures are equal or higher in the left atrium, the valve closes the foramen ovale (G1). AV, atrioventricular; LV, left ventricle; RV, right ventricle. *Source:* Reproduced from Moore et al [115] with permission of Elsevier.

Ventricular septation

After looping of the heart tube, differentiation and re-initiation of cell division by the primary myocardium of the outer curvature causes the ventricles to expand caudally in a pouch-like fashion on either side of the bulboventricular groove (Fig. 5.9). Disappearance of the cardiac jelly results in the formation of trabeculations on the luminal side, producing a spongy-type myocardium. The myocardium becomes compacted when epicardially-derived fibroblasts infiltrate the epicardial side, at which time proliferation in the trabeculations ceases.

Ventricular septation begins in the fifth week and continues into the seventh week of gestation [27]. The *muscular* portion of the interventricular septum is formed by apposition and merging of the medial walls of the expanding ventricles, with cells added mainly from the adjacent LV free wall [27,33]. The space between the free rim of the muscular septum and the fused AV cushions is the *primary interventricular foramen*. Although the primary interventricular foramen allows for communication between the primitive ventricles, initially, blood from the primitive atrium can only reach the primitive RV via the interventricular foramen. It is only after the AV junction develops that the RA will communicate directly with the RV. Closure of the interventricular foramen occurs by fusion of the superior and inferior endocardial cushions, the muscular interventricular septum, and the endocardial cushions of the outflow tract (conal cushions). The site of fusion represents the *membranous* portion of the ventricular septum.

Defects in ventricular septation

Ventricular septal defects (VSDs) can be found in isolation or can coexist with other congenital cardiovascular malformations. These can result from a deficiency of one or more structures, namely the components of the ventricular septum (muscular, AVC endocardial cushion, and outflow tract (conal) cushion), and/or from their malalignment.

Muscular VSDs, the most common types, are those that occur in the *muscular* portion of the interventricular septum. These defects are completely surrounded by a muscular rim. They can be multiple and can be located anywhere along the muscular trabecular septum.

The *membranous* portion of the ventricular septum is adjacent to the anteroseptal commissure of the tricuspid valve (TV) and below the non-coronary leaflet of the aortic valve (AoV). Small defects can close spontaneously by surrounding aneurysmal fibrous tissue. Defects that extend beyond the

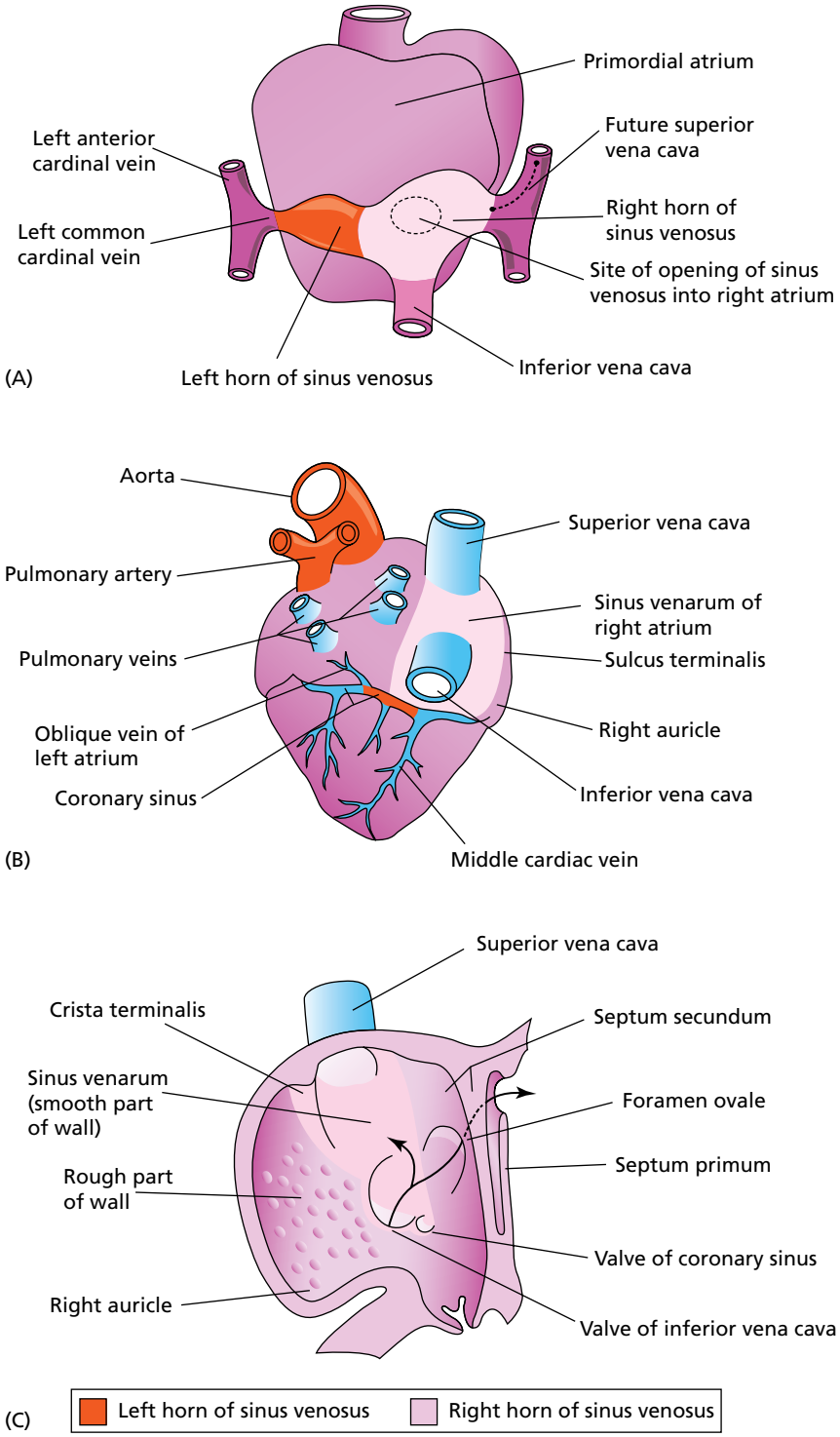

Figure 5.8 Fate of the sinus venosus. (A) Dorsal view of the heart (approximately 26 days) showing the primordial atrium and sinus venosus. (B) Dorsal view at 8 weeks after incorporation of the right horn of the sinus venosus into the right atrium. The left horn of the sinus horn becomes the coronary sinus. (C) Internal view of the fetal right atrium showing: (1) the smooth part of the wall of the right atrium (sinus venarum) derived from the right horn of the sinus venosus and (2) the crista terminalis and valves of the inferior vena cava and coronary sinus that are derived from the right sinuatrial valve. The primordial right atrium becomes the right auricle, a conical muscular pouch. The *arrows* indicate the flow of blood. *Source:* Reproduced from Moore et al [115] with permission of Elsevier.

region of the membranous septum are called *para- or perimembranous VSDs*.

A *conoventricular* or *subaortic VSD* is situated between the conal and muscular portions of the ventricular septum [39]. These defects are often related to malalignment of the muscular and conal regions of the ventricular septum.

A *subpulmonary, conal, supracristal*, or *doubly committed subarterial VSD* is located in the outflow tract (conal septum) just underneath the pulmonary valve (PV). The AoV can prolapse into the defect resulting in aortic regurgitation.

A defect that opens to the *inlet* portion of the RV can be perimembranous, muscular, or AVC-type [40]. The location of

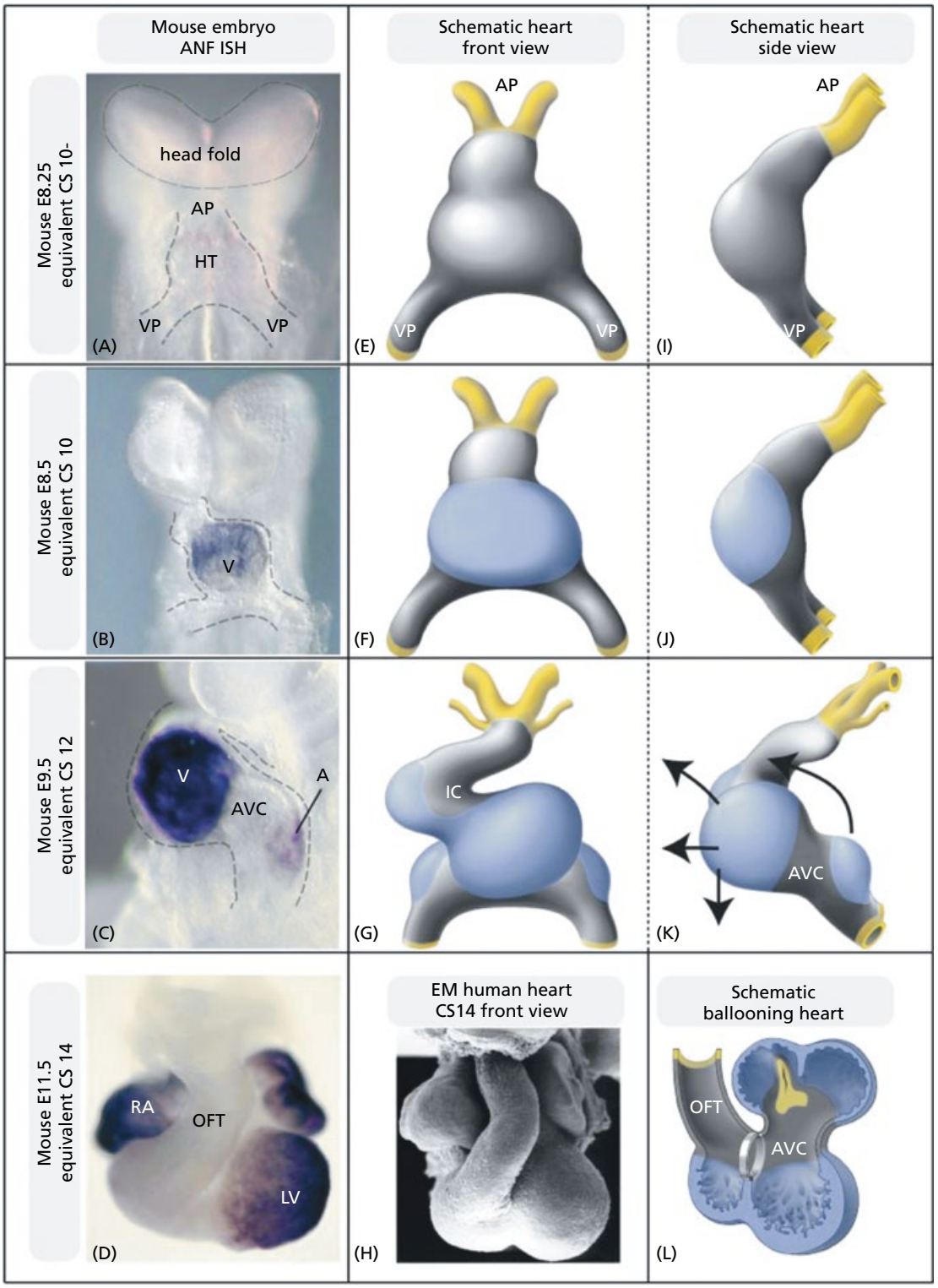

Figure 5.9 Formation of the cardiac chambers. (A–D) Developmental series of mouse embryos. Whole mount RNA *in situ* hybridization for the embryonic chamber marker atrial natriuretic factor (ANF) is used as a marker for differentiation into chamber myocardium. (E–G and I–L) Schematic drawings of these chamber-forming hearts. Gray, primary myocardium; blue, chamber-forming myocardium; arrows in K indicate the expansion of the chambers eventually leading to the adult configuration, with the ventricles positioned ventro-caudally to the atria. (H) Electron micrograph of a CS14 human heart, demonstrating the similarity with the mouse E11.5 heart and the schematic shown in (L). For didactic purposes, in the schematic in (L), the outflow tract is hinged toward the right side; ***in vivo*** it is positioned ventrally to the heart, as depicted in (D) and (H). (A, E, and I) The heart tube (HT) consists solely of primary myocardium from venous (VP) to arterial pole (AP). (B, F, and J) The first chamber to start ballooning is the embryonic ventricle (V) at the outer curvature of the heart. (C, G, and K) The heart tube has started to loop and acquire an S shape. An embryonic left and right ventricle are now visible. The atria (A) also start to balloon towards the left and right side. The myocardium of the outflow tract (OFT), inner curvature (IC), and atrioventricular canal (AVC) remains as primary myocardium. RA, right atrium; LV, left ventricle. Equivalent Carnegie stage (CS) noted on left margin of figures. *Source:* Reproduced with permission from Sylva et al [27] with permission of John Wiley and Sons.

the AV node and the course of the bundle of His differ for these types of VSDs, having implications for surgical repair.

A *common* or *single* ventricle, characterized by the presence of two AV valves with one ventricular chamber or a large dominant ventricle with a diminutive or hypoplastic opposing ventricle, can result from different mechanisms. The pathology can be due to the arrest of or a defect in interventricular septation or poor alignment of the common AV valve with the ventricles [41]. A wide spectrum of functional single ventricles is recognized.

Septation of the atrioventricular canal and development of the atrioventricular valves

The endocardial cushions arise from cells of the endocardium that undergo endocardial-to-mesenchymal transformation [42]. The endocardial cushions and underlying myocardium prevent the backflow of blood prior to valve formation. Central fusion of the inferior and superior cushions forms the AV septum, thereby separating the AVC into the left (mitral) and right (tricuspid) components [43]. The *atrial portion of the AV septum* extends from the primary atrial septum to the level of the valve annuli, whereas the *ventricular portion of the AV septum* extends from the level of the valve annuli to the muscular component and forms the inlet portion of the interventricular septum.

The AV valves and subvalvar apparatus are formed by cavitation and remodeling of the cushions and excavation of the underlying ventricular myocardium to form leaflets and chordal structures (Fig. 5.10) [44,45]. The primitive leaflets undergo lengthening and delamination with the disappearance of the myocardial layer late in development.

After fusion of the endocardial cushions, the fibroblast-like cells of the cushions are replaced by myocardial cells in a process called myocardialization. Fusion of the non-myocardial mesenchymal cushions and myocardialization create portions of the atrial septum, ventricular septum, and conal septum, as well as the substrate for the crux of the heart [46].

Defects of the atrioventricular canal and the atrioventricular valves

Abnormalities in the structures derived from the endocardial cushions can produce a spectrum of malformations referred to as endocardial cushion defects (as previously noted, they are also termed AVC or AV septal defects).

An isolated *cleft in the anterior mitral valve (MV) leaflet represents the mildest form of pathology*. An *ostium primum ASD* is the result of incomplete fusion of the septum primum with the superior endocardial cushion, and is frequently associated with a MV cleft. The combination of these defects is referred to as a *partial AVC defect*. An *inlet* or *AVC-type* VSD occurs when the inferior endocardial cushion does not fuse with the muscular component of the ventricular septum. A *transitional AVC defect* consists of an ostium primum ASD with a very small to moderate (restrictive) inlet VSD, often occluded by AV valve tissue. A *complete AV canal defect (CAVC)* comprises an ostium primum ASD, an inlet VSD, and a common AV valve. In an *unbalanced CAVC defect*, usually one ventricle is hypoplastic and the other receives most of the AV valve tissue. Approximately 40% of patients with trisomy 21 (Down syndrome) have AVC defects [45].

Ebstein anomaly is characterized by displacement of the septal and posterior TV leaflets into the RV. This anomaly is considered the most important cause of congenital tricuspid regurgitation. The pathology is thought to be due to abnormal delamination of the inlet portion of the RV [47]. The portion of the RV that extends from the true TV annulus to the level where the septal and posterior leaflets attach is thin due to partial absence of myocardium and termed the "atrialized" portion, whereas the trabecular and outlet portions make up the functional RV.

Tricuspid atresia is characterized by agenesis of the TV and associated RV hypoplasia. The pathology can be found within the context of normally related great arteries or transposition of the great arteries, and with an intact ventricular septum or a VSD. Isolated *tricuspid stenosis* is exceedingly rare.

Mitral stenosis is commonly associated with other left-sided obstructive lesions. The disease spectrum of the obstructive pathology is quite variable. *Congenital mitral regurgitation* is more common than mitral stenosis.

Septation of the outflow tract and development of the semilunar valves

Cardiac neural crest cells are critical for normal cardiovascular development [25]. These cells contribute to outflow tract septation, semilunar valvulogenesis, development of cardiac neuronal tissue, insulation of the cardiac conduction system, and remodeling of the aortic arch arteries [48].

The outflow tract has been traditionally divided into three sections: the conus (proximal), the truncus (middle), and the aortic sac (distal) [49]. Outflow tract septation begins with the formation of a shelf of mesenchyme (the aorticopulmonary septum) in the dorsal wall of the aortic sac in the area between the fourth and sixth pairs of aortic arch arteries [50]. This shelf elongates towards the truncus, thereby dividing the lumen of the aortic sac into the future portions of the aorta and pulmonary trunk. Cardiac neural crest cells migrate into the pharyngeal arches (arches 3, 4, and 6) and a subset of these cells migrates into the outflow tract (Fig. 5.11). The outflow endocardial cushions are ridges of mesenchyme, formed by endocardial-to-mesenchymal transformation of the underlying endocardium, that spiral into the outflow tract. Mesenchymal cells from the pharynx, followed by neural crest cells, invade the truncal cushions to form two centrally placed columns or prongs (Fig. 5.12) [51]. These prongs eventually fuse with the conal cushions proximally and the aorticopulmonary septum distally. Rotation of the developing PV is associated with spiraling of the aorticopulmonary septum and prongs in such a fashion that the developing aorta will connect with the rightward and cranial component of the aortic sac and the developing pulmonary trunk will connect with the leftward and caudal component of the aortic sac [52].

The convergence of the inflow and outflow poles during cardiac looping, combined with the processes of rotation and wedging, brings the atria and outflow vessels into appropriate alignment with the AV valves and ventricles (Fig. 5.13) [49,51]. In the conus, myocardial cells invade the cushions, which then bulge further into the lumen and subsequently meet and fuse in the midline. These conal cushions fuse most proximally with the AV cushion tissue and the crest of the muscular ventricular septum.

Early in development, both a subpulmonary conus and a subaortic conus can be found above the RV. Subsequent regression and shortening cause the AoV to sink inferiorly

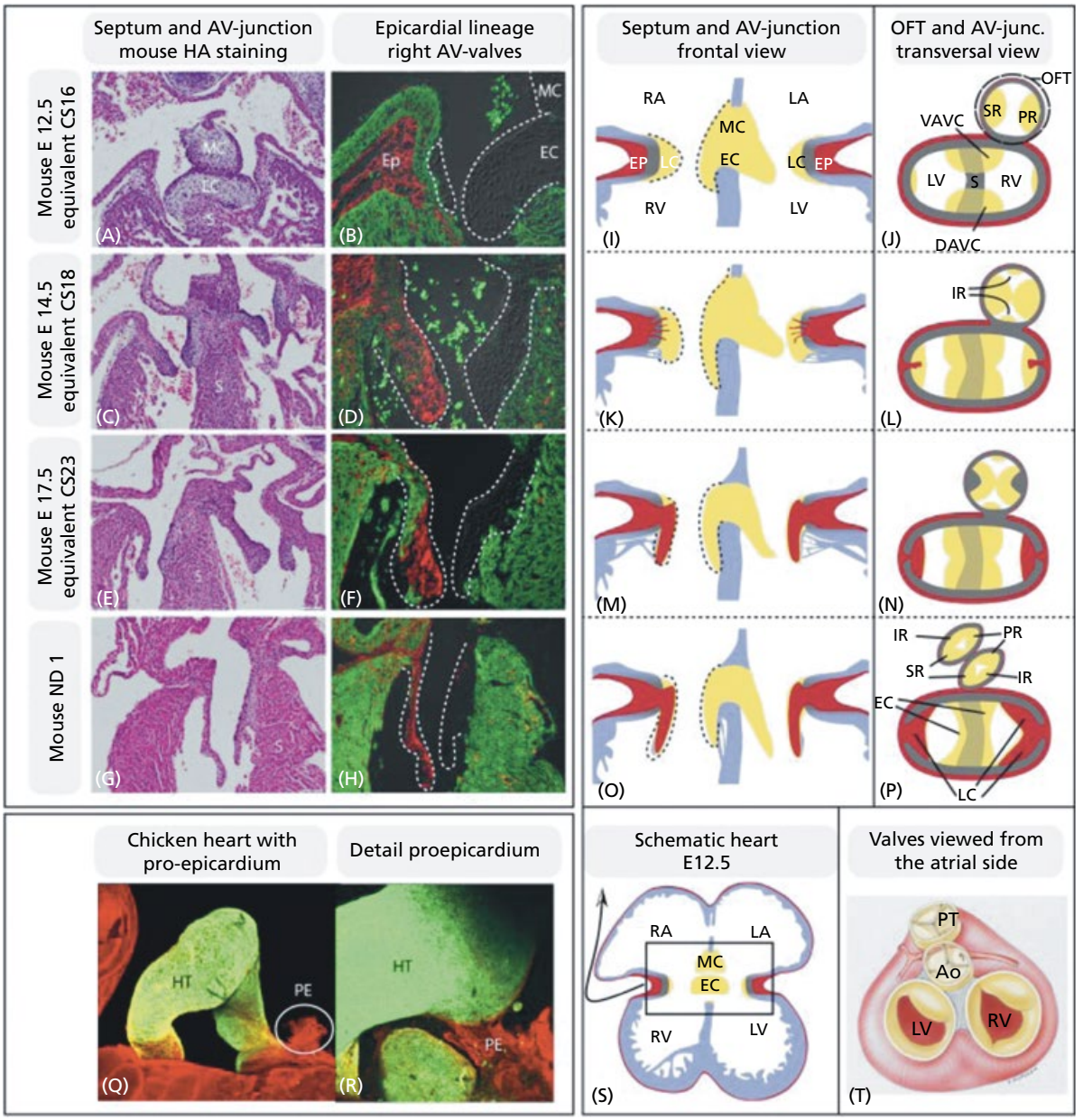

Figure 5.10 Development of the atrioventricular (AV) and outflow tract (OFT) valves and their contributing tissues. (A–H) Sections through mouse hearts in a plane comparable to the schematic heart in (S). (B, D, F, and H) The lineage contributions of the epicardium are displayed at different developmental stages. The epicardial lineage marker WT1 was used; epicardial lineage is depicted in red, myocardium in green. (I–P) Schematic drawings of valve development in both the atrioventricular canal and outflow tract. Red, epicardium (Ep); gray, primary myocardium; and yellow, endocardial cushion tissue (EC). Note that in the outflow tract the cells are primarily neural crest derived and not endocardial derived as in the atrioventricular canal. (P) The contribution of the different cushions and ridges to the eventual valves (T) is depicted. (Q and R) The proepicardium (PE) in a 3-day-old chick embryo. (R) The PE is attached to the heart tube (HT) and spreading out to form the epicardium. Ao, aorta; DAVC, dorsal AV cushion; IR, intercalated ridge; LA, left atrium; LC, lateral cushion; LV, left ventricle; MC, mesenchymal cap; PR, parietal ridge; PT, pulmonary trunk; RA, right atrium; RV, right ventricle; S, septum; SR, septal ridge; VAVC, ventral AV cushion. Equivalent Carnegie stage (CS) noted on left margin of figures. *Source:* Reproduced from Sylva et al [27] with permission of John Wiley and Sons.

and posteriorly so that it comes to lie directly over the LV and in fibrous continuity with the MV [53]. The transition from the primitive, single in-series circulation to the double in-series circulation begins during the fifth week of development.

After outflow tract septation, the semilunar valves are formed as the mesenchyme in the outflow cushions is remodeled into the trileaflet aortic and pulmonary valves. Cells from the endocardium are the primary source of semilunar and AV valve fibroblasts, but fibroblasts derived from the epicardium also contribute to valve formation [50]. Although neural crest cells are found in the tips of the leaflets, their contribution to valve formation is not completely understood.

Abnormalities of outflow tract septation

The loss or dysfunction of cardiac neural crest cells produces a wide spectrum of conotruncal abnormalities that are associated with syndromes linking defects in the heart, face, thymus, parathyroids, and brain [49,51]. These include 22q11 deletion syndromes, such as DiGeorge and velocardiofacial syndromes, CHARGE syndrome, fetal alcohol syndrome,

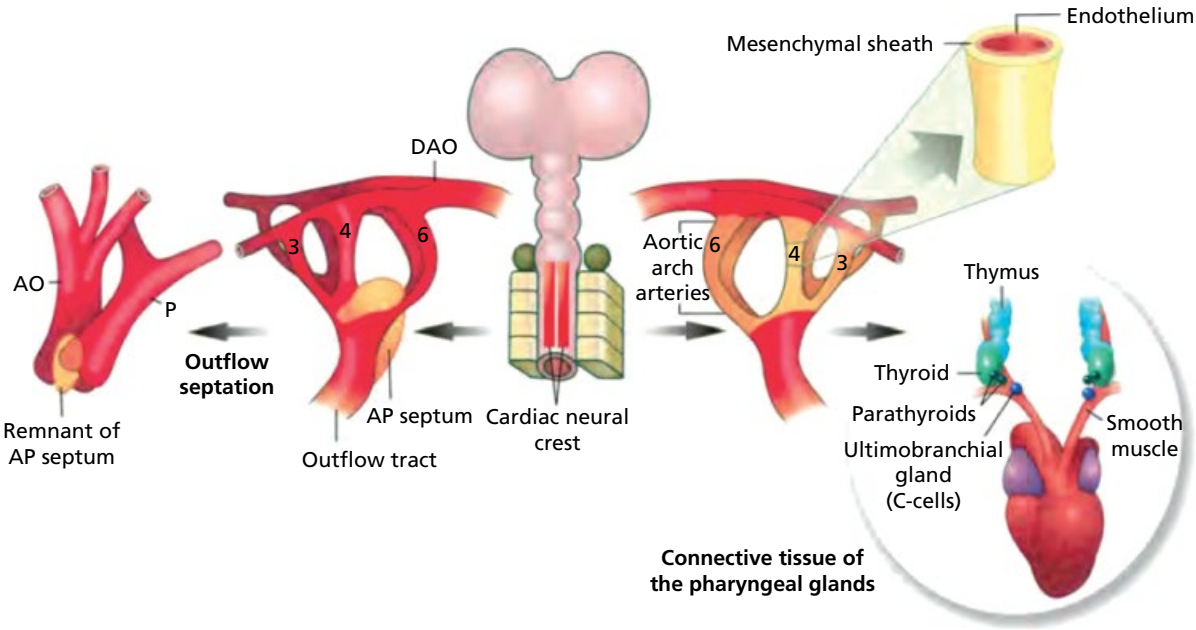

Figure 5.11 Derivatives of the cardiac neural crest cells. Cardiac neural crest cells support development of and patterning of the persisting aortic arch arteries into the great arteries of the thorax and form smooth muscle tunics. In addition, the cells contribute to the development of the thymus, parathyroids, and thyroid glands, and provide stromal cells after gland development. *Source:* Reproduced from Keyte and Hutson [49] with permission of Elsevier.

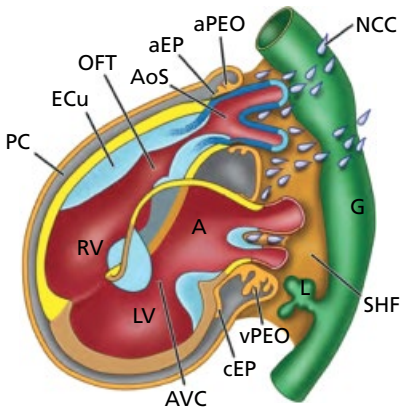

Figure 5.12 Schematic representation of the looped heart tube. The second heart field (SHF: ocher) has contributed new myocardium (yellow) to the right ventricle (RV) and the atrium (A). The first heart field derived myocardium of the left ventricle (LV) and atrioventricular canal (AVC) is brown. Neural crest cells (NCC) mainly contribute a population to the arterial pole including the wall of the aortic sac (AoS) and the endocardial cushions (ECu) of the outflow tract (OFT). At the venous pole also some NCCs are found in the area of the AVC endocardial cushions. In the pericardial cavity (PC) a proepicardial organ protrudes at the venous pole (vPEO) as well as a homologous organ at the arterial pole (aPEO). Arterial epicardium (aEP) spreads over the AoS while the epicardium from the venous pole will eventually cover the complete cardiac myocardium (cEP). G, foregut; L, lung bud. *Source:* Reproduced from Gittenberger-de Groot et al [26] with permission of Elsevier.

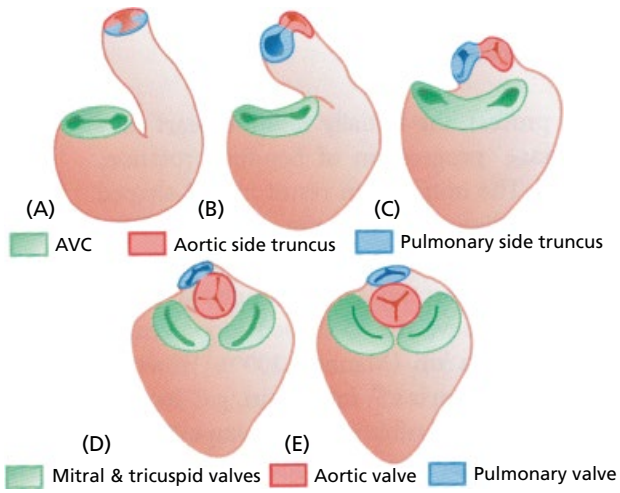

Figure 5.13 Steps in aortic wedging. The aortic side of the outflow tract nestles between the mitral and tricuspid valves as the outflow myocardium is remodeled. AVC, atrioventricular canal. *Source:* Reproduced from Kirby [34] with permission of Oxford University Press.

retinoic acid embryopathy, Alagille syndrome, Noonan, and LEOPARD syndromes [49].

Persistent truncus arteriosus results from failure in outflow tract septation (conotruncus and aorticopulmonary septum) combined with the absence of the subpulmonary infundibulum and, thus, a VSD [54]. In this defect, the aortic and pulmonary valves are fused forming a single semilunar truncal valve. The pulmonary arteries (PAs) originate from the truncal root in variable fashion, dependent on the extent of the septation deficiency. An *aortopulmonary window* is the result of incomplete outflow tract septation. An *aortoventricular tunnel* is thought to be due to abnormal excavation and maturation of the outflow cushions during the formation of the semilunar valves [52]. *Aorta or PA hypoplasia* can result from unequal outflow tract septation.

Tetralogy of Fallot is thought to result from underdevelopment of the subpulmonary infundibulum (conus) [55]. The smaller infundibulum causes anterior deviation of the conal septum and malalignment between the conal and muscular septa. This leads to RV outflow tract obstruction and a subaortic VSD [56]. The PV is usually abnormal, and the reduced blood flow contributes to PA underdevelopment. Variants of tetralogy include *pulmonary atresia* associated with varying degrees of PA hypoplasia.

Transposition of the great arteries (TGA) is thought to be the result, among other theories, of either resorption of the subpulmonary conus, causing the PV to move inferiorly and posteriorly to lie above the LV [57], or failure of spiraling of the aorticopulmonary septum [58]. In D-TGA, the most common form of transposition, there is AV concordance and VA discordance. *Congenitally or physiologically corrected transposition of the great arteries* is characterized by TGA and AV discordance (i.e. double discordance). The malformation is also referred to as L-transposition, as in most cases it is characterized by L-looping of the heart with levocardia and situs solitus of the atria.

Double outlet RV is associated with persistence of both the subpulmonary and subaortic coni, whereas *double outlet LV* (very rare) is linked to a deficiency of both. A VSD is almost always present in these anomalies.

Pulmonary valve stenosis in most cases is characterized by fused or absent valve commissures. *Critical pulmonary stenosis* in the neonate is a ductal-dependent lesion because pulmonary blood flow relies on patency of the ductus arteriosus (PDA).

Obstruction of the LV outflow tract can also occur at the valvar, subvalvar, or supravalvar levels. The most common AoV anomaly is a *bicuspid AoV*, which is the most common congenital cardiac defect (occurring in 1–2% of the population) [1]. There are several phenotypes, the most prevalent being characterized by commissural fusion. *Critical AoV stenosis* in the neonate is a ductal-dependent lesion in that a PDA is necessary to provide systemic blood flow. The AoV usually exhibits dysplastic features and may be unicommissural or bicommissural, with thickened, redundant, and rolled edges and leaflets [59]. *Severe aortic stenosis* or *aortic atresia* can be part of a spectrum of left-sided obstructive lesions associated with hypoplasia of the LV, ascending aorta, and/or aortic arch, MV stenosis or atresia, and endocardial fibroelastosis of the LV (i.e. hypoplastic left heart syndrome) [60].

Subvalvar aortic stenosis has several embryological etiologies. *Malalignment* of the conal septum posteriorly relative to the muscular septum can result in LV outflow tract obstruction. This pathology along with a VSD can be seen in an *interrupted aortic arch*. *Familial hypertrophic cardiomyopathy* is an autosomal dominant disorder most commonly resulting from mutations in the contractile protein genes [61]. A discrete *subaortic fibromuscular ridge or membrane* can also cause subaortic stenosis.

Congenital supravalvar aortic stenosis (SVAS) is associated with deletions of or a loss of function in the elastin gene (chromosome 7). In the majority of cases, SVAS occurs in association with Williams-Beuren or Williams syndrome [62,63]. This condition is frequently characterized by developmental disabilities, elfin facies, distinctive behavioral traits, and neonatal hypocalcemia. Non-syndromic SVAS can also be inherited as an autosomal dominant disorder or can result from sporadic mutations [64]. The arterial media in these children has a reduced elastin content, pathological alignment of the elastin fibers, increased collagen content, and an increased number of hypertrophied smooth muscle cells. The clinical manifestations can also be the result of the arteriopathy that can involve the aorta, renal, and/or pulmonary arteries.

KEY POINTS: CARDIAC SEPTATION

- Cardiac septation begins after looping with the eventual creation of four chambers and two distinct circulations
- The process of cardiac septation involves the muscular septa in the atrial and ventricular chambers, the AV and outflow tract endocardial cushions, and the dorsal mesenchymal protrusion.
- Abnormalities in cardiac septation can result in defects at the atrial and/or ventricular levels, altered AV valve development, abnormalities of outflow tracts, and semilunar valve pathology

Development of the endocardium

Endocardial cells develop from a pre-specified or multipotent population of cardiac progenitor cells that undergo vasculogenesis during cardiac tube formation. Morphologically, these specialized endothelial cells line the inner myocardium and connect with the vascular network [65]. Epithelial to mesenchymal transformation of endocardial cells overlying the AV and outflow tract cushions is essential for formation of the cardiac valves and for completion of cardiac septation [66]. Endocardial cells also sense hemodynamic forces induced by blood flow (shear stress) and radial wall stretching and contraction (mechanical stress) that via mechanosensitive pathways contribute to cardiac morphogenesis and physiology [65]. Endocardial progenitor cells also contribute to the development of coronary arteries and veins [67]. Finally, some endocardial cells constitute a stem cell niche and angiocrine signaling center that contribute to cardiac repair and regeneration [68].

Development of the epicardium and coronary arteries

The epicardium develops after looping to invest the heart and roots of the great arteries. In the pericardial cavity, a *proepicardial organ* (PEO) derived from splanchnic mesoderm of the ventral pharynx protrudes at the venous pole (vPEO) and arterial pole (aPEO) (see Fig. 5.12) [26,69]. The epicardium originating from the vPEO will cover the atria, AVC, and ventricles, and that from the aPEO will cover the outflow tract. Gittenberger-de Groot and colleagues have shown that after the epicardium has invested the myocardium, a subset of cells undergoes epithelial-to-mesenchymal transformation and migrates into the subepicardial space [70]. These epicardially derived cells (EPDCs) invade the myocardium and endocardial cushions and differentiate into fibroblasts, coronary smooth muscle cells, and endothelial and hematopoietic cells. The epicardially-derived fibroblasts become the interstitial fibroblasts, the annulus fibrosus, and the adventitial coronary fibroblasts. The epicardium is necessary for myocardial growth, and interstitial fibroblasts are crucial to the formation of the thick compact myocardium.

Nutrient delivery to the myocardium occurs in three sequential and overlapping phases [46]. Although the early myocardium is avascular, the inner trabecular zone of the myocardial wall has venous sinusoids (trabecular channels) lined by endocardium through which nutrients diffuse. The coronary vessels are derived from the epicardium, sinus

venosus, and endocardium. With the formation of the epicardium, a subepicardial endothelial plexus forms from the EPDCs and undergoes vasculogenesis, angiogenesis, and arteriogenesis (coating of the initial coronary plexus by smooth muscle cells and pericytes) [71]. The contribution of the epicardium to coronary vessel development is smaller than was previously proposed [72]. Venous endothelial cells of the sinus venosus sprout, dedifferentiate, and migrate to the subepicardial space on the dorsal side of the heart [67,73]. These cells then penetrate the myocardial wall and differentiate into arterial and venous endothelial cells. On the ventral side of the heart and ventricular septum, endocardial endothelial cells give rise to the coronary plexus. Some channels of the coronary plexus will communicate with the intertrabecular venous sinusoids. The density of the coronary plexus is not uniform across the myocardial wall, being higher on the outer epicardial than on the inner endocardial side [69]. The subepicardial vascular network later undergoes remodeling to produce the coronary arteries and veins with adult branching characteristics. The final step in the development of the coronary circulation is ingrowth of the peritruncal coronary capillary plexus into the base of the aorta (Fig. 5.14) [71,74]. Each coronary sinus has an ostium, which receives multiple small vessels. In the right and left aortic sinuses, the multiple channels coalesce to form the main stems of the right and left coronary arteries, whereas the channels in the remaining (non-coronary) sinus regress.

Abnormalities of epicardial development and the coronary arteries

Normal development of the compact myocardium requires a trophic interaction between the cardiomyocytes and EPDCs [26,75]. *Ventricular non-compaction,* a cardiomyopathy characterized by a spongy myocardium with a predilection for the LV, is the result of abnormal EPDC function.

Coronary artery fistulae may arise from the coronary arteries and frequently terminate in the right heart. Fistulae can occur in isolation or in association with other lesions. Flow into a lower pressure chamber can produce ventricular volume overload and myocardial ischemia (coronary steal).

Anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) results from penetration of vascular channels from the peritruncal ring into the PA instead of the aortic sinuses [76]. In this setting, coronary steal can occur, in which the direction of blood flow is reversed in the anomalous vessel because of drainage into the lower vascular resistance and pressure of the PA and/or the higher pressure of a collateral coronary circulation from the normal right coronary artery.

Anomalous aortic origin of a coronary artery from the opposite sinus of Valsalva and *congenital atresia of the left coronary artery* are relatively rare anomalies, but have been associated with sudden death [76].

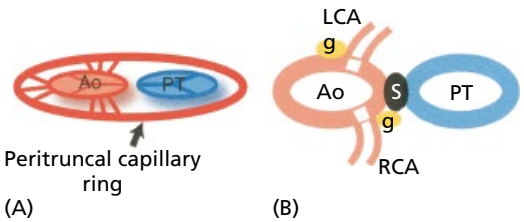

Figure 5.14 Left (LCA) and right (RCA) coronary artery development. (A) Multiple channels penetrate the aortic (Ao) wall in all of the aortic sinuses from the peritruncal ring. (B) Only the ones in the right and left sinuses survive and coalesce to form the main stems of the LCA and RCA. PT, pulmonary trunk; g, cardiac ganglia; S, aorticopulmonary septum. *Source:* Reproduced from Kirby [34] with permission of Oxford University Press.

KEY POINTS: EPICARDIUM AND CORONARY ARTERY DEVELOPMENT

- The coronary vessels are derived from the epicardium, sinus venosus, and endocardium
- The development of the coronary circulation involves various steps, culminating in ingrowth of the peritruncal coronary capillary plexus into the base of the aorta
- Abnormal epicardial development can result in certain types of cardiomyopathies and coronary artery anomalies

Development of the conduction system

The primitive cardiac pacemaker is located at the junction of the sinus venosus and the primitive atrium. Prior to valve formation, a unidirectional, slowly transmitted, depolarizing wave generates a peristaltic contraction that allows the blood to move in the heart tube from the venous pole to the arterial pole. With elongation of the heart tube, the myocardial cells differentiate into a *working* myocardial phenotype characterized by fast-conducting gap junctions, well-developed sarcomere components, and low automaticity [77]. Myocardial cells at the venous pole, AVC, and outflow tract differentiate into specialized *conductive* myocardium with high automaticity, poorly developed sarcomeres, and slow transmission. With differentiation of myocytes into working and conductive myocardium, the electrocardiogram resembles that of the formed heart [78].

The *sinoatrial node* (SAN), detectable at approximately 32 days of gestation, develops from myocardial cells located at the junction of the right common cardinal vein and the RA [79]. The *atrioventricular node* (AVN), detectable at approximately 33 days of gestation, develops from slow-conducting myocardium within the AVC, and retains its primary phenotype of slow conduction. The *AV bundle, left and right bundle branches*, and *Purkinje fibers* develop from fast-conducting ventricular myocardium. The AV conduction system provides the only myocardial continuity between the atria and ventricles.

Abnormalities of the conduction system

Normal development of the conduction system is dependent upon a concordant relation between the atrial and ventricular chambers, correct alignment of the atrial and ventricular septa, and complete closure of the ventricular septum [80]. Anomalies known to be or that can be associated with an abnormal location of the conduction system, and therefore potential vulnerability, include corrected TGA, AVC defects, perimembranous VSDs, and single ventricles.

Accessory pathways are bundles of cardiomyocytes that electrically connect the atria and ventricles, providing the substrate for supraventricular arrhythmias (e.g. Wolff-Parkinson-White

syndrome) [81]. Ebstein anomaly is frequently associated with Wolff-Parkinson-White syndrome and other accessory connections.

Atrial conduction disturbances and arrhythmias are frequently related to sinus venosus myocardium and, thus, tend to take place at specific anatomical sites [81]. The structure of the AVN is complex and in many normal hearts it provides the substrate for dual AVN physiology (two pathways with different electrophysiological characteristics) and *AV nodal reentry tachycardia*.

At the molecular level, gene mutations that affect ion channels give rise to the *cardiac channelopathies*; the most important of these are long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, and short QT syndrome [82].

KEY POINTS: DEVELOPMENT OF THE CONDUCTION SYSTEM

- The primitive cardiac pacemaker is located at the junction of the sinus venosus and the primitive atrium
- The AV node retains its primary phenotype of slow conduction allowing for appropriate AV delay, whereas the AV bundle, left and right bundle branches, and Purkinje fibers develop from fast-conducting ventricular myocardium
- Abnormalities of the conduction system are expected in defects that alter AV concordance, proper alignment of the atrial and ventricular septa, and complete closure of the ventricular septum

Development of the aortic arches

The dorsal aortae are bilateral, parallel channels that form in the mesoderm on either side of the notochord, adjacent to the ventral pharyngeal endoderm. The aortic sac is connected to the paired dorsal aortae by the artery of each pharyngeal arch, referred to as the pharyngeal arch arteries (PAAs) or the aortic arch arteries [15]. Cardiac neural crest cells migrate into the mesoderm of the pharyngeal arches and surround the endothelial cells to form the smooth muscle of the PAAs [25,83–85]. The PAAs form over time in a symmetrical pattern cranially to caudally. The neural crest cells are critical for remodeling, whereby some segments of the aortic arch apparatus and dorsal aortae regress, whereas other segments transform and persist to produce the mature asymmetrical pattern (Fig. 5.15).

The dorsal aortae fuse, starting caudally, up to the seventh somite. The seventh somite is supplied by the seventh intersegmental artery, which forms the left subclavian artery and contributes to formation of the right subclavian artery. The dorsal aortae give off dorsal intersegmental arteries, which supply the spinal cord and developing somites. Longitudinal anastomoses form between the intersegmental arteries, with those from the first to the seventh forming the vertebral artery. The first six intersegmental arteries regress after the vertebral artery is formed, and the vertebral artery arises from the seventh intersegmental artery.

Abnormalities of the aortic arches

Abnormalities of the aortic arch can be regarded as variations in regression of segments in the primitive double aortic arch as explained using Edwards' hypothetical double aortic arch model (Fig. 5.16) [86]. The aortic arch is referred to as left- or right-sided to indicate which mainstem bronchus is crossed by the arch [87]. The normal left aortic arch (LAA) results from regression of the segment of the right aortic arch between the right subclavian artery and the descending aorta. Conversely, a *right aortic arch (RAA) with mirror-image branching* occurs when the left aortic arch regresses between the left subclavian artery and the descending aorta. An RAA with mirror-image branching is frequently associated with CHD. An *LAA with an aberrant right subclavian artery* arises from regression of the segment between the right subclavian and right carotid arteries, whereas regression of the segment between the left carotid and left subclavian arteries results in an *RAA with an aberrant left subclavian artery*. A *double aortic arch* results from the persistence of both fourth aortic arches. An *interrupted aortic arch* (IAA) is considered to be due to the regression of both the right and left fourth aortic arches. The most common type of IAA is type B, in which there is interruption between the left carotid and left subclavian arteries and normal regression of the RAA. In a *vascular ring* the trachea and esophagus are completely encircled by vascular structures, which may be patent or consist of fibrous remnants such as the ligamentum arteriosum. When the trachea and esophagus are not completely encircled, the abnormality is referred to as a *vascular sling*. Aortic arch anomalies can result in tracheobronchial and/or esophageal compression. A PA sling, in which the left PA arises from the right PA and passes to the left between the trachea and esophagus, can be associated with airway malformations [88].

Coarctation of the aorta is an obstructive pathology to systemic blood flow that may take the form of a focal narrowing of the descending aorta opposite to the insertion of the ductus arteriosus (juxtaductal) or tubular arch hypoplasia. The malformation is thought to be due to ductal tissue extending into the wall of the aorta and/or an abnormal blood flow pattern in the presence of associated anomalies that lead to decreased flow into the ascending aorta.

Isolated *patent ductus arteriosus* in full-term infants is most likely a malformation with a genetic origin, with the persistent vascular structure having different histological features than the normal ductus arteriosus [89]. A PDA may occur in isolation, particularly with prematurity, or in association with almost any congenital cardiac anomaly. It is required for survival in some forms of CHD.

KEY POINTS: DEVELOPMENT OF THE AORTIC ARCHES

- The initial pattern of the aortic arches becomes modified throughout development allowing for the definitive vascular pattern present at birth
- Neural crest cells play a critical role in the development of the aortic arches
- Abnormalities of the aortic arch occur when segments of the primitive double aortic arch fail to regress or regression occurs at an abnormal site

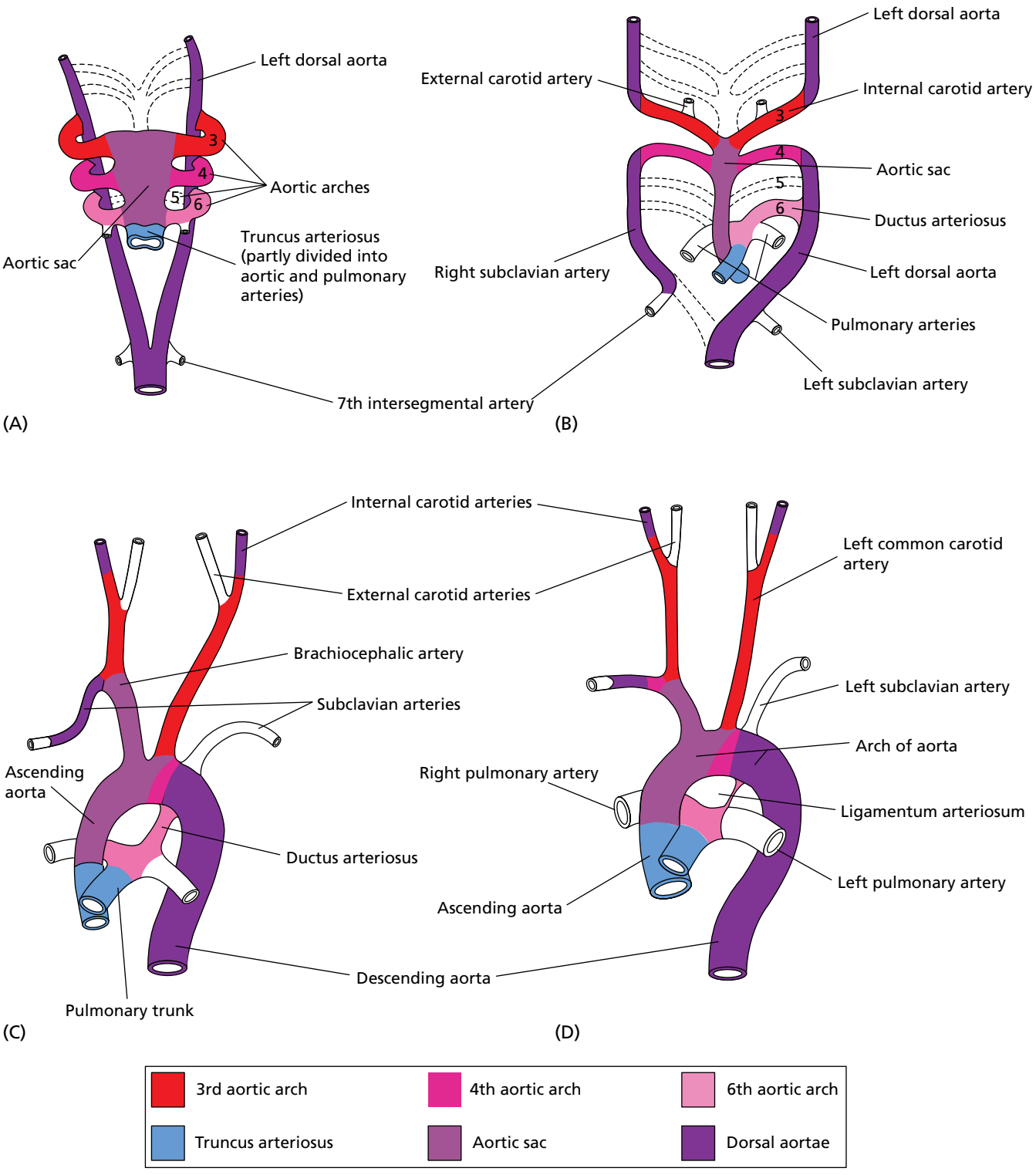

Figure 5.15 Schematic drawings illustrating the arterial changes that result during transformation of the truncus arteriosus, aortic sac, pharyngeal arch arteries, and dorsal aortae into the adult arterial pattern. The vessels that are not colored are not derived from these structures. (A) Pharyngeal arch arteries at 6 weeks; by this stage, the first two pairs of arteries have largely disappeared. (B) Pharyngeal arch arteries at 7 weeks; the parts of the dorsal aortae and pharyngeal arch arteries that normally disappear are indicated with *broken lines*. (C) Arterial arrangement at 8 weeks. (D) Sketch of the arterial vessels of a 6-month-old infant. Note that the ascending aorta and pulmonary arteries are considerably smaller in (C) than in (D). This represents the relative flow through these vessels at the different stages of development. Observe the large size of the ductus arteriosus in (C) and that it is essentially a direct continuation of the pulmonary trunk. The ductus arteriosus normally becomes functionally closed within the first few days after birth. Eventually the ductus arteriosus becomes the ligamentum arteriosum, as shown in (D). *Source:* Reproduced from Moore et al [115] with permission of Elsevier.

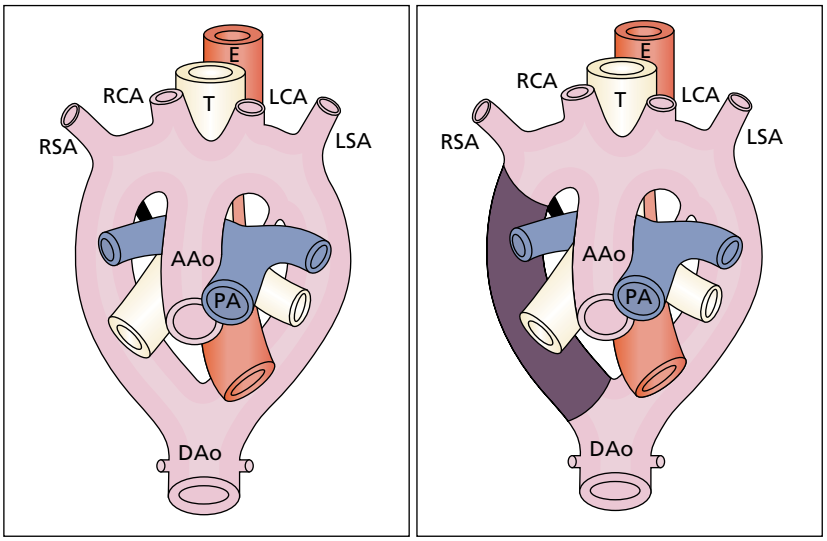

Figure 5.16 Diagram of Edwards' developmental model of the aortic arch. (A) Hypothetical double aortic arch system in which there is an aortic arch and ductus arteriosus on each side encircling the trachea (T) and esophagus (E), with the carotid and subclavian arteries arising bilaterally from the respective arches. The descending aorta is in the midline. (B) Normal arch branching results from interruption of the dorsal segment of the right arch between the right subclavian artery and descending aorta with regression of the right ductus arteriosus. AAo, ascending aorta; DAo, descending aorta; LCA, left carotid artery; LSA, left subclavian artery; PA, pulmonary artery; RCA, right carotid artery; RSA, right subclavian artery. *Source:* Reproduced from Türkvatan A, Büyükbayraktar F.G, Ölçer T, and Cumhur T. Congenital anomalies of the aortic arch: evaluation with the use of multidetector computed tomography. *Kor. J Radiol*. 2009;10:176–184 with permission of the publisher.

Development of the pulmonary and systemic veins

Pulmonary veins

The tracheobronchial tree and lungs develop from a ventral outgrowth from the foregut referred to as the respiratory diverticulum. Early in development, the lungs have the same venous drainage as the foregut, namely via the splanchnic plexus into the cardinal and umbilicovitelline (systemic) veins (Fig. 5.17).

The primary pulmonary vein develops by canalization within the dorsal mesocardium to form a channel [36]. Further canalization of the primary pulmonary vein brings it into continuity with developing LA, and by the end of the first month of gestation the primary pulmonary vein has established a connection between the pulmonary venous plexus of the lung bud and the sinoatrial portion of the heart. Once this occurs, the pulmonary venous plexus loses its connections with the systemic veins; thereafter the common pulmonary vein incorporates into the LA so that the individual pulmonary veins connect separately and directly to the LA.

Abnormalities of the pulmonary veins

Total anomalous pulmonary venous connection (TAPVC) results from a failure to establish the normal connection between the common pulmonary vein and the pulmonary venous plexus before the connections with the splanchnic venous system regress. In most cases, all the pulmonary veins join a confluence behind the LA, which can drain via the supracardiac, cardiac, or infracardiac (infradiaphragmatic) route into the right heart circulation. *Partial anomalous pulmonary venous connection* (PAPVC) results from atresia of only the right or left portions of the common pulmonary vein before regression of connections with the splanchnic venous system, leading to drainage into derivatives of the left or right cardinal systems. Both TAPVC and PAPVC produce a left-to-right shunt and can be associated with pulmonary venous obstruction. Pulmonary veins can also be *hypoplastic* or *atretic*, with the most common variation in the number of pulmonary veins being a *single pulmonary vein* on either the right or left side [90]. *Cor triatriatum* is an oblique fibromuscular membrane that divides the LA into two chambers: a posterosuperior chamber that receives the pulmonary veins, and an anteroinferior chamber that communicates with the MV and LA appendage [91]. The malformation is thought to arise from incomplete incorporation of the common pulmonary vein into the primitive LA. *Sinus venosus atrial septal defects* are associated with drainage of some, and less frequently, of all the right pulmonary veins into the right superior vena cava or RA with normal connection of the pulmonary veins to the LA (superior vena cava type defect). In rare cases, the defect is by the entrance of the inferior vena cava (inferior vena cava type defect) and the right pulmonary veins drain near this region. Congenital *pulmonary vein stenosis* typically occurs at the pulmonary vein–LA junction but can be progressive in its length, degree of stenosis, and number of pulmonary veins affected. The basis for this anomaly appears to be abnormal incorporation of the common pulmonary vein into the LA [92].

KEY POINTS: DEVELOPMENT OF THE PULMONARY VEINS

- The lungs and tracheobronchial tree develop from a ventral outgrowth of the foregut
- Establishment of a normal connection between the primary pulmonary vein and the left atrium is associated with the loss of the initial connection of the pulmonary venous plexus to the systemic veins
- Abnormalities of pulmonary vein development result from failure of normal connections between rudimentary pulmonary venous structures to be established before the connections with the splanchnic venous system regress

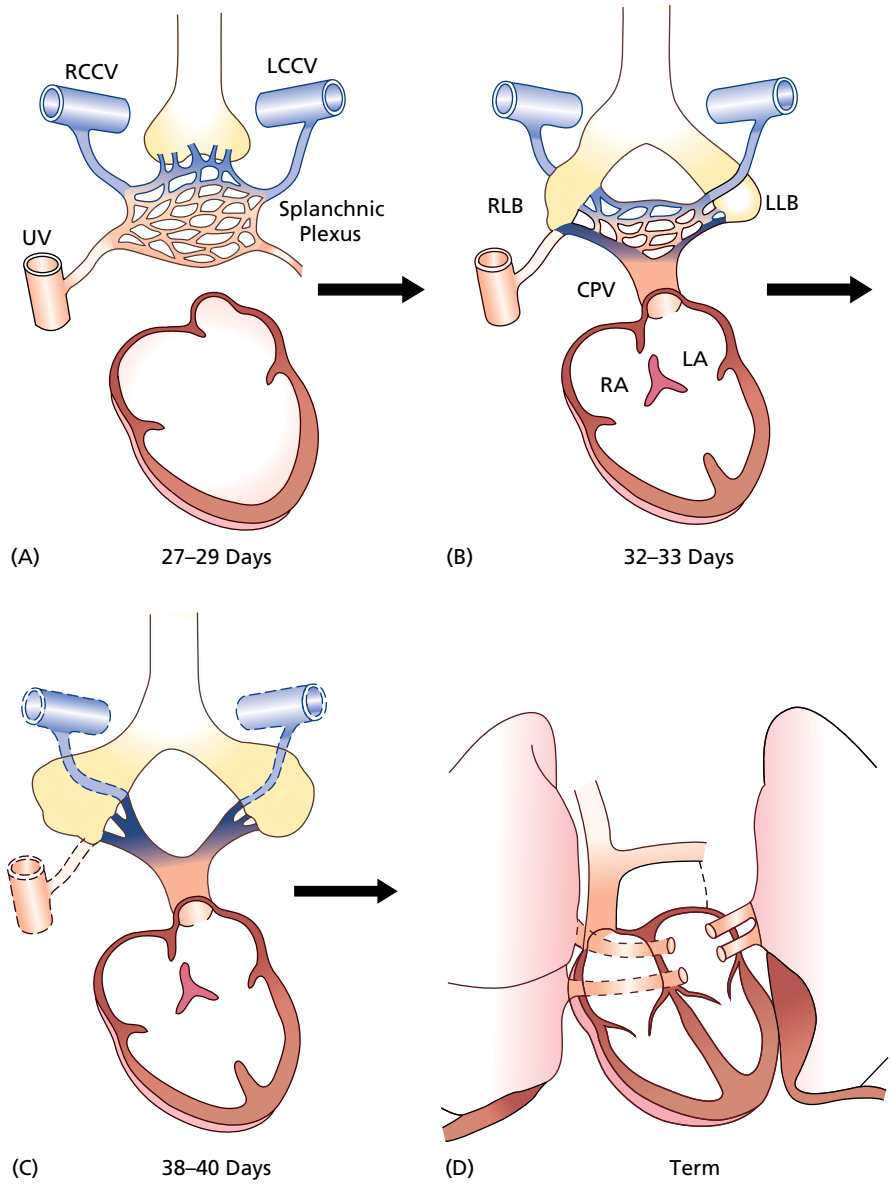

Figure 5.17 Development of the pulmonary veins. (A) At 27–29 days of gestation, the primordial lung buds are enmeshed by the vascular plexus of the foregut (splanchnic plexus). At this stage, there is no direct connection to the heart. Instead, there are multiple connections to the umbilicovitelline and cardinal venous systems. A small evagination can be seen in the posterior wall of the left atrium to the left of the developing septum secundum. (B) By the end of the first month of gestation, the common pulmonary vein establishes a connection between the pulmonary venous plexus and the sinoatrial portion of the heart. At this time, the connections between the pulmonary venous plexus and the splanchnic venous plexus are still patent. (C) Next, the connections between the pulmonary venous plexus and the splanchnic venous plexus involute. (D) The common pulmonary vein (CPV) incorporates into the left atrium, so that the individual pulmonary veins connect separately and directly to the left atrium. LA, left atrium; LCCV, left common cardinal vein; LLB, left lung bud; RA, right atrium; RCCV, right common cardinal vein; RLB, right lung bud; UV, umbilical vein. *Source:* Reproduced from Brown and Geva [92] with permission of Wolters Kluwer.

Systemic veins

By the end of the fourth week of development, the primitive venous system consists of three bilaterally symmetrical systems that each drain into the right and left horns of the sinus venosus: the *vitelline* veins, the *umbilical* veins, and the *cardinal* veins. The vitelline veins drain the yolk sac and gastrointestinal derivatives, and develop into the portal system; the *umbilical* veins, which carry oxygenated blood from the placenta, regress during the second month of gestation (right) and after birth (left); and the *cardinal* veins, which drain the head, neck, and body wall, develop into the caval system (Fig. 5.18). The shift of the systemic venous return to the RA is associated with regression and remodeling to yield the adult asymmetrical venous pattern (Fig. 5.19) [93].

Abnormalities of systemic veins

The complex development of the venous system results in a wide spectrum of systemic venous anomalies [94]. A *persistent left superior vena cava* (LSVC) results from failure of the left anterior and left common cardinal veins to regress. It may be found in association with a right SVC (*bilateral SVCs*) or may be the only SVC if the right anterior and right common cardinal veins have regressed. In the majority of cases, an LSVC will drain via the coronary sinus into the RA, but in other

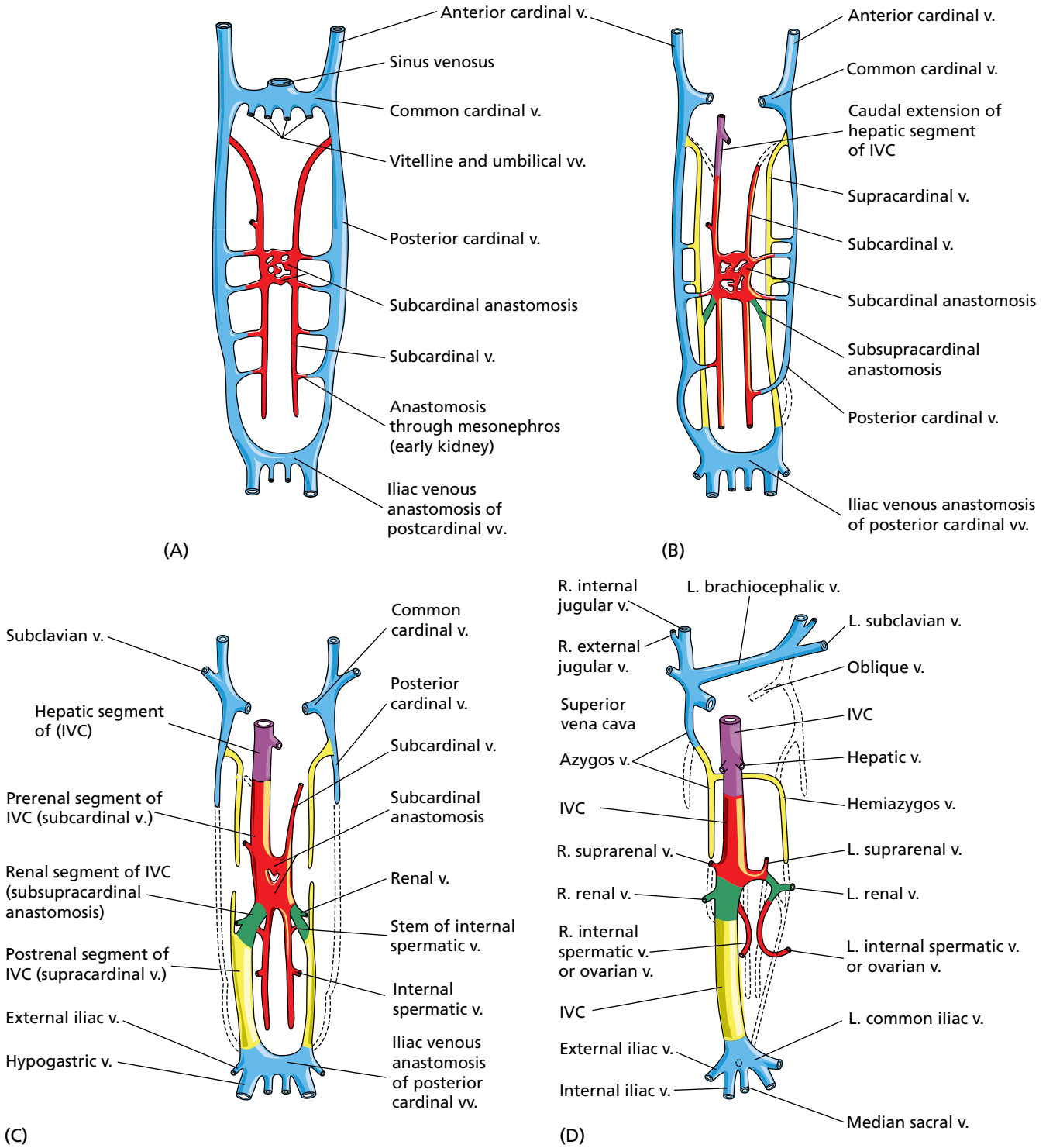

Figure 5.18 Illustrations of the primordial veins of bodies (trunks) of embryos (ventral views). Initially, three systems of veins are present: the umbilical veins from the chorion, vitelline veins from the umbilical vesicle, and cardinal veins from the body of the embryos. Next the subcardinal veins appear, and finally the supracardinal veins develop. (A) At 6 weeks. (B) At 7 weeks. (C) At 8 weeks. (D) Adult. This drawing illustrates the transformations that produce the adult venous pattern. IVC, Inferior vena cava; L., left; R., right; v., vein; vv., veins. *Source:* Reproduced from Arey [116] and Moore et al [115] with permission of Elsevier.

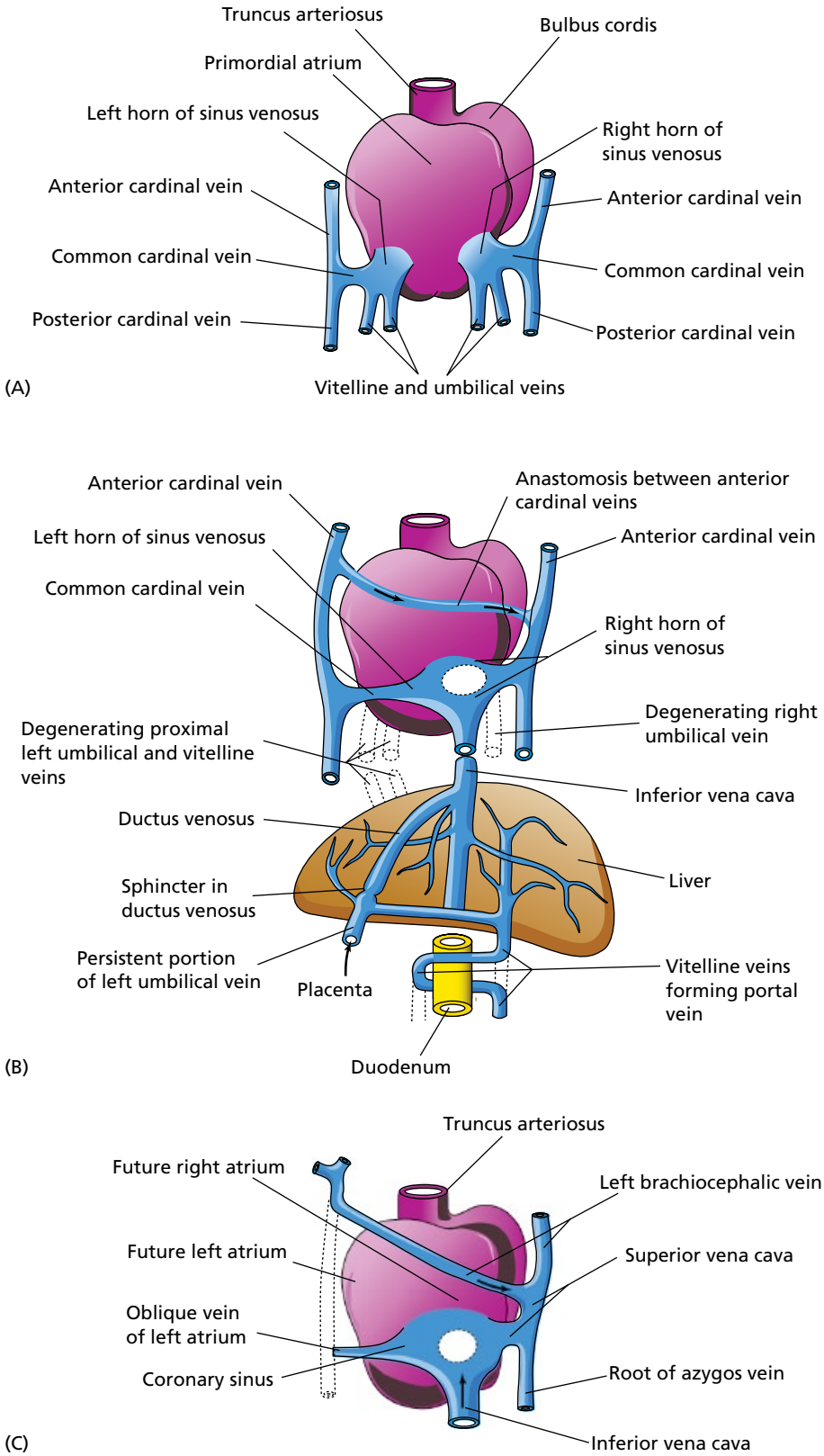

Figure 5.19 Development of the venous system. Dorsal views of the developing heart. (A) During the fourth week (approximately 24 days), showing the primordial atrium and sinus venosus and the veins draining into them. (B) At 7 weeks, showing the enlarged right sinus horn and venous circulation through the liver. The organs are not drawn to scale. (C) At 8 weeks, indicating the adult derivatives of the cardinal veins shown in A and B. *Source:* Reproduced from Moore et al [115] with permission of Elsevier.

instances it can drain into the LA if the coronary sinus is partially or completely unroofed [95]. Bilateral SVCs with an unroofed coronary sinus usually occur in association with other congenital heart defects. Heterotaxy syndrome results from disorders of left-right axis determination during early embryonic development and is frequently associated with systemic venous abnormalities.

An *interrupted inferior vena cava* with azygos/hemiazygous continuation into the right or left SVC is due to failure of formation of the hepatic segment of the IVC; in this setting, the hepatic veins drain directly into the RA. Multiple variations of *bilateral inferior venae cavae* can occur.

KEY POINTS: DEVELOPMENT OF THE SYSTEMIC VEINS

- The primitive systemic venous circulation consists of three bilaterally symmetrical systems: the vitelline veins, the umbilical veins, and the cardinal veins
- The shift of the systemic venous return to the right atrium is associated with regression and remodeling of vascular structures throughout development resulting in the asymmetrical venous pattern seen at birth
- Alterations in the complex development of the venous system lead to a wide spectrum of systemic venous anomalies

Innervation of the developing heart

The heart has both sensory (afferent) and motor (efferent) innervation that is derived from neural crest (Fig. 5.20) [96,97]. Sensory afferents relay information from the heart to the brain via both parasympathetic and sympathetic pathways. The motor (efferent) pathways are part of the autonomic nervous system, and both the parasympathetic and sympathetic pathways use preganglionic to postganglionic relays.

The cardiac nervous system develops and matures slowly, becoming fully functional well after birth [97]. Parasympathetic innervation precedes sympathetic and sensory innervation, so the parasympathetic–cholinergic system becomes functional before the sympathetic–adrenergic system [98]. Autonomic receptor-mediated effector mechanisms are present before functional innervation, thereby allowing a cardiac response to circulating catecholamines to mitigate the effects of hypoxia and bradycardia [99]. The primary neurotransmitter of the parasympathetic neurons is acetylcholine, whereas that of the sympathetic neurons is norepinephrine.

Abnormalities of cardiac innervation

Dysautonomias result from impaired autonomic interactions due to inadequate development, migration, survival, and function of sensory and autonomic neurons; in this regard, the sympathetic system is affected more often than the parasympathetic system [100]. *Familial dysautonomia* (Riley–Day syndrome), the best known of the hereditary sensory and autonomic neuropathies, is associated with orthostatic hypotension and an increased risk of sudden death. Abnormal autonomic nervous system control in patients with CHD contributes to the pathophysiology of long-term sequelae [101].

Sudden infant death syndrome has been linked to abnormal development of the autonomic nervous system, resulting in immature cardiorespiratory autonomic control and failure of the arousal responsiveness from sleep [102]. Two of the brainstem nuclei with frequent abnormalities are the dorsal motor nucleus of the vagus and the nucleus of the solitary tract, both playing a role in cardiac innervation [101].

Autonomic dysfunction likely plays a role in Down syndrome given that the heart rate and blood pressure responses to exercise are reduced [103,104] and the risk of bradycardia is increased during induction of anesthesia [105].

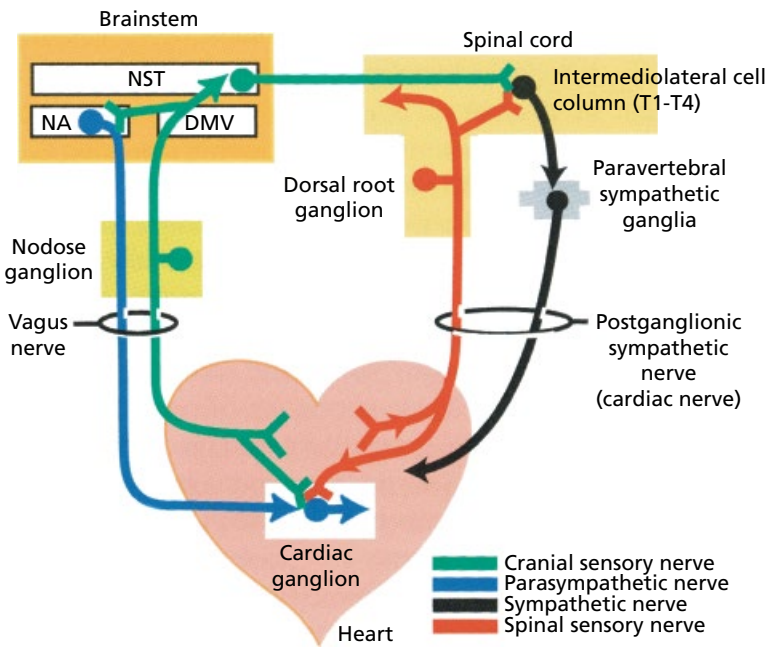

Figure 5.20 Schematic of the general plan of the innervation of the heart. Direction of the impulse is indicated by the arrow. DMV, dorsal motor nucleus of vagus; NA, nucleus ambiguus; NST, nucleus of the solitary tract. *Source:* Reproduced from Kirby [34] with permission of Oxford University Press.

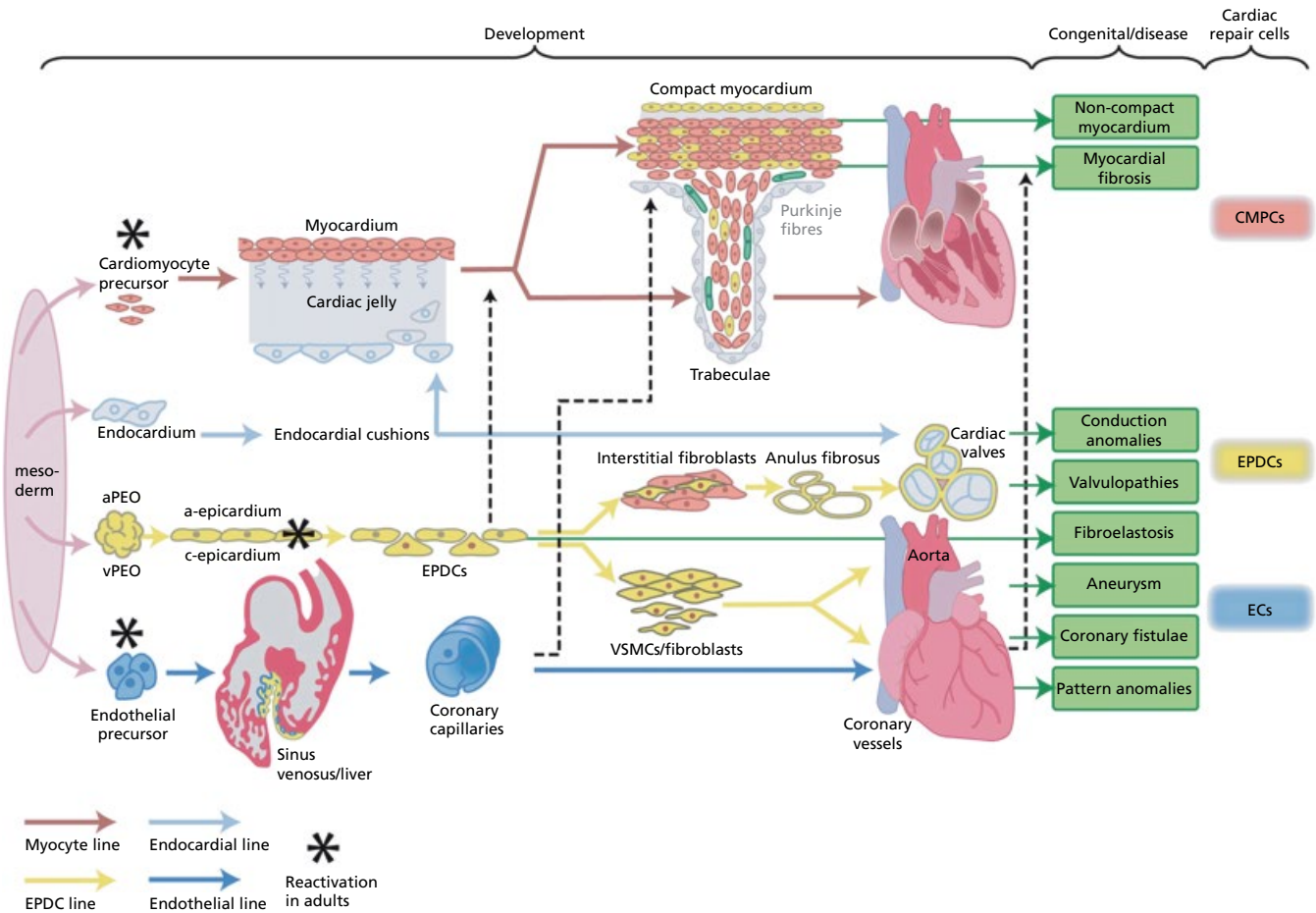

Figure 5.21 Schematic presentation of cellular contribution to heart development with special focus on role of epicardium and epicardium-derived cells during normal development, disease, and repair processes. Four mesodermal cell lines (cardiomyocytes, endocardium, epicardium, and endothelium) are considered to form the main building blocks of the heart. The differentiation of each line is depicted together with the main interactions with the other cell lines. The most frequent epicardium-derived cells (EPDCs)-related congenital malformations and (acquired) disease processes are boxed in green, while three cardiac (stem) cell populations that may become reactivated are presented on the far right side. *Source:* Reproduced from Gittenberger-de Groot et al [26] with permission of Elsevier.

KEY POINTS: INNERVATION OF THE DEVELOPING HEART

- The heart has both sensory (afferent) and motor (efferent) innervation
- The cardiac nervous system develops and matures slowly, and is not fully functional until well after birth
- Parasympathetic innervation precedes sympathetic innervation
- Abnormalities in cardiac innervation may result from impaired autonomic interactions and abnormal development of the autonomic nervous system

Cardiac stem cell therapy and heart regeneration

A resident pool of cardiac stem cells that are multipotent, clonogenic, and self-renewing exists in the normal human heart [106]. Although research has predominantly focused on recovery or regeneration of ischemic myocardium in adults, stem cell therapy is now emerging as a novel treatment modality for CHD [107–109] and has the potential to be more successful than in adults [110]. The heart is not a terminally differentiated, post-mitotic organ [106] and cardiac regeneration has been demonstrated in humans [111]. Possible mechanisms for cardiomyocyte regeneration after injury include: (1) activation, proliferation, and differentiation of resident cardiac progenitor cells; (2) dedifferentiation of mature cardiomyocytes that reenter the cell cycle; (3) activation of the epicardium with new blood vessel growth and/or new cardiomyocyte proliferation; and (4) release of paracrine factors by non-cardiomyocyte cells to promote proliferation of existing cardiomyocytes [112]. Reactivation of cardiac stem cells has opened the door for using regenerative medicine and novel therapies for treating congenital and acquired heart disease [113].

Conclusion

The heart is the first functional organ to develop in the embryo. Recent insights into the process of cardiac development have challenged many prior paradigms in classic embryology and morphogenesis, including the segmental model of heart development. It is now well established that not all cardiac chamber progenitors are derived from the early heart tube. The current concept is that only precursors of the LV are present in the straight heart tube and multiple heart-forming surrounding fields contribute to cardiac development.

The heart originates from mesoderm and neural crest precursors. The mesoderm gives rise to four cell lines (cardiomyocytes, endocardium, epicardium, and endothelium) to form the building blocks of the heart and vascular system (Fig. 5.21) [26]. Cardiac neural crest cells are critical to the formation and remodeling of the aortic arch arteries, outflow tract septation, semilunar valvulogenesis, cardiac neuronal tissue, and the insulation of the conduction system [48]. The progressive stages of human development along with a timeline of the corresponding events in the development of the cardiovascular system, as discussed in this chapter, are depicted in Table 5.1 [27].

Table 5.1 Stages of human development with corresponding events in cardiac development

Carnegie stage	Human DPC	Mouse DPC	
CS8	17–19	7	The cardiac crescent forms
CS9	19–21	7.5	The embryo folds, the pericardial cavity is placed in its final position, gully of myocardium forms, the endocardial plexus forms, cardiac jelly forms
CS10	22–23	8	The heart beats, the endocardial tubes fuse, the mesocardium perforates, looping starts, the ventricle starts ballooning
CS11	23–26	8.5	The atria balloon, the proepicardium forms
CS12	26–30	9.5	The septum primum appears, the right venous valve appears, the muscular part of the ventricular septum forms, cells appear in the cardiac jelly, epicardial growth starts
CS13	28–32	10.5	The atrioventricular cushions form, the pulmonary vein attaches to the atrium, the left venous valve appears, epicardial mesenchyme appears first in the atrioventricular sulcus
CS14	31–35	11.5	The atrioventricular cushions approach one another, the outflow ridges become apparent, capillaries form in the epicardial mesenchyme
CS15	35–38	12	The atrioventricular cushions oppose one another, the secondary foramen forms, the distal outflow tract septates, the outflow tract ridges reach the primary foramen
CS16	37–42	12.5	The primary atrial septum closes, the outflow tract ridges approach the interventricular septum. The entire heart is covered in epicardium
CS17	42–44	13.5	Secondary atrial septum appears, the sinus node becomes discernible, the left and right atrioventricular connection becomes separate, the proximal outflow tract becomes septated, the semilunar valves develop
CS18	44–48	14.5	Papillary muscles appear, the atrioventricular valves start to form
CS19	48–51	15	The left venous valve fuses with the secondary septum, the mural leaflets of the mitral and tricuspid valve are released
CS21	53–54	16	The main branches of the coronary artery become apparent
CS22	54–56	16.5	The chordae tendineae form
CS23	56–60	17.5	The septal leaflet of the tricuspid valve delaminates

DPC, days post coitum.

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Ongoing scientific work into cellular and molecular mechanisms involved in the development of the cardiovascular system has shown that this is a complex process. The availability of sophisticated research techniques over the last several decades continues to unravel many aspects of normal and abnormal cardiovascular development. Although it is well established that abnormal cardiac development leads to CHD, our understanding of important factors and mechanisms underlying congenital cardiovascular malformations continues to evolve.

Acknowledgment

Please note: major portions of this chapter were previously published as Chapter 4: Development of the Cardiovascular System and Nomenclature for Congenital Heart Disease, authors Barry D. Kussman and Wanda C. Miller-Hance; *Anesthesia for Congenital Heart Disease*, 3rd edition, 2015, John Wiley and Sons, Hoboken NJ.

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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Further reading

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Rosenthal N, Harvey RP. Heart Development and Regeneration. London: Academic Press, 2010. Comprehensive textbook on the developmental biology of the cardiovascular system. The first volume reviews the early stages of cardiovascular determination, growth and morphogenesis across the phylogenetic tree, while the second volume addresses advances in transcriptional and post-transcriptional regulation, epigenetic circuits, systems analysis, the theory and evolution of stem cells, and the molecular and cellular basis of cardiac repair.

CHAPTER 6

Developmental Physiology of the Cardiovascular System

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Introduction

The circulatory system in congenital heart disease continually changes and develops in response to both normal and pathological stimuli. Response to anesthetic and surgical interventions must be understood in this framework, and is often radically different from the usual, expected pediatric and adult situations with a "normal" cardiovascular system. This chapter will review developmental changes of the cardiovascular system from fetal life through adulthood, in both the normal and pathophysiological states associated with congenital heart disease. Not much is known about the development of the normal and diseased human heart. Much of the information discussed in this chapter was derived from animal models, and undoubtedly new information will be discovered as human myocardial tissue is studied.

Development from fetus to neonate

Circulatory pathways

The fetus receives oxygenated and nutrient-rich blood from the placenta via the umbilical vein, and ejects desaturated blood through the umbilical arteries to the placenta; thus it is the placenta, not the lung, that serves as the organ of respiration. Blood flow thus largely bypasses the lungs *in utero*, accounting for only about 7% of the fetal combined ventricular output [1]. Pulmonary vascular resistance is high, and the lungs collapsed and filled with amniotic fluid. This is the basis for the fetal circulation, which is a parallel circulation, rather than the series circulation seen postnatally. Three fetal circulatory shunts exist to carry better-oxygenated blood from the umbilical vein to the systemic circulation: the ductus venosus, ductus arteriosus, and foramen ovale (Fig. 6.1A) [2]. Approximately 50% of the umbilical venous blood, with an oxygen tension of about 30–35 mmHg, passes through the ductus venosus, and then into the right atrium. There it streams preferentially across the foramen ovale, guided by the valves of the sinus venosus and Chiari network into the left atrium. Thus the brain and upper body preferentially receive this relatively well-oxygenated blood, which accounts for 20–30% of the combined ventricular output. Blood returning in the inferior vena cava represents about 70% of the total venous return to the heart, and two-thirds of this deoxygenated blood passes into the right atrium and ventricle. About 90% of the blood flows through the ductus arteriosus to supply the lower fetal body.

After birth, there is a dramatic fall in pulmonary vascular resistance and increase in pulmonary blood flow, with inflation and oxygenation of the lungs (Fig. 6.2) [3]. The placental circulation is removed, and all of these changes lead to closure of the ductus venosus, constriction of the ductus arteriosus, and reversal of pressure gradients in the left and right atria, leading to closure of the foramen ovale. This leads to a state called the transitional circulation (Fig. 6.1B), characterized by

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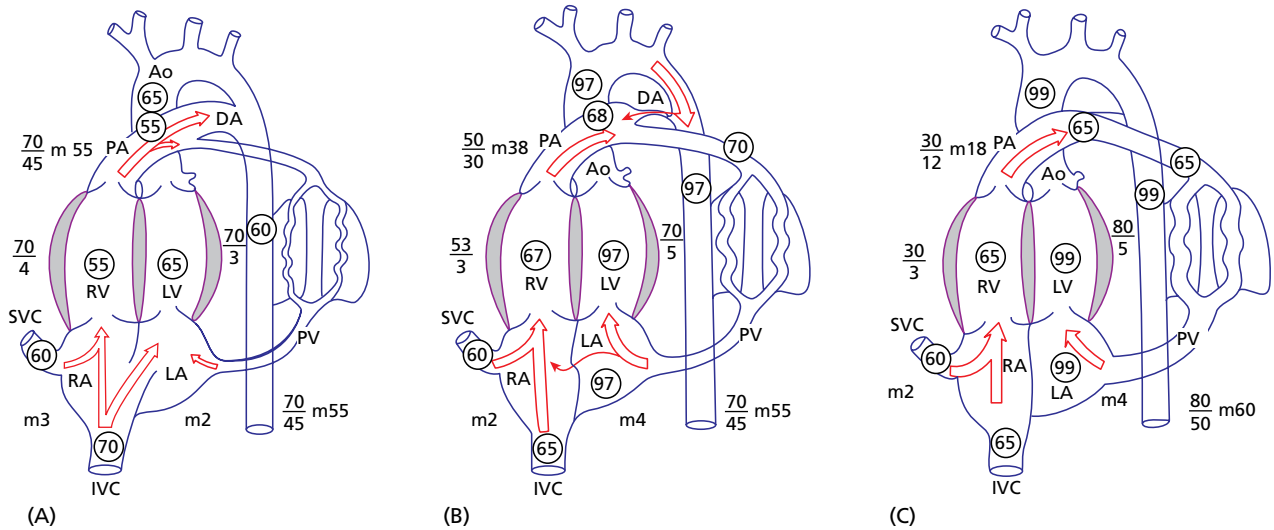

Figure 6.1 Transition from fetal to mature circulation. (A) Fetal circulation. (B) Transitional circulation. (C) Mature circulation. Circled numbers are oxygen saturations, uncircled numbers are pressures in mmHg. m, Mean pressure; RV, right ventricle; LV, left ventricle; RA, right atrium; LA, left atrium; DA, ductus arteriosus; Ao, aorta; PA, pulmonary artery; SVC, superior vena cava; IVC, inferior vena cava; PV, pulmonary vein. *Source:* Reproduced from Rudolph [2] with permission of John Wiley and Sons.

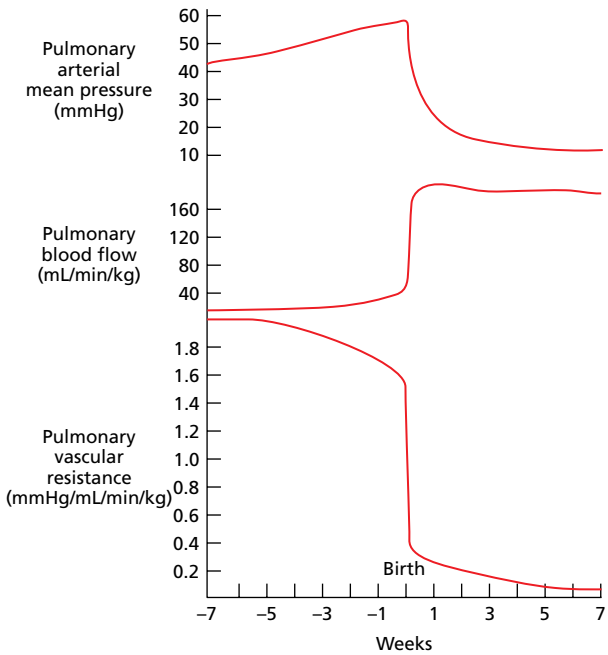

Figure 6.2 Changes in pulmonary artery pressure, pulmonary blood flow, and pulmonary vascular resistance in the lamb after birth. *Source:* Reproduced from Rudolph [3] with permission of John Wiley and Sons.

high pulmonary artery pressures and resistance (much lower than *in utero*, however), and a small amount of left-to-right flow through the ductus arteriosus. This is a labile state, and failure to maintain lower pulmonary vascular resistance can rapidly lead to reversion to fetal circulatory pathways and right-to-left shunting at the ductus arteriosus and foramen ovale. This maintenance of fetal circulatory pathways is necessary for survival in many congenital heart diseases, particularly those dependent on a patent ductus arteriosus for all or a significant portion of systemic or pulmonary blood flow, or atresia of atrioventricular valves. Maintenance of ductal patency with PGE1 is crucial in these lesions. In the two-ventricle heart with large intracardiac shunts, maintenance of the fetal circulation leads to right-to-left shunting at the foramen and ductal levels, and thus hypoxia. Conversion to the mature circulation (Fig. 6.1C) in the normal heart occurs over a period of several weeks, as pulmonary vascular resistance falls further, and the ductus arteriosus closes permanently by thrombosis, intimal proliferation, and fibrosis. Factors favoring the transition from fetal to mature circulation include normal oxygen tensions and physical expansion of the lungs, normal pH, nitric oxide, and prostacyclin. Factors favoring reversion to fetal circulation include low oxygen tension, acidotic pH, lung collapse, and inflammatory mediators (leukotrienes, thromboxane A2, platelet activating factor) as seen in sepsis and other related conditions, and endothelin A receptor activators [4].

Myocardial contractility

The fetal myocardium is characterized by poorly organized cellular arrangements, and fewer myofibrils with a random orientation, in contrast to the parallel, well-organized myofibrillar arrangement of the adult myocardium [5]. Fetal hearts develop less tension per gram than adult hearts because of increased water content and fewer contractile elements. Calcium cycling and excitation contraction coupling are also very different, with poorly organized T-tubules and immature sarcoplasmic reticulum, leading to more dependence on free cytosolic ionized calcium for normal contractility. Despite this immature state, the fetal heart can increase its stroke volume in a limited fashion up to left atrial pressures of 10–12 mmHg according to the Frank–Starling relationship, as long as afterload (i.e. arterial pressure) is kept low [6]. These features continue throughout the neonatal and early infancy period.

KEY POINTS: DEVELOPMENT FROM FETUS TO NEONATE

- Transition from fetus to neonate involves decrease in pulmonary vascular resistance, elevation of left heart pressures, and closure of shunts at the ductus arteriosus, foramen ovale, and ductus venosus
- The transitional circulation is an intermediate state between fetal and adult circulation and may revert to fetal circulation with persistence of hypoxemia, acidosis, or congenital heart disease or other conditions with elevated pulmonary pressures
- The fetal heart develops less tension per gram of resistance than mature hearts and has limited ability to increase stroke volume up to left atrial pressure of only 10–12 mmHg

Development from neonate to older infant and child

At birth the neonatal heart must suddenly change from a parallel circulation to a series circulation, and the left ventricle in particular must adapt immediately to dramatically increased preload from blood returning from the lungs, and increased afterload as the placental circulation is removed. The very high oxygen consumption of the newborn necessitates a high cardiac output for the first few months of life. However, animal models have demonstrated that the fetal and newborn myocardium develops less tension in response to increasing preload (sarcomere length), and that cardiac output increases less to the same degree of volume loading [7,8] (Fig. 6.3). Resting tension, however, is greater in the newborn compared to the mature heart. This information suggests that the newborn heart is operating near the top of its Frank–Starling curve, and that there is less reserve in response to both increased afterload and preload. This observation is borne out clinically in newborns after complex heart surgery, who are often intolerant of even small increases in left atrial pressure or mean arterial pressure. The newborn myocardium also has only a limited ability to increase its inotropic state in response to exogenous catecholamines, and is much more dependent on heart rate to maintain cardiac output than is the mature heart. One reason for this is the high levels of circulating endogenous catecholamines that appear after birth, necessary to make the transition to extrauterine life [9]. As these levels decrease in the weeks after birth, contractile reserve increases.

The neonatal myocardium is less compliant than the mature myocardium, with increased resting tension as noted above, and a significantly greater increase in ventricular pressure with volume loading [10]. This implies that diastolic function of the neonatal heart is also impaired compared to the mature heart [11]. The myofibrils of the newborn heart also appear to have a greater sensitivity to calcium, developing a greater tension than adult myofibrils when exposed to the same free Ca^{2+} concentration *in vitro* [12].

It must again be emphasized that nearly all of these data were obtained from animal models, and although the information appears to agree with what is observed clinically, there exists a need for non-invasive studies of normal human hearts from the neonatal period through adulthood to confirm these impressions of cardiac development.

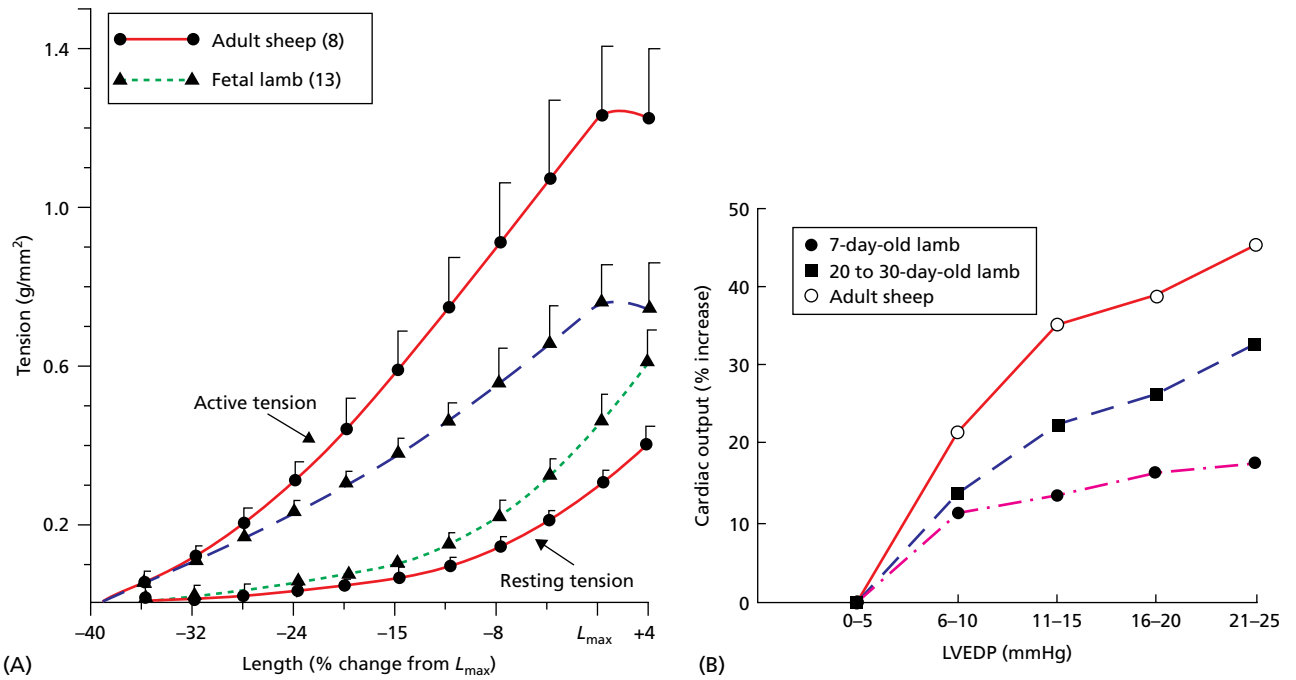

Figure 6.3 (A) Isometric resting and active length–tension relationships in fetal and adult lamb cardiac muscle strips. *Source:* Reproduced from Friedman [7] with permission of Elsevier. (B) Response to volume load of normal saline at 5 mL/kg/min, at constant heart rate. LVEDP, left ventricular end-diastolic pressure. *Source:* Reproduced from Friedman and George [8] with permission of Elsevier.

Gene expression in cardiac development

Progress has recently been made in understanding the genetic aspects of human cardiac development, and in contrast to the physiological studies that are almost exclusively performed in animal models, small amounts of human cardiac tissue obtained from biopsy or autopsy specimens can be used for these studies. Some aspects of these developmental changes will be reviewed.

Myosin is the major protein component of the thick filaments of the cardiac myofibril, and differences in the expression of this protein may play a significant role in myocardial contractility. Chromosome 14 has the genetic material responsible for producing the myosin heavy chain that makes up the backbone of the thick filaments, and two major isoforms, α and β, exist. The β isoform predominates and does not change significantly with maturation [13]. The myosin light chain has multiple isoforms; the relative proportions of these isoforms change with development, and also in response to pressure loading of the heart. The isoforms that predominate in the newborn myocardium appear to confer a greater sensitivity to Ca^{2+} than those seen in the mature heart [14] and may contribute to the increased sensitivity of the neonatal myocardium to Ca^{2+}.

Troponins I, C, and T are critical proteins that bind Ca^{2+} and regulate the interaction between myosin and actin, directly affecting the force of contraction. Troponin C, the Ca^{2+} binding portion of the troponin moiety, does not change with development. Troponin I, however, has two major isoforms, a slow skeletal muscle type that predominates in the heart in fetal and neonatal life, and the cardiac isoform, which is the only isoform expressed in the mature heart [15]. Only the cardiac (mature) isoform responds to β-adrenergic stimulation, producing a faster twitch development and greater twitch tension. However, contractility in the neonatal myofibrils containing the immature myosin light chain isoform is more resistant to acidosis. Four isoforms of troponin T are expressed in the fetal and neonatal heart, but only one in the mature heart. These isoforms exhibit different levels of ATPase activity and Ca^{2+} sensitivity, with greater ATPase activity and Ca^{2+} sensitivity seen in the immature forms [12]. Tropomyosin [16] has two and actin [17] has three isoforms which are expressed in different proportions as developmental changes occur, but the functional significance of these changes has yet to be elucidated.

Some enzymes are affected by the loading conditions of the heart. Protein kinase C (PKC) is an enzyme with a major role in transmembrane signal transduction through phosphorylation of a number of downstream intracellular components (see section "Calcium cycling in the normal heart") [18]. There are six isoforms of this enzyme, and they are not affected during development. However, in aortic stenosis producing left ventricular hypertrophy, all isoforms except PKC-β are dramatically upregulated, and in dilated cardiomyopathy there is a dramatic upregulation of PKC-β. Phosphodiesterase (PDE) is an enzyme involved in the termination of the action of cyclic AMP, which regulates the contractile state of the myocardium. Expression of the isoform PDE-5 is dramatically increased in the hypertrophied human right ventricle in patients with pulmonary hypertension, and inhibition of this enzyme improves ventricular contractility [19].

New information is available about the molecular and cellular basis for normal cardiac development and the causes of congenital heart disease [20]. A missense mutation in the myocardial protein actin has been discovered to be the cause of isolated secundum ASD in some patients [21]. Pluripotent cardiac progenitor cells reside in the human neonatal myocardium in relatively high numbers during the first month of life [22]. This knowledge has given rise to the exciting notion that these stem cells could potentially be used to facilitate recovery from cardiac morbidity, or to enhance surgical repair.

The extracellular matrix

The extracellular matrix of the heart is important in translating the force generated from shortening of sarcomere length to the cardiac chambers, resulting in stroke volume. The major components of the extracellular matrix are collagen types I and II, glycoproteins, and proteoglycans, and the expression of these elements changes with development. The neonatal heart has a higher content of both total and type I collagen (which is stiffer and less compliant than type III collagen) when compared to the total protein content of the heart [23]. The collagen to total protein ratio reaches mature levels by about 5 months of life. This change, along with greater water content of the immature myocardium, may partially explain the diminished diastolic function. Also, this relative lack of contractile elements reduces the ability of the neonatal myocardium to increase its inotropic state. A network of collagen-based connections, called the weave network, develops rapidly after birth, connecting myocytes and capillaries and allowing greater functional integrity to develop in response to the greater afterload stress on the heart [24]. This development of the extracellular matrix appears to be complete by approximately 6 months of age, and results in a much more efficient transfer of force generated by sarcomere shortening to the cardiac chambers (Fig. 6.4) [12].

The connection of the cardiac myocyte to the extracellular matrix is maintained by two specialized complexes that together are comprised of over 20 proteins, the costameres, and the dystrophin-associated glycoprotein complexes [25,26] (Fig. 6.5). The costameres produce a physical connection between the sarcomeres at the Z disk and the extracellular matrix. Transmembrane proteins called integrins connect the sarcolemma to the extracellular matrix. Integrins are receptors which are specific for collagen and fibronectin and cause the attachment of the extracellular matrix to the myocytes, allowing force transduction to occur [27]. Collagen and vinculin, another cytoskeletal protein, are attached to the sarcomere at the Z disk. The integrins have two subunits, α and β, which express several isoforms, the relative proportions of which change during development to those that afford greater adherence of the cytoskeletal proteins to the myocytes, resulting in greater structural integrity.

Dystrophin-associated glycoprotein complexes also contribute to a substantial mechanical linkage from the extracellular matrix to the cardiac cytoskeleton, and contribute to force transduction [25,26]. The proteins dystrophin, sarcoglycans, dystroglycan, and dystrobrevins are included in these complexes. These complexes play an integral role in cardiac function, and mutations in these proteins can be associated with cardiomyopathies, especially the muscular dystrophy

Figure 6.4 Longitudinal sections through an adult rabbit cardiac myocyte (A), and a 3-week-old rabbit cardiac myocyte (B). Note the differences between myofibril organization and structure, as well as cell size. *Source:* Reproduced from Nassar et al [12] with permission of Wolters Kluwer.

associated cardiomyopathies. Reduction of dystrophin activity results in dilatation of all four cardiac chambers and reduced ventricular function. Mutations in dystrobrevins have been associated with left ventricular non-compaction.

Cell-to-cell connectivity

The intercalated disks mediate the cell-to-cell interactions that coordinate cardiac myocyte activity resulting in synchronous contraction and maintaining the structural integrity of cardiac tissue [28] (Fig. 6.6). These disks are situated between cardiac myocytes at the longitudinal ends of the cells and consist of three types of connections: desmosomes, fascia adherens junctions, and gap junctions. The desmosomes have both intracellular and intercellular components. This structure serves to integrate signals from both cell-to-matrix and cell-to-cell interactions, ensuring force transmission, cell membrane integrity, and biochemical signaling. The fascia adherens junctions are responsible for holding the cardiac myocytes tightly together, and they anchor myofibrils and ensure transmission of contractile forces from cell to cell. Finally, the gap junctions form the electrical coupling apparatus between individual myocytes, ensuring rapid propagation of the electrical impulse, forming and electrical syncytium and thus triggering the coordinated contraction of cardiac myocytes. Mutations in intercalated disk proteins have recently been found to be associated with cardiac disorders. These include adherens junctions mutations associated with heart failure and dilated cardiomyopathy, and desmosome complex mutations associated with some forms of arrhythmogenic right ventricular cardiomyopathy.

The preceding short review is meant to give the reader an idea of some of the aspects of the cellular biology of the developing circulation. The explosion of new information in this area, and especially new data from human tissue, will lead to a more thorough understanding of the pathophysiology of disease states and suggest avenues for future treatment. For a more complete treatment of this area, the reader is referred to several excellent reviews [29–31].

Innervation of the heart

Clinical observations in newborn infants have led to the hypothesis that the sympathetic innervation and control of the cardiovascular system is incomplete in the newborn infant compared to older children and adults, and that the parasympathetic innervation is intact [5]. Examples of this include the frequency of bradycardia in the newborn in response to a number of stimuli, including vagal, and vagotonic agents, and the relative lack of sensitivity in the newborn to sympathomimetic agents. Histological studies in animal models have demonstrated incomplete sympathetic innervation in the neonatal heart when compared to the adult, but no differences in the number or density of parasympathetic nerves [32,33].

Autonomic cardiovascular control of cardiac activity can be evaluated by measuring heart rate variability in response to both respiration and beat-to-beat variability in systolic blood pressure [34]. The sympathetic and parasympathetic input into sinoatrial node activity contribute to heart rate variability changes with greater heart rate variability resulting from greater parasympathetic input into sinoatrial node activity [35]. Studies using these methodologies for normal infants during sleep suggest that the parasympathetic predominance gradually diminishes until approximately 6 months of age, coinciding with greater sympathetic innervation of the heart similar to adult levels [36].

KEY POINTS: DEVELOPMENT FROM NEONATE TO OLDER INFANT AND CHILD

- The neonatal heart exhibits heart rate dependence, limited ability to increase contractile state, and limited tolerance for excessive afterload and preload
- The costameres and dystrophin-associated glycoprotein complexes play central roles in connection of the cardiac myocyte to the extracellular matrix and thus force transduction in the heart
- The intercalated disks maintain cell-to-cell connectivity between cardiac myocytes, allowing tight adhesion and electrical impulse transition to facilitate coordinated cardiac contraction

Development from child to adult

Beyond the transition period from fetal to newborn life and into the first few months of postnatal life, there is not much

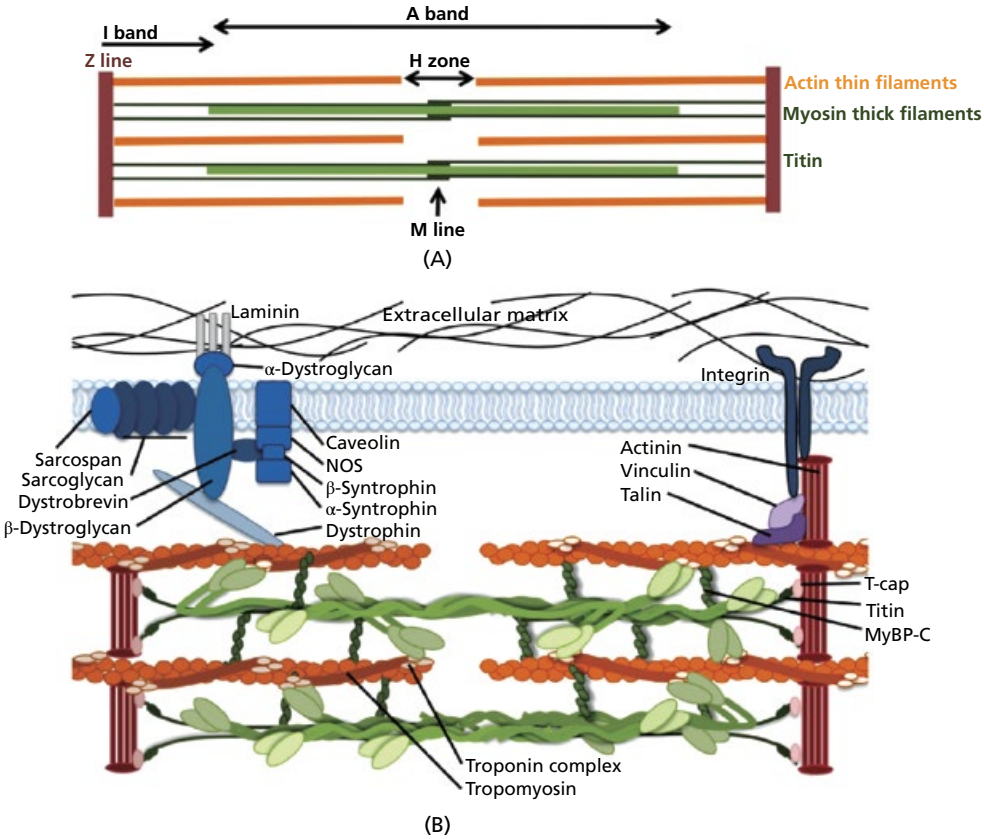

Figure 6.5 Anatomy of the cardiac sarcomere. (A) Basic organization of the sarcomere. The sarcomere forms the basic contractile unit. Thin filaments composed of actin are anchored at the Z line and form transient sliding interactions with thick filaments composed of myosin molecules. The M line, I band, and A band are anatomical features defined by their components (actin, myosin, and cytoskeletal proteins) and appearance in polarized light. Titin connects the Z line with the M line and contributes to the elastic properties and force production of the sarcomere through its extensible region in the I band. Coordinated shortening of the sarcomere creates contraction of the cardiomyocyte. (B) Major proteins of the sarcomere. Attachment to the extracellular matrix is mediated by costameres composed of the dystroglycan–glycoprotein complex and the integrin complex. Force transduction and intracellular signaling are coordinated through the costamere. The unique roles of each of these proteins are critical to appropriate function of the heart. T-cap, titin cap; MyBP-C, myosin-binding protein C; NOS, nitric oxide synthase. *Source:* Reproduced from Harvey and Leinwand [26] with permission of Rockefeller University Press.

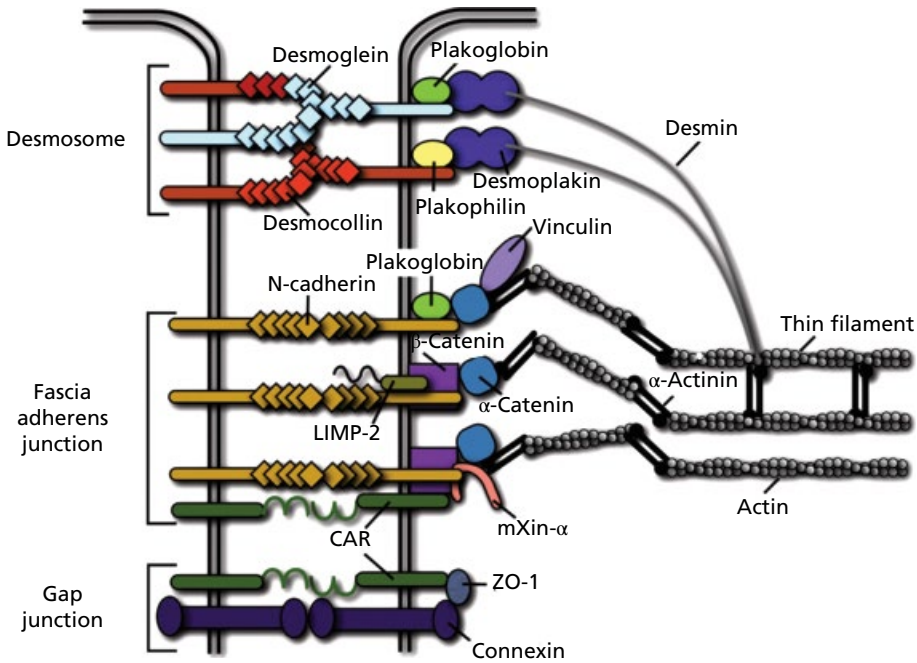

Figure 6.6 Major complexes and components of the cardiac intercalated disk. LIMP-2, lysosomal integral membrane protein 2; CAR, coxsackievirus and adenovirus receptor; mXinα, muscle-specific mouse Xinα; ZO-1, zona occludens 1. *Source:* Reproduced from Sheikh et al [28] with permission of Elsevier.

human or animal information concerning the exact nature and extent of cardiac development at the cellular level. Most studies compare newborn or fetal to adult animals [37]. Cardiac chamber development is assumed to be influenced by blood flow [38]. Large flow or volume load in a ventricle results in ventricular enlargement. Small competent atrioventricular valves, as in tricuspid stenosis, result in lower blood flow and a small ventricle. Increases in myocardial mass with normal growth, as well as in ventricular outflow obstruction, are mainly due to hypertrophy of myocytes. Late gestational increases in blood cortisol are responsible for this growth pattern, and there is concern that antenatal glucocorticoids to induce lung maturity may inhibit cardiac myocyte proliferation. In the human infant, it is assumed that the cellular elements of the cardiac myocyte, i.e. adrenergic receptors, intracellular receptors and signaling, calcium cycling and regulation and interaction of the contractile proteins, are similar to the adult by approximately 6 months of age. Similarly, cardiac depression by volatile agents is greater in the newborn, changing to adult levels by approximately 6 months of age [39].

Normal values for physiological variables by age

It is useful for the anesthesiologist to be aware of normal ranges for physiological variables in premature and full-term newborns of all sizes, and in infants and children of all ages (Table 6.1, Fig. 6.7) [40]. Obviously, acceptable ranges for these variables are highly dependent on the individual patient's pathophysiology, but the wide range of "normal" values may reassure the practitioner to accept "low" blood pressure, for example, if other indices of cardiac function and tissue oxygen delivery are acceptable. Values for awake, healthy infants and children are often significantly different than in anesthetized patients and those with significant cardiac disease undergoing invasive procedures, especially with regard to the higher resting blood pressure values [41–43].

A very important study of over 116,000 ASA I and II patients from 10 centers undergoing non-cardiac procedures with mostly sevoflurane anesthesia reported the range of blood pressure values in the preparation (presurgical) phase and the surgical phase in patients from 0 to 18 years of age, measured by non-invasive oscillometric method (NIBP) [44] (Fig. 6.8). The data were reported from electronic anesthesia medical records and were carefully refined to remove artifacts. Age- and gender-specific reference curves were calculated which specified the systolic, diastolic, and mean blood pressures. The range at each age from +2 to –2 standard deviations (SD), representing 95% of all blood pressure values and thus

Table 6.1 Normal heart rates and systolic blood pressure as a function of age

Age	Range of normal heart rates (beats/minute)	Range of normal systolic blood pressures, measured by oscillometric blood pressure device (mmHg)
Neonate (<30 days)	120–160	60–75
1–6 months	110–140	65–85
6–12 months	100–140	70–90
1–2 years	90–130	75–95
3–5 years	80–120	80–100
6–8 years	75–115	85–105
9–12 years	70–110	90–115
13–16 years	60–110	95–120
>16 years	60–100	100–125

Blood pressure data are from references [40–43].

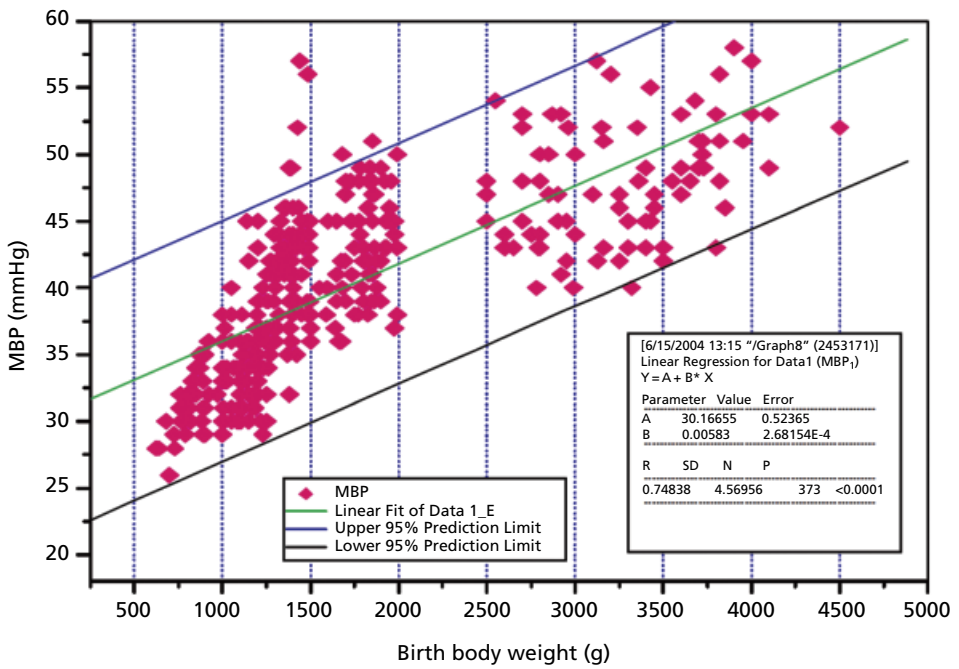

Figure 6.7 Linear regression of mean arterial pressure in 1-day-old neonates free of cardiopulmonary disease, measured by oscillometric methods in the awake state; 292 were premature and 81 full-term neonates. Middle green line is 50th percentile, upper blue line 95th percentile, and lower black line 5th percentile. Note that in the 3.0 kg full-term neonate, normal mean arterial pressure can range from 37 to 56 mmHg. *Source:* Reproduced from Pejovic et al [40] with permission of Springer Nature.

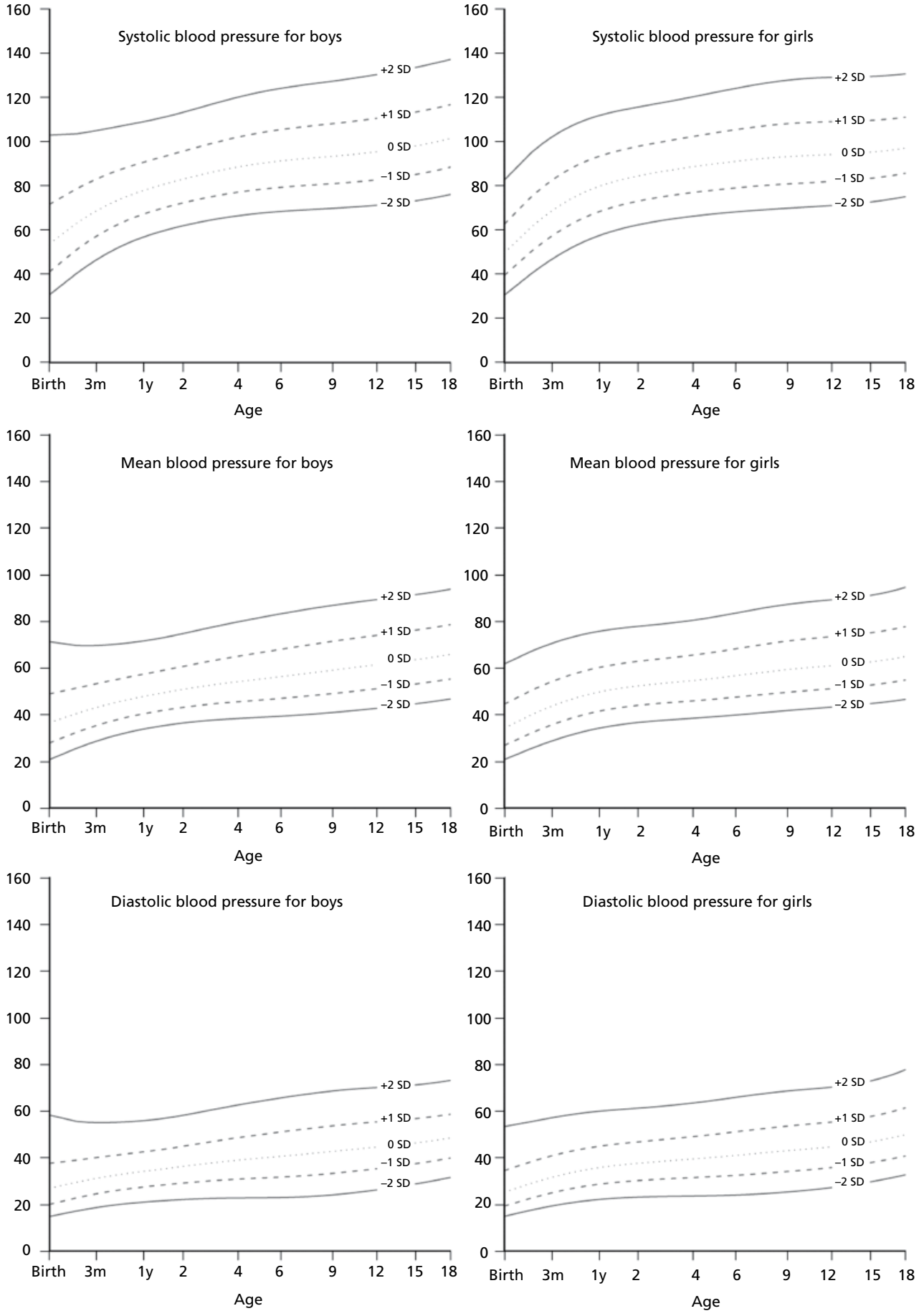

Figure 6.8 Reference curves for noninvasive blood pressure for boys and girls during anesthesia during the surgical phase in relation to age. *Source:* Reproduced from de Graaff et al [44] with permission of Wolters Kluwer.

constituting the range of "normal" blood pressures, was included. For example, the 50th percentile (0 SD) of mean arterial pressure ranged from 33 mmHg at birth to 66 mmHg at age 18 years in boys. The –2 SD (2.5th percentile) values for mean blood pressure ranged from 17 mmHg at birth to 47 mmHg at 18 years. The lowest reference ranges for anesthetized children are much lower (approximately 20 mmHg) than those for awake children; the 2.5th percentiles (–2 SD) of the systolic and mean NIBP of a 4-year-old boy are 85 and 60 mmHg, respectively, when non-anesthetized, and 68 and 38 mmHg, respectively, when anesthetized.

Myocardial sequelae of long-standing congenital heart disease

Hypertrophy of the cardiac chambers is a common response to a number of different chronic pathophysiological states. Wall thickness increases through hypertrophy of the cardiac myocytes and non-contractile elements. The hypertrophy reduces wall stress in the dilated heart, but also serves to reduce ventricular function, particularly diastolic function. This reduction in function serves to reduce myocardial oxygen consumption in response to a wide variety of chronic stresses, both in pressure and volume overloaded ventricles [45].

Pressure overload hypertrophy results in altered gene expression in the cardiomyocyte. Myosin isoform expression changes from the faster-reacting α-myosin to the slower β-myosin, reducing myocardial function [46]. Integrin-linked kinase expression is increased in patients with hypertrophic cardiomyopathy and induces hypertrophy in an animal model [47]. Altered expression or mutations of other genes that regulate production of cardiac cytoskeletal proteins, such as dystrophin, occur in patients with end-stage cardiomyopathy [48,49].

Cardiomyocyte receptor function in normal and diseased hearts

The adrenergic receptor

The adrenergic receptors (AR) are part of a large superfamily of receptors that mediate their biological responses through the coupling of a specific guanine nucleotide regulatory protein or G protein [50]. This superfamily of receptors shares a common structural motif, characterized by seven hydrophobic domains spanning the lipid bilayer. The seven domains are attached by three internal loops and three external loops between the amine terminus and the cytoplasmic carboxy terminus. The function of this receptor family is dependent on a specific agonist (or ligand) binding to the receptor, which causes a conformational change in the receptor. This structural change permits the interaction between the intracellular portion of the receptor and guanine nucleotide regulatory protein (or G protein). This interaction, also referred to as coupling, inevitably links the activated receptor to a specific biological response. The regulation of the biological response is initiated by the specificity of the receptor for a particular extracellular agonist and the coupling of a specific G protein to that activated receptor.

Once an extracellular ligand (or agonist) is specifically recognized by a cell surface receptor, the receptor goes through a conformational change that exposes a specific region of the receptor complex to the intracellular side of the plasma membrane [51] (Fig. 6.9). This conformation change triggers the interaction of the G protein with the amino acids of the third intracellular loop of the receptor and hence leads to G protein activation. There are three different G proteins: stimulatory G protein (Gs), inhibitory G protein (Gi), and Gq. Under normal conditions, all of the β receptors interact with Gs, the α_1 interacts with Gq, and α_2 interacts with Gi. Each G protein is a heterotrimer made up of three subunits: α, β, and γ. The activation of the G protein-coupled receptor causes an exchange of bound guanosine diphosphate (GDP) for guanosine triphosphate (GTP) within the α subunit and initiates the disassociation of the β-γ subunit from the α subunit. The GTP-activated α subunit modulates the activity of a specific effector enzyme within a specific signaling pathway by catalyzing the hydrolysis of GTP to GDP and inorganic phosphate. This causes the transference of a high-energy phosphate group to an enzyme and in turn causes the deactivation of the α subunit. This process will eventually lead to the deactivation of the α subunit and the reassociation with the β-γ complex. This cycle is continuously repeated until the agonist becomes unbound from the receptor. Downstream of enzyme activation, the production of a second messenger regulates the biological response.

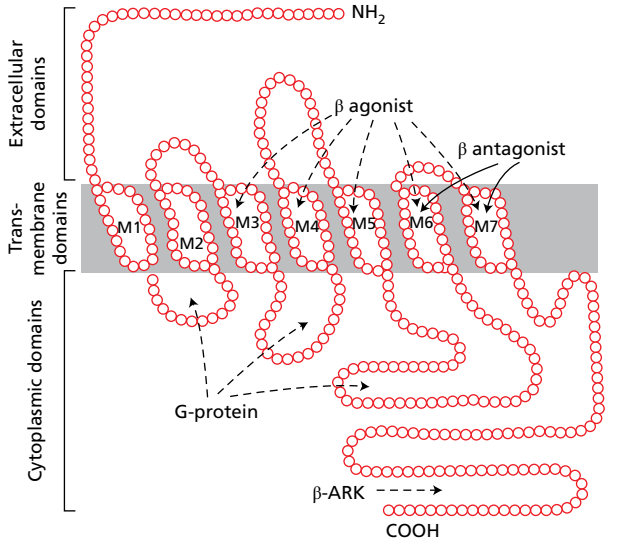

Figure 6.9 Molecular structure of the β-adrenergic receptor, demonstrating its three domains. The transmembrane domains serve as ligand-binding pockets for agonists (dashed arrows) and antagonists (solid arrows). The cytoplasmic domains interact with G proteins and β-adrenergic receptor kinases. *Source:* Reproduced from Moss and Renz [50] with permission of Elsevier.

Adrenergic receptors (AR) have been subdivided into two groups of receptors based on the results of binding studies using a series of selective agonists and antagonists. In 1948 Ahlquist used the difference in rank orders of potency of a series of agonists to separate the ARs into two principal receptor groups, the α and β receptor group [52]. These findings have been confirmed repeatedly with the development of drugs that function to selectively antagonize the α receptor with no effect on the β receptor. Soon after the distinction between the α and β receptor type was understood, it became more evident that the separation of α and β receptors was not sufficient to explain pharmacological studies using rank order

of potency for an antagonist, differing from an agonist because it blocks the biological response. With the advent of radioligand-labeled antagonists and new molecular cloning techniques examining receptor gene expression, it became clear that the two principal receptor groups could be further subdivided into additional subtypes.

To date, within the β-adrenergic group four different subtypes have been identified: β_1, β_2, β_3, and β_4. Pharmacologically, β_1 and β_2 are differentiated by their affinities to different catecholamines: epinephrine, norepinephrine, and isoproterenol. β_1 has similar affinity for epinephrine and norepinephrine, while β_2 has a higher affinity for epinephrine than for norepinephrine. Both β_1 and β_2 have the same affinity for isoproterenol. The β_3 and β_4 receptors have minor roles in cardiovascular function and will not be further discussed.

The expression and distribution of each subtype is highly dependent on the organ, which adds another level of specificity. Distribution of a particular receptor in two different tissue types may result in two different functions. When examining cardiovascular response to adrenergic stimulation, the β_1 receptor is predominantly expressed in heart tissue. The stimulation of the receptor subtype leads to both inotropic and chronotropic effects on cardiac function, resulting in an increase in the myocardial contractile force and a shortening of contractile timing, respectively. While β_2 can also be found in the heart, it is mostly expressed in vascular smooth muscle tissue. The distribution and functional relevance of this receptor subtype in the heart is controversial and may change with alterations in cardiac function. The percentage of β_2 receptors in the non-failing heart averages about 20% in the ventricle [53] and 30% in the atrium. The percentage of β_1 to β_2 receptors is approximately 75%:25% in the ventricles of younger hearts [54,55].

Each signaling pathway is specific to each adrenergic receptor. Once the agonist binds to the β_1 receptor causing the coupling of the G protein, the G protein α-subunit becomes activated followed by an increase in adenylate cyclase (AC) activity, which induces the conversion of ATP to cAMP. The second messenger, cAMP, phosphorylates protein kinase A (or PKA). The function of a kinase is to phosphorylate other target proteins, which initiates a biological response. PKA phosphorylates many intracellular targets including calcium channels, troponin I, and ryanodine receptors. PKA also plays a central role in regulating calcium sensitivity [56].

The β_2 receptor also been shown to function through the cAMP signaling pathway causing the activation of PKA, but not nearly to the extent of $\beta_{1\,in}$ cardiomyocytes [57]. The response of this stimulation appears to have a larger effect on smooth muscle, for example the vascular smooth muscle. In this tissue type, the stimulation of β_2 and the subsequent increase in cAMP promotes the vasodilation of vascular smooth muscle and may lead to alterations in blood pressure. In these tissues, the effect of β_1 stimulation appears to be minimal, due to lack of β_1 receptors in the smooth muscle.

Similar to the β receptor, the α receptors can be pharmacologically subdivided into α_1 and α_2. The α1 receptor is distributed in most vascular smooth muscle and to a lesser extent in the heart. The α_2 receptor has been found in some vascular smooth muscle; however its major functional importance is as a presynaptic receptor in the central and peripheral nervous systems. The use of molecular techniques has identified three additional subtypes of the α_1 receptor (α_{1A}, α_{1B}, and α_{1D}) and three additional subtypes of the α_2 receptor [50]. Binding of an agonist to an α_1 receptor in the heart or vascular smooth muscle results in activation of the Gq subunit of the G protein, which activates phospholipase C, producing diacylglycerol and inositol-1,4,5-triphosphate, which releases Ca^{2+} from the sarcoplasmic reticulum and increases vascular smooth muscle tone or cardiac contractility. A schematic classification of adrenergic receptors incorporating recent knowledge of molecular pharmacology and signal transduction is presented in Figure 6.10 [50].

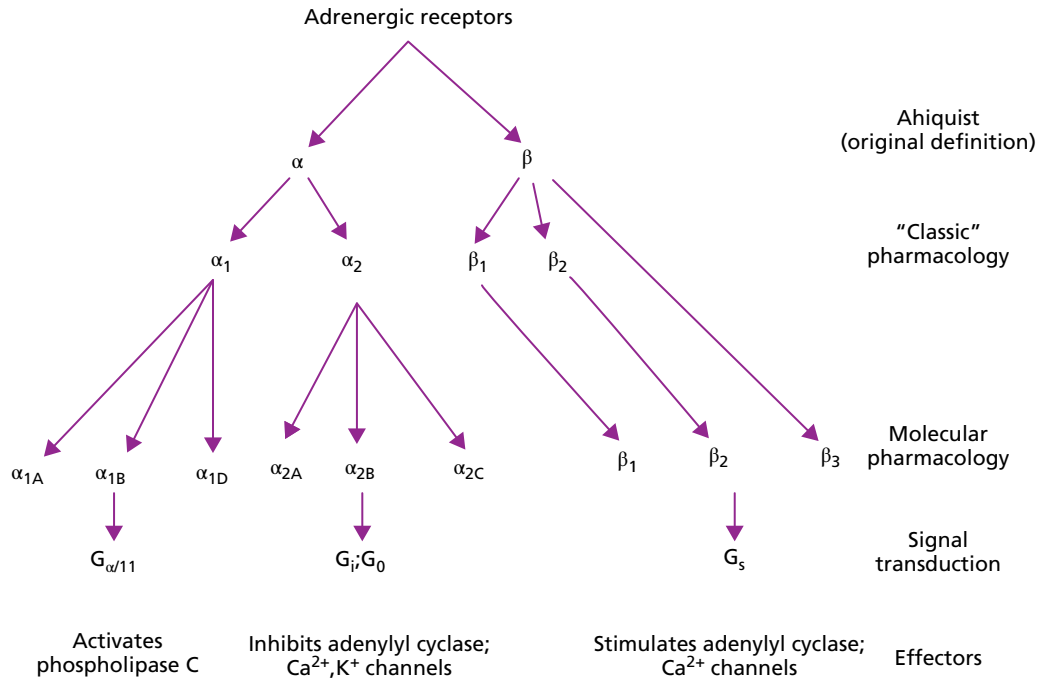

Figure 6.10 A schematic classification of adrenergic receptors. *Source:* Reproduced from Moss and Renz [50] with permission of Elsevier.

The adrenergic receptor concentration in cardiac tissue is very small and measured as femtomoles per milligram of protein. However, the response to stimulation of the receptor is greatly amplified by the signal that occurs downstream of the receptor. In rat ventricular myocytes, the ratio between the β receptors and the next two downstream signaling components (β receptor: G protein: adenylate cyclase) is 1:200:3 [58]. This demonstrates how a large response can be initiated by the activation of a small number of receptors. In addition, it also shows that the rate-limiting component that ultimately regulates intracellular production of cAMP is receptor density and the enzyme concentration of adenylate cyclase.

Developmental changes in adrenergic receptor signaling

Information concerning changes in adrenergic receptor function during the transition from neonatal to more mature myocardial development is limited to a few animal studies. As noted previously, the neonatal heart has a limited inotropic response to catecholamine administration.

β-Adrenergic receptor density is higher in the ventricular myocardium of neonatal versus adult rabbits, but the inotropic response to the same concentration of isoproterenol is significantly greater in adult tissue [59]. In the neonatal rat, the mechanism of β-adrenergic mediated increase in contractility is entirely due to β_2 stimulation, whereas in the adult rat it is due solely to β1 receptor activation. Coupling of the β_2 receptor to Gi protein action is apparently defective in the neonatal rat, because the ratio of Gi to Gs subunits is much higher in the neonate. The relative proportion of β_1 and β_2 receptors is the same in neonatal versus adult hearts (17% β_2) and approximates the ratio measured in children with simple acyanotic congenital heart disease, which is about 22% [60].

There is animal and human evidence that α-adrenergic receptor-mediated chronotropic and inotropic effects on the cardiac myocyte change with development. In the neonatal animal model, α stimulation produces positive inotropic and chronotropic effects, whereas in the adult it produces negative effects [60,61]. The chronotropic response to α_1 stimulation diminished with increasing age in children being evaluated for autonomic dysfunction after vagal and sympathetic blockade [62].

Calcium cycling in the normal heart

Calcium assumes a central role in the process of myocardial contraction and relaxation, serving as the second messenger between depolarization of the cardiac myocyte and its contraction mediated by the actin–myosin system. Calcium's role in this excitation–contraction coupling in the normal mature heart will be reviewed briefly before discussion of developmental changes and changes with heart failure [63].

Cardiac muscle cell contraction depends on an increase in intracellular Ca^{2+} above a certain threshold, and relaxation ensues when intracellular Ca^{2+} falls below this threshold. Two major regions of Ca^{2+} flux occur: across the sarcolemmal membrane (slow response), and release from internal stores–the sarcoplasmic reticulum (rapid release and reuptake) [64,65] (Fig. 6.11). The primary site of entry of Ca^{2+} through the sarcolemmal membrane is through the L-type, or low-voltage-dependent Ca^{2+} channels, which occurs in two types: a low-threshold, rapidly inactivating channel; and a higher threshold, more slowly inactivating channel [66]. Depolarization of the sarcolemmal membrane triggers opening of these channels, resulting in the release of large amounts of Ca^{2+} from the sarcoplasmic reticulum (SR), the major internal Ca^{2+} storage organelle. Ca^{2+} entry through the slowly inactivating channels serves to fill the SR with adequate Ca^{2+} stores. Removal of Ca^{2+} from the cytoplasm to the exterior of the cell occurs via two major mechanisms: the sodium–calcium (NaO–Ca^{2+}) exchanger, and the calcium ATPase pump. The NaO–Ca^{2+} exchanger usually serves to exchange three sodium ions (moving into the cell) for one Ca^{2+} (moving out of the cell), although the reverse action, as well as a 1:1 exchange, is possible [67]. The Ca^{2+}-ATPase pump actively transports Ca^{2+} (in a 1:1 Ca^{2+}-ATP ratio) out of the cell in an energy-dependent high-affinity but low-capacity manner [68]. The affinity of the sarcolemmal Ca^{2+}-ATPase pump is enhanced by calmodulin, which binds free cytoplasmic Ca^{2+}. Although the calcium movement through the sarcolemma plays an important role in balancing internal and external Ca^{2+} concentrations and in supplying Ca^{2+} to replenish SR Ca^{2+} stores, and in initiating the Ca^{2+}-induced release of Ca^{2+} from the SR, it is important to recognize that the amount of Ca^{2+} flux is far less than across the SR, the far more important mechanism for excitation–contraction coupling in the mature heart [69]. The sarcolemmal Ca^{2+} flux mechanisms play a much more important role in the excitation–contraction coupling of the neonatal (immature) heart.

The massive release and reuptake of Ca^{2+} responsible for activation and deactivation of the actin–myosin complex and cardiocyte contraction and relaxation occurs at the level of the SR. The SR is a closed, intracellular membranous network that is intimately related to the myofilaments responsible for contraction [70,71] (Fig. 6.12). The SR is connected to the sarcolemmal membrane via the transverse tubule (T-tubule) system. Depolarization of the sarcolemmal membrane results in transfer of charge down the T-tubules to the SR, resulting in the opening of SR Ca^{2+} channels and the release of large amounts of Ca^{2+} into the cytoplasm, where it can then bind to troponin and initiate the actin–myosin interaction. The SR is divided into longitudinal SR and terminal cisternae; the latter connect to the T-tubules. The terminal cisternae are primarily involved in the release of Ca^{2+}, and the longitudinal SR in its reuptake [72].

The primary Ca^{2+} release mechanism of the SR is the ligand-gated Ca^{2+} release channels (also known as the ryanodine receptors) that bind to the drug ryanodine. The channels are activated by two primary mechanisms: depolarization via the T-tubules, and binding of intracellular Ca^{2+} itself; the predominance of one mechanism over the other differs in cardiac versus skeletal muscle. The close proximity of the L-type sarcolemmal Ca^{2+} channels in the T-tubules to the ligand-gated Ca^{2+} release channels allows the depolarization to rapidly allow Ca^{2+} into the cell and open the SR Ca^{2+} channels. These ligand-gated Ca^{2+} release channels close when the cytosolic Ca^{2+} concentration increases; normally they open at 0.6 μM Ca^{2+} and close at 3.0 μM Ca^{2+}.

The reuptake and sequestration of Ca^{2+} leads to relaxation of the cardiac myocyte and is an active transport mechanism, primarily involving hydrolysis of ATP by the SR Ca^{2+}-ATPase

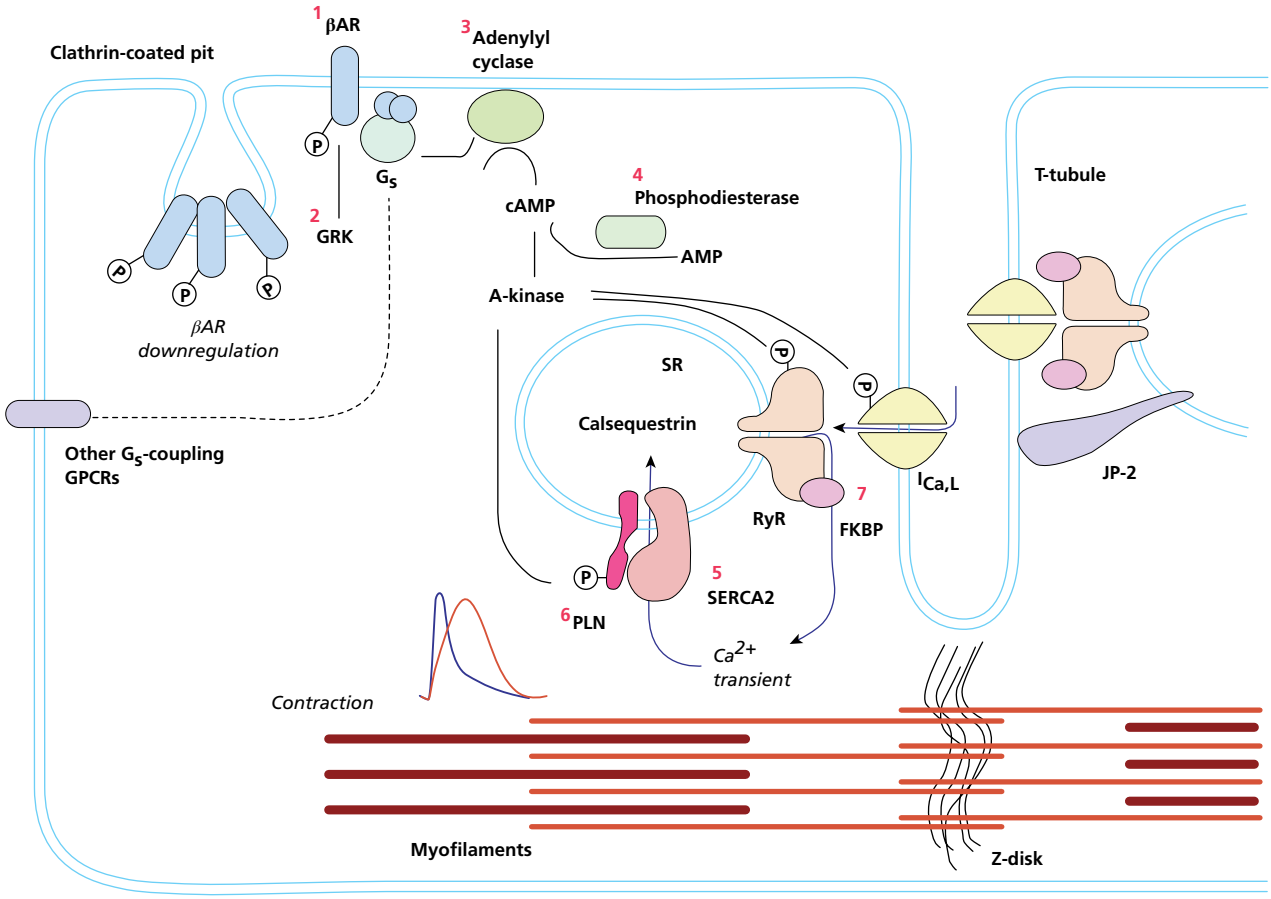

Figure 6.11 Calcium cycling and its relationship to the β-adrenergic receptor system and myocyte myofilaments. See text for discussion. βAR, β-adrenergic receptor; Gs, stimulatory G protein; GRK, G-receptor kinase; cAMP, cyclic AMP; A-kinase, protein kinase A; SR, sarcoplasmic reticulum; RyR, ryanodine receptor; SERCA2, sarcoplasmic reticulum Ca^{2+}-ATPase; PLN, phospholamban; $I_{Ca,L}$, L-type Ca^{2+} channel; FKBP, FK-506 binding protein; JP-2, junctophilin-2; GPCR, G-protein coupling receptor. Encircled P represents sites of phosphorylation by the various kinases. Numbers 1 through 7 represent targets for pharmacological therapy in cardiac failure. *Source:* Reproduced from Hoshijima and Chien [65] with permission of Journal of Clinical Investigation.

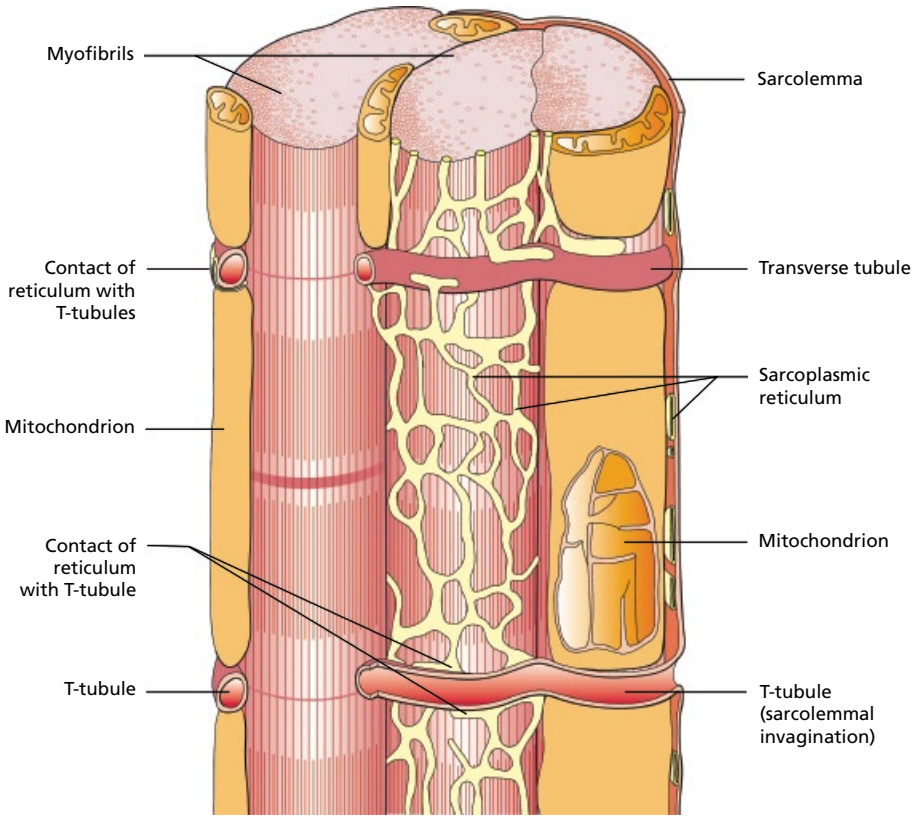

Figure 6.12 Normal, mature cardiac myocyte structure. *Source:* Reproduced from Bloom and Fawcett [71] with permission of Elsevier.

(SERCA), located in the longitudinal SR [73]. It binds two Ca^{2+} ions with high affinity and rapidly transports them to the inside of the SR. This transport system differs from the sarcolemmal membrane: it has higher affinity, allows for more rapid transport, and is not sensitive to calmodulin. Ca^{2+} is stored in the SR by calsequestrin, a high-capacity, low-affinity protein that acts as a Ca^{2+} sink.

There are two other proteins with essential roles in the regulation of Ca^{2+} flux: phospholamban and calmodulin [74,75]. Phospholamban is associated with the SERCA and can be phosphorylated by at least four different protein kinases: cAMP-dependent, Ca^{2+}/calmodulin dependent, cGMP-dependent, or protein kinase C. When phosphorylated, phospholamban increases the affinity of the SERCA for Ca^{2+}, facilitating Ca^{2+} flux back into the SR, thus affecting the inotropic and lusitropic state of the heart. Phospholamban plays an important role in the β-adrenergic mediated increase in inotropic state of the heart. Calmodulin is a Ca^{2+} storage protein with four binding sites, found in the cytoplasm, which interacts with the sarcolemmal Ca^{2+}-ATPase (increasing its affinity for Ca^{2+}) and the SR ligand-gated Ca^{2+} release channel (inhibiting its activity at optimal cytoplasmic Ca^{2+}), and binds to the Ca^{2+}/calmodulin dependent protein kinase [75]. Mutations in the phospholamban gene have been described, and may be a rare cause of dilated cardiomyopathy [76].

The increase in intracellular cytoplasmic Ca^{2+} initiates the contractile process. Myosin is the major component of the thick filaments, which make up the microscopic structure of the myofibril, and its interaction with actin (the major component of the thin filaments) provides the mechanical basis of cardiac muscle cell contraction [77]. Actin and myosin make up approximately 80% of the contractile apparatus and are arranged in a parallel, longitudinal fashion, projecting from a Z-line or band (Fig. 6.13) to form the basic contractile unit called the sarcomere [78]. A three-dimensional lattice consisting of interdigitated thick and thin filaments in a hexagonal array with three thin filaments in close proximity to each thick filament is formed. The actin and myosin are linked by projections on the myosin protein called S1 cross-bridges, which bind to actin and, via an energy-dependent hinge-like mechanism, produce the sliding filament cross-bridge action that is thought to produce sarcomere shortening and lengthening. The lattice is held together by connecting proteins such as titin, nebulin, and α-actinin [79]. The actin–myosin interaction is initiated when Ca^{2+} binds to troponin, a protein closely connected to actin which consists of three subunits: a Ca^{2+} binding subunit (TNC), a tropomyosin binding unit (TNT), and an inhibitory subunit (TNI). TNC can bind up to four Ca^{2+} ions, and this produces a conformational change on the thin filament, which allows the S1 myosin head cross-bridges to attach [80]. This also changes the TNI subunit's conformation and allows tropomyosin, another protein integral in filament interaction, to move aside and expose the binding sites on actin, allowing strong binding to the S1 cross-bridges. With Ca^{2+} present, actin causes myosin ATPase to hydrolyze one ATP molecule, providing energy that results in the S1 myosin head pulling on the thin filament, resulting in sarcomere shortening. Troponin C is the most important aspect of the regulation of cardiocyte contraction, and has a steep response curve to local levels of Ca^{2+}. The reuptake of Ca^{2+} into the SR causes Ca^{2+} levels to decline rapidly and the inhibitory form of the troponin, tropomyosin, actin complex returns, resulting in the reversal of the cross-bridge binding and thus sarcomere relaxation.

Besides calcium, many other regulatory mechanisms exist to influence the interaction and sensitivity of Ca^{2+} binding to troponin. These mechanisms include β-adrenergic stimulation, thyroid hormone, and phosphorylation by cAMP-dependent protein kinases.

Developmental changes in calcium cycling

Several aspects of the excitation–contraction system are different in the immature heart. The T-tubule is not fully formed [81]. The sarcoplasmic reticulum has less storage capacity and less structural organization [82], less mRNA expression [83,84], and less responsiveness to chemical blockade [85,86].

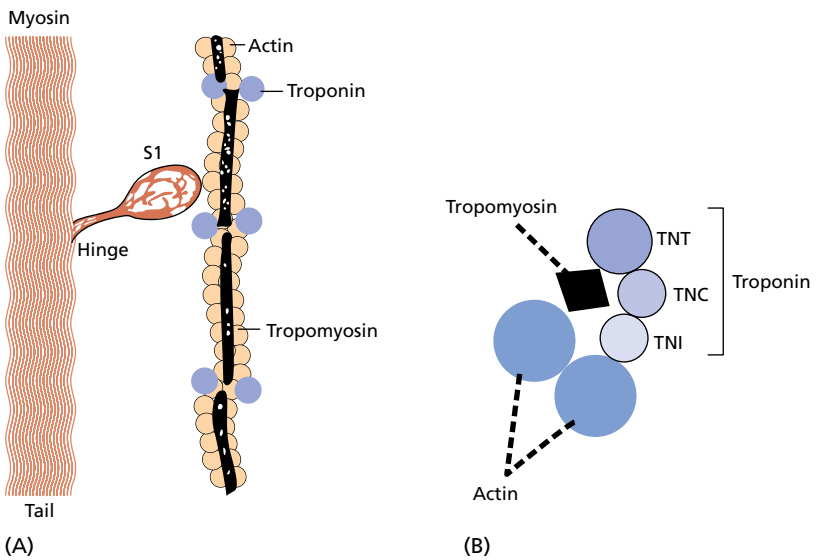

Figure 6.13 (A) Single thick and thin filament showing the S1 cross-bridge and hinge mechanism. (B) Relationship of actin to tropomyosin and the three troponin subunits. See text for explanation. *Source:* Reproduced from Michael [78] with permission of Wolters Kluwer.

The inhibitory subunit of troponin (TNI) changes from a predominately cAMP-insensitive form to a cAMP-responsive form by 9 months of age, an additional factor contributing to the increased responsiveness seen with β-adrenergic stimulation after the neonatal period [86]. All of this information has led to the theory that the neonatal cardiac myocyte is more dependent on free cytosolic Ca^{2+} fluxes than is the mature heart, and more susceptible to blockade of the L-type Ca^{2+} sarcolemmal channels as a mechanism of myocardial depression. The latter is thought to be the mechanism producing greater myocardial depression observed with halothane in neonatal rat models compared with sevoflurane, and the same phenomenon seen clinically [87]. A summary of the major differences in cardiac development and function between the neonatal and mature heart is presented in Table 6.2.

Thyroid hormone

Tri-iodothyronine (T3) has a critical role in both the development of the cardiovascular system and also acute regulation and performance. Normal T3 levels are essential for normal maturation and development of the heart through expression of genes responsible for the production of the cardiac contractile proteins, elements of the calcium cycling apparatus, and development and density of β-adrenergic receptors [88]. There are cell nucleus mediated effects from exogenous T3 that occur from an increase in protein synthesis and require at least 8 h to develop. These include an upregulation of β-adrenergic receptors, increase in cardiac contractile protein synthesis, increase in mitochondrial density, volume, and respiration, increase in SR Ca^{2+}-ATPase mRNA, and changes in myosin heavy chain isoforms. However, there are acute effects of T3 on cardiac myocytes that occur in minutes from interactions with specific sarcolemmal receptors, and include stimulation of L-type Ca^{2+} pump activity, stimulation of SR Ca^{2+}-ATPase activity, increased protein kinase activity, and decrease in phospholamban [89]. Cardiac surgery and cardiopulmonary bypass interfere with the conversion of thyroxine (T4) to T3, and serum levels decrease significantly after cardiac surgery in infants and children [90]. T3 infusions improve myocardial function in children after cardiac surgery and reduce intensive care unit stay [91].

KEY POINTS: CARDIOMYOCYTE RECEPTOR FUNCTION IN NORMAL AND DISEASED HEARTS

- The adrenergic receptor system, particularly the β-receptor system, plays a central role in regulating cardiac contractility through G protein and adenylate cyclase coupling
- Calcium cycling in the neonatal heart is characterized as immature, with underdeveloped T-tubules and sarcoplasmic reticulum, not reaching the mature state until an estimated 6–12 months of age
- Thyroid hormone is essential for normal gene expression for production of cardiac contractile proteins, calcium cycling apparatus, and adrenergic receptor density, as well as acute effects to increase sensitivity of adrenergic receptors and efficiency of calcium cycling

Regulation of vascular tone in systemic and pulmonary circulations

The regulation of vascular tone is an important consideration in the understanding and treatment of congenital heart disease. Both the systemic and pulmonary circulations have complex systems to maintain a delicate balance between vasodilating and vasoconstricting mediators in normal patients. Abnormal responses may develop which lead to pulmonary or systemic hypertension or, conversely, vasodilation. A schematic representation of some of these mediators is shown in Figure 6.14 [92]. To some extent, the control mechanisms reviewed are present in both the systemic and pulmonary circulations; however certain mechanisms are more important in one circulation. For example, the endothelial-mediated systems (nitric oxide–cGMP pathways, etc.) predominate in the pulmonary

Table 6.2 Summary of major differences between neonatal and mature hearts

	Neonatal	Mature
Physiology		
Contractility	Limited	Normal
Heart rate dependence	High	Low
Contractile reserve	Low	High
Afterload tolerance	Low	Higher
Preload tolerance	Limited	Better
Ventricular interdependence	Significant	Less
Ca^{2+} cycling		
Predominant site of Ca^{2+} flux	Sarcolemma	SR
Dependence on normal Ca^{2+}	High	Lower
Circulating catecholamines	High	Lower
Adrenergic receptors	Down-regulated, insensitive	Normal
	β_2, α_1 predominant	β_1 predominant
Innervation	Parasympathetic predominates; sympathetic incomplete	Complete
Cytoskeleton	High collagen and water content	Lower collagen and water content
Cellular elements	Incomplete SR, disorganized myofibrils	Mature SR, organized myofibrils

SR, sarcoplasmic reticulum.

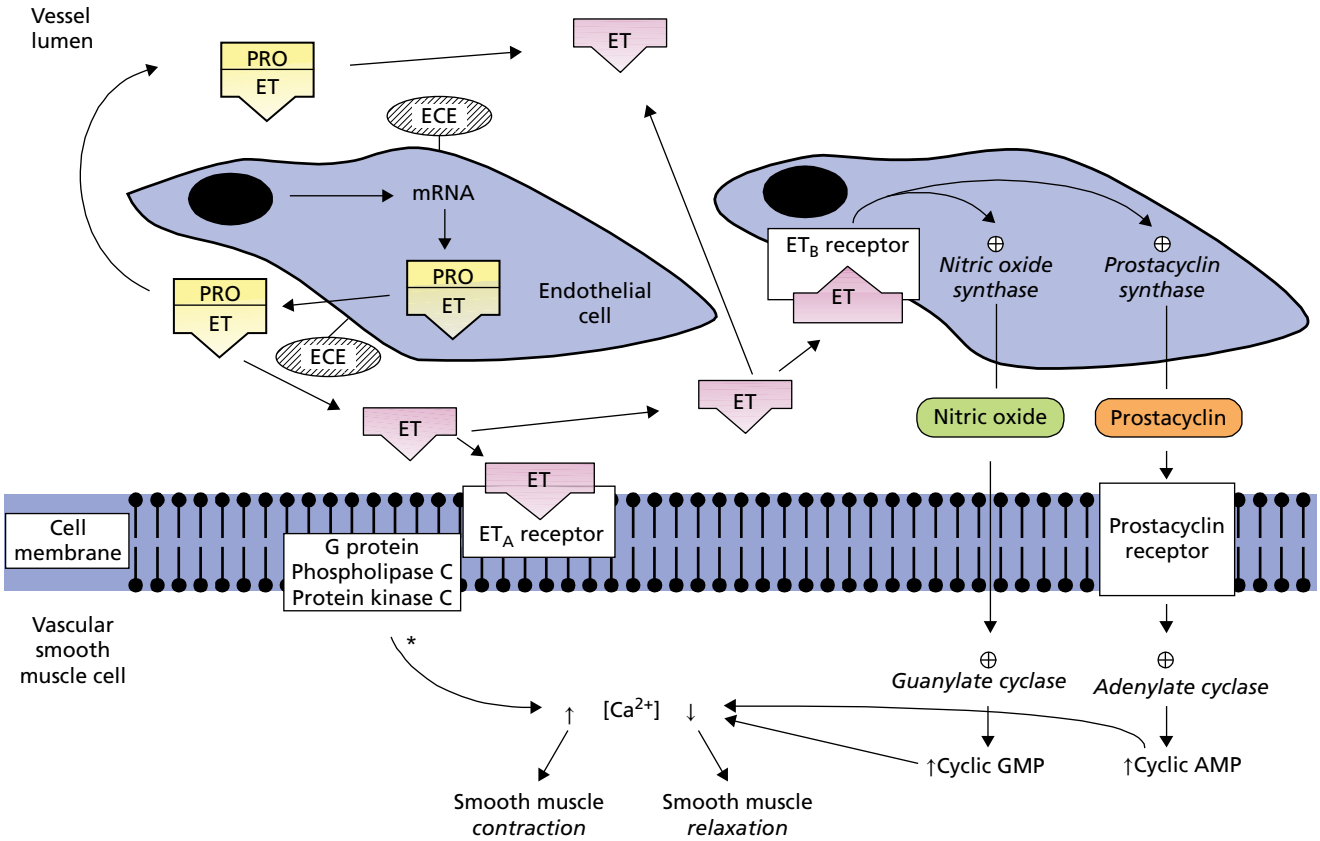

Figure 6.14 Schematic of some major mediators of vascular tone in the pulmonary circulation. ET, endothelin-1; PROET, proendothelin-1; ECE, endothelin-converting enzyme. See text for explanation. *Source:* Reproduced from Haynes and Webb [92] with permission of Portland Press.

circulation (low-resistance circulation), whereas the phospholipase systems predominate in the systemic circulation (high-resistance circulation). The endothelium-dependent control of vascular tone plays a significant role in the transition from fetal to postnatal circulation, with pathological persistence of fetal endothelial milieu contributing to the transitional circulation and pulmonary hypertension, both of which may influence the pathophysiology of congenital heart disease [93].

Pulmonary circulation

Vasoactive metabolites of arachidonic acid, called eicosanoids, are produced in cell membranes. Eicosanoids metabolized via the lipoxygenase pathway will form leukotrienes, and those metabolized via the cyclo-oxygenase pathway form the prostaglandins. Important vasodilating prostaglandins include PGE_1, which also promotes and maintains patency of the ductus arteriosus. Prostacyclin, PGI_2, is a potent pulmonary vasodilator [94]. Prostaglandins act in vascular smooth muscle of the systemic and pulmonary circulations by binding to receptors in the smooth muscle cell membrane, activating adenylate cyclase and increasing cAMP concentrations, which lead to lower Ca^{2+} levels and a reduction of vascular tone. Thromboxane A2 is a potent leukotriene that has the opposite effects of the prostaglandins, producing vasoconstriction and platelet aggregation. Imbalance in this system caused by chronic hypoxia can lead to chronic pulmonary hypertension [95–97].

Nitric oxide (NO) is an endothelium-derived relaxant factor that causes relaxation of vascular smooth muscle cells after diffusing into the cell and activating guanylate cyclase, increasing the concentration of cGMP, leading to a reduction in the local concentration of Ca^{2+} and thus reducing vascular tone [96]. Calcium-sensitive potassium channels contribute to the vasodilatation caused by NO via a cGMP-dependent protein kinase [98]. NO is formed from L-arginine by NO synthase, and is almost immediately inactivated by binding to hemoglobin. Phosphodiesterase V breaks down cGMP, so the phosphodiesterase-inhibiting drugs, like sildenafil, potentiate NO-mediated vasodilation [99].

Endothelins are powerful endothelium-derived vasoactive peptides, and endothelin-1 (ET-1) is the best characterized. ET-1 is produced from proendothelin-1 by endothelin-converting enzymes in the endothelial cells of the systemic and pulmonary vasculature. Increased pressure, shear stress, and hypoxia can lead to increased production of ET-1 in the pulmonary circulation. Two ET-1 receptors, ETA and ETB, mediate effects on smooth muscle vascular tone [100]. The ETA receptor is found on the smooth muscle cell membrane and mediates vasoconstriction, while the ETB receptor is located on the endothelial cell itself, and results in increased NO synthase activity, producing vasodilation. The primary activity of ET-1 appears to be to stimulate the ETA receptor, and indeed increased levels of ET-1 are found in many pulmonary hypertensive states such as Eisenmenger syndrome and primary pulmonary hypertension [101]. ET-1 increases in response to shear stress, hypoxia, or ischemia, and results in elevated intracellular Ca^{2+} and increased sensitivity to Ca^{2+}, increasing pulmonary vascular tone and pressure [95].

Systemic circulation

There are multiple levels of control over the peripheral circulation. Neural control by the sympathetic and parasympathetic nervous systems is produced from stimulation of receptors on the afferent limb such as stretch receptors within the walls of the heart, and baroreceptors in the walls of arteries, such as the aortic arch and carotid sinuses. Stretch in the arterial wall stimulates the baroreceptors producing vasodilation and heart rate slowing, mediated by the vasomotor centers of the medulla [102]. Atrial stretch receptors inhibit secretion of vasopressin from the hypothalamus. The efferent limb of the autonomic nervous system consists of sympathetic and parasympathetic nerve fibers. The sympathetic nerves can be divided into vasoconstrictor and vasodilator fibers. When stimulated, the vasoconstrictor fibers release norepinephrine-activating α-adrenergic receptors producing vasoconstriction. The vasodilator fibers release acetylcholine or epinephrine, and are mainly present in skeletal muscle. Parasympathetic fibers are vital in control of heart rate and function, but have only a minor role in controlling the peripheral circulation [103].

Hormonal control and receptor-mediated intracellular signaling are other important mechanisms. Norepinephrine primarily stimulates peripheral α receptors and causes vasoconstriction. It is secreted by the adrenal medulla and by sympathetic nerves in proximity to the systemic blood vessels. Epinephrine is also secreted by the adrenal medulla, but its primary action is to stimulate the β_2 receptors in the peripheral circulation, causing vasodilation through cAMP-mediated reductions in intracellular Ca^{2+} concentrations.

Angiotensin II is produced by activation of the renin–angiotensin–aldosterone axis in response to reduced flow and pressure sensed by the juxtaglomerular apparatus in the kidney. Renin produces angiotensin I by cleaving angiotensinogen, and angiotensin II is produced when angiotensin I passes through the lung by angiotensin-converting enzyme. Angiotensin II is a potent vasoconstrictor, and also induces the hypothalamus to secrete vasopressin (antidiuretic hormone), which also has vasoconstrictor properties.

Atrial natriuretic factor (ANF) is released from atrial myocytes in response to stretch (elevation of right or left atrial pressure) on the atrium. It has vasodilatory and cardioinhibitory effects, and acts to retain sodium by decreasing tubular reabsorption of sodium in the kidney [104]. B-type natriuretic peptide is released by ventricular myocardium, also in response to stretch, and causes an increase in cGMP, leading to vasodilatation in both arterial and venous systems. In addition, it increases urinary sodium and water excretion [105].

Second messenger systems affect the activation of receptors on systemic vascular cell membranes leading to changes in vascular tone. The phosphoinositide signaling system is the common pathway for many of these agonists [102] (Fig. 6.15). Membrane kinases phosphorylate phosphatidylinositol, which is an inositol lipid located mainly in the inner lamella of the plasma membrane, producing phosphatidylinositol 4,5 biphosphate. The second

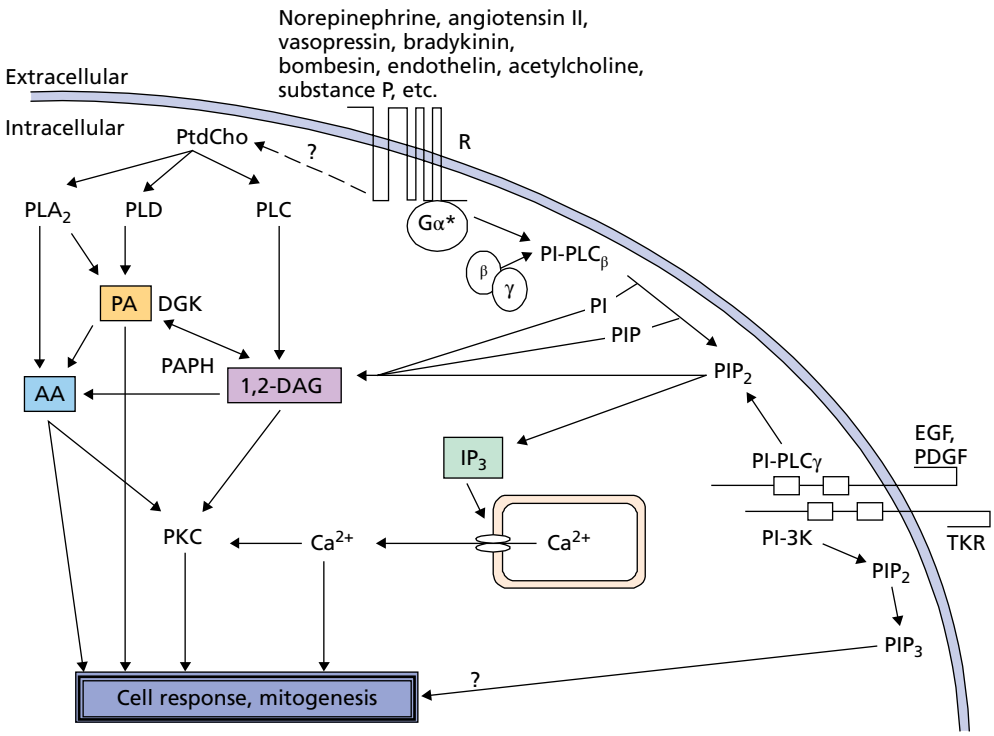

Figure 6.15 Phospholipase C system. Diagram summarizing the major receptor-activated pathways for production of inositol 1,4,5-triphosphate (IP3) and 1,2-diacyglycerol (1,2-DAG). The binding of an agonist to a receptor (R) with seven membrane-spanning domains results in the activation of the phosphatidylinositol-specific phospholipase Cβ (PI-PLCβ), whereas the stimulation of tyrosine kinase receptors (TKR) by polypeptide growth factors will activate phosphatidylinositol-specific phospholipase Cγ (PI-PLCγ). Both pathways will result in the hydrolysis of phosphatidylinositol 4,5-biphosphate (PIP2) and the formation of IP3 and 1,2-DAG. In addition, agonists that act on the heterotrimeric receptors may stimulate phosphatidylcholine (PtdCho) hydrolysis, and activation of tyrosine kinase receptors will stimulate the production of phosphatidylinositol 3,4,5-triphosphate (PIP3). DGK, diacylglycerol kinase; PAPH, phosphatidic acid phosphohydrolase; G*, activated G protein subunit; β, β-adrenergic receptor subunits; γ, γ-adrenergic subunits; PLD, phospholipase D; PKC, protein kinase C; PI-3K, phosphatidylinositol 3-kinase; PI, phosphatidylinositol; PIP, phosphatidylinositol 4-phosphate; EGF, epidermal growth factor; PDGF, platelet-derived growth factor; PLA2, phospholipase A2; AA, arachidonic acid. *Source:* Reproduced from Izzard et al [102] with permission of Elsevier.

messenger, inositol 1,4,5-triphosphate, is produced from this compound by the action of the enzyme phospholipase C (PLC) [106]. The sequence begins with the binding of an agonist, such as angiotensin II, vasopressin, norepinephrine, or endothelin to a receptor with seven membrane spanning domains. This receptor is linked to activated Gq protein subunit, which in turn stimulates phosphatidylinositol-specific phospholipase C (PI-PLC) to produce inositol 1,4,5,-triphosphate, which acts to cause release of Ca^{2+} from the sarcoplasmic reticulum, activating the actin–myosin system in the smooth muscle cells and producing vasoconstriction. Another second messenger, 1,2-diacylglycerol, is also produced, which goes on to activate protein kinase C, which in turn has a role in mitogenesis and thus proliferation of smooth muscle cells. There are many isozymes of phospholipase C; the form implicated in this series of events is the PLCβ form. The PLCγ isoform is activated when cell growth factors such as platelet-derived growth factor bind to their receptors on the cell surface and active tyrosine kinases. This results in the production of phosphatidylinositol 3,4,5-triphosphate, which is also implicated in mitogenesis.

Vasodilatation of the systemic circulation results from the formation of NO by nitrovasodilators, or by activation of β_2-adrenergic receptors in the peripheral vasculature, both of which result in the activation of guanylate cyclase and the production of cGMP, which reduces intracellular Ca^{2+} concentrations, producing vasodilation [107].

The vascular beds in various peripheral tissues differ in the amount of local metabolic control of vascular tone. For example, pH has much more influence on the pulmonary circuit, with low pH leading to vasoconstriction and higher pH leading to vasodilatation, than in the vascular tone of other tissues. Local CO_2 concentration is much more important to central nervous system vasculature, with high levels leading to vasodilatation. Decrease in oxygen tension will often lead to vasodilatation, as adenosine is released in response to the decreased oxygen delivery; however decreased oxygen tension increases tone in the pulmonary circulation. Autoregulation, or maintaining relatively constant blood flow over a wide range of arterial pressures, predominates in the cerebral circulation but is not as critical in other tissue beds. Autoregulation and CO_2 responsiveness are both blunted in the fetal and immature brain [108].

KEY POINTS: REGULATION OF VASCULAR TONE IN SYSTEMIC AND PULMONARY CIRCULATIONS

- The pulmonary vascular endothelium exerts major control of vascular tone and resistance, maintaining low resistance through complex pathways including nitric oxide, prostaglandins, and cyclic GMP
- Systemic vascular tone and resistance are maintained in a higher resistance state than the pulmonary vascular circulation with more neurohormonal activation that includes the sympathoadrenal, renin–angiotensin–aldosterone, and phospholipase C systems
- Pathophysiological derangements in vascular tone of pulmonary and systemic circulations have led to therapeutic approaches such as inhaled nitric oxide and endothelin receptor antagonists

Receptor signaling in myocardial dysfunction, congenital heart disease, and heart failure

A discussion of receptor signaling and calcium cycling in myocardial dysfunction is useful to serve as the basis for understanding many of the therapies discussed later in this text, and this section will focus on receptor physiology and calcium flux in three settings: acute myocardial dysfunction as seen after cardiac surgery and cardiopulmonary bypass; changes seen as responses to chronic cyanotic heart disease; and changes seen with chronic congestive heart failure and cardiomyopathy.

Receptor signaling in acute myocardial dysfunction

Acute myocardial dysfunction, such as that sometimes seen after cardiopulmonary bypass, is often treated with catecholamines. These drugs are sometimes ineffective, especially when used in escalating doses. In children, the number and subtype distribution of β-adrenergic receptors in atrial tissue is not affected by cardiac surgery with bypass; however, the activation of adenylate cyclase by isoproterenol is significantly reduced after bypass [109]. There is an uncoupling of β receptors from the Gs–protein–adenylate cyclase complex. Desensitization to moderate or high doses of catecholamines may occur after only a few minutes of administration, because increased cAMP concentrations result in uncoupling from the Gs protein [110].

After only a few minutes of high-dose catecholamine administration there may be inactivation of the phosphorylated adrenergic receptors from sequestration. These receptors can be sequestered by endocytosis, in a process involving a protein called β-arrestin, which binds to the receptor and a sarcolemmal protein called clathrin (Fig. 6.16) [51]. These sequestered receptors may either be recycled back to the cell membrane surface, or be destroyed by lysosomes [111]. This permanent destruction and degradation of receptors occurs after hours of exposure to catecholamines, and is accompanied by decreased mRNA and receptor protein synthesis, resulting in prolonged decrease in adrenergic receptor concentrations, which is reversed by decreasing exogenous catecholamines, but only as fast as new receptors can be synthesized.

Neonatal hearts may exhibit a different response to the acute or prolonged administration of catecholamines. Instead of desensitization, neonatal animal models demonstrate an enhanced β-adrenergic receptor response, accompanied by an increase in adenylate cyclase activity [112]. Desensitization occurs later in development. The exact translation of these data to humans is not clear.

Treatment with catecholamines may also increase the concentration of Gi protein subunits, decreasing the sensitivity of the β-adrenergic receptor. This relative decrease in the ratio of Gs to Gi protein subunits has been demonstrated in rat and dog models [113,114]. Another possible mechanism of catecholamine-induced desensitization of the neonatal myocyte was demonstrated in a rat model, where prolonged exposure to norepinephrine caused an initial increase in functional L-type Ca^{2+} channels on the sarcolemmal membrane. Continued

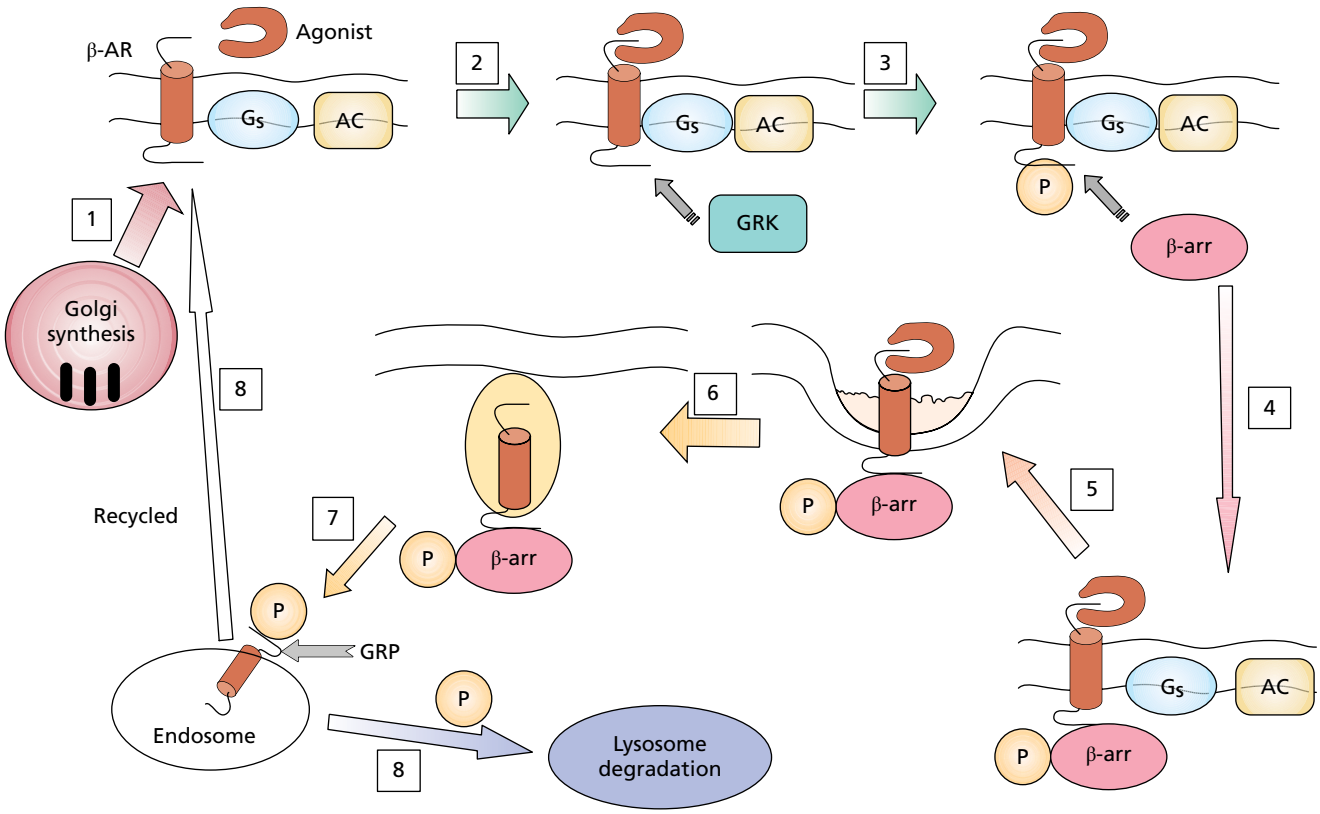

Figure 6.16 Desensitization and downregulation of the β-adrenoreceptor (β-AR). (1) Agonist binding. (2) Phosphorylation of the β-AR by G-protein coupled receptor kinases (GRK). (3) β-Arrestin binds to the GRK-phosphorylated β-AR, which is bound to the Gs protein. The receptor is then sequestrated to the endosomal compartment (4–7), to be dephosphorylated, and then either recycled back to the sarcolemma (8) or translocated to lysosomes for further degradation (8). AC, adenylate cyclase; GRP, G protein-coupled receptor phosphatase; P, inorganic phosphate groups; β-arr, β-arrestin. *Source:* Reproduced from Booker [51] with permission of John Wiley and Sons.

exposure caused a decrease in L-type Ca^{2+} channel mRNA to 50% of control values [115]. Sarcoplasmic reticulum Ca^{2+}-ATPase concentrations are reduced with chronic norepinephrine administration in the dog [116]. Finally, exposing adult or neonatal rat myocytes to high concentrations of catecholamines for 24 h leads to increased apoptosis of myocardial cells, a genetically programmed energy-dependent mechanism for cell death and removal [117,118]. This effect was mediated through β-adrenergic receptors in the adult model and α-receptors in the neonatal model.

All of these studies provide the theoretical basis for the argument that administration of catecholamines to patients with acute myocardial dysfunction should be limited in dose and duration. Obviously, this is difficult to accomplish in the setting of weaning a hemodynamically unstable patient from cardiopulmonary bypass. Strategies that may limit catecholamine dose include administering low doses of catecholamines together with phosphodiesterase inhibitors, as well as adding corticosteroids, tri-iodothyronine, and vasopressin [119].

Receptor signaling in congenital heart disease

In the past decade new information has become available concerning adrenergic receptor signaling in patients with congenital heart disease. A study of 71 infants and children undergoing cardiac surgery used tissue from the right atrial appendage to study β-adrenergic receptor density, distribution of β_1 and β_2 receptor subtypes, and coupling to adenylate cyclase [120]. This study found that patients with severe or poorly compensated acyanotic (e.g. congestive heart failure) or cyanotic (e.g. severe cyanosis) heart disease had significantly reduced β-adrenergic receptor densities. Outside of the newborn period, this downregulation was β_1 selective, but in newborns with critical aortic stenosis or transposition of the great arteries there was additional significant downregulation of the β_2 subtype. In tetralogy of Fallot patients, those treated with propranolol had a significant increase in the number and density of β-adrenergic receptors, when compared with untreated patients. β-Adrenergic receptor downregulation correlated with increased circulating norepinephrine levels. Finally, in severely affected patients, adenylate cyclase activity was reduced, demonstrating a partial decoupling, as noted previously. Other studies have determined that symptomatic tetralogy of Fallot patients, i.e. those with cyanotic spells, have a significantly greater number of β-adrenergic receptors in their right ventricular outflow tract muscle, and their adenylate cyclase activity was greater when compared to patients without cyanotic spells [121]. α_1-Adrenergic receptors are also affected by congenital heart disease. A study of atrial tissue excised at surgery in 17 children evaluated α- versus β-adrenergic receptor stimulation with pharmacological agents. The α component was responsible for 0–44% of the inotropic response, and β stimulation for 56–100% of the response, with the degree of right ventricular hypertrophy and pressure load correlating with the amount of α stimulation found [122].

A study of the myocellular changes and adaptation of the β-adrenergic receptor system that occur in the systemic RV of children with hypoplastic left heart syndrome (HLHS) compared 14 patients listed for transplant with normal RV function and no heart failure or inotropic therapy (compensated) with 12 HLHS patients listed for transplant with RV failure (decompensated) [123]. The control group was 12 organ donors whose hearts could not be matched due to size or blood type mismatch. Compared with non-failing control RVs, the HLHS RV demonstrated decreased sarcoplasmic reticulum calcium-adenosine triphosphatase 2α and α-myosin heavy chain gene expression, decreased total β-adrenergic receptors due to downregulation of β_1 receptors, preserved cyclic adenosine monophosphate levels, and increased calcium/calmodulin-dependent protein kinase II activity. There was increased atrial natriuretic peptide expression only in the HLHS group. There was myosin isoform switching, increased adenylyl cyclase 5, and increased phosphorylation of phospholamban threonine 17 only in the decompensated HLHS group; this signifies unique adaptation occurring only in these failing ventricles.

Receptor signaling in congestive heart failure and cardiomyopathy

Like adults with heart failure, children with congestive heart failure due to chronic left-to-right shunting and volume overload of the heart have elevated levels of circulating norepinephrine. This leads to a downregulation in β-adrenergic receptor density [124]. The degree of elevation of pulmonary artery pressure and amount of left-to-right shunting correlates with the plasma catecholamine levels, and is inversely correlated with β-adrenergic receptor density. All of these abnormalities return to normal levels after corrective surgery. The degree of receptor downregulation in congestive heart failure correlates with postoperative morbidity in infants and children. Children with an intensive care unit stay of greater than 7 days or those who died during the early postoperative period (9 of the 26) had significantly less β_1 and β_2 mRNA gene expression than those who had better outcomes [125]. In addition, the children receiving propranolol for treatment of their congestive heart failure had higher β-adrenergic receptor mRNA levels and tended to have improved outcomes. Finally, children with dilated cardiomyopathy also have a reduced response to catecholamines with one study showing no significant increase in ejection fraction during dobutamine stress test, with infusion of dobutamine at 5 and then 10 μg/kg/min [126]. Generally, studies in excised right atrial tissue in infants and children with congenital heart disease or cardiomyopathy demonstrate decreased density of β_1 and β_2 receptors, and decreased downstream adenylate cyclase function, with larger decreases associated with worse ventricular function [127]. A recent study of adrenergic receptor genetic variations assessed by single-nucleotide polymorphism analysis in 135 children with heart failure assessed α_2 receptor genotypes associated with increased norepinephrine (NE) release, and β_1 receptor genotypes associated with greater NE sensitivity [128]. In addition, β_2 receptor genotypes associated with receptor downregulation and impaired vasorelaxation were assayed. Patients with higher numbers of these abnormal genotypes had a linear increase in central venous pressure, pulmonary capillary wedge pressure, indexed pulmonary vascular resistance, and systemic vascular resistance. Patients with abnormal genotypes had much better response to β-blockers in preserving cardiac function.

An increasing number of children with heart failure are receiving therapy with left ventricular assist devices (LVAD), and in many the devices serve as a bridge to cardiac transplantation. In a very interesting study of hearts explanted for transplant, 11 hearts from transplanted LVAD children were compared with 20 heart failure patients transplanted without LVAD, and 16 control hearts explanted from donors which could not be transplanted for technical reasons [129]. Failing hearts without LVAD had a downregulation in total and β_1 receptors which was restored to normal non-failing levels with LVAD therapy. Other signaling pathways that were abnormal in failing hearts were also restored to normal non-failing levels, including G protein-coupled receptor kinase 2, indicative of reverse remodeling and suggesting that the use of LVAD more frequently as a bridge to recovery may be feasible in children.

The preceding has been a brief discussion of receptor signaling in pediatric heart disease. This emerging field has many implications for treatment strategies, and the reader is referred to excellent reviews for more detailed information on this subject [130].

KEY POINTS: RECEPTOR SIGNALING IN MYOCARDIAL DYSFUNCTION, CONGENITAL HEART DISEASE, AND HEART FAILURE

- High catecholamine doses in acute myocardial dysfunction can desensitize the myocardium through uncoupling of G protein adenylate cyclase complex and sequestration of β-adrenergic receptors
- Significant cyanotic or acyanotic congenital heart disease with heart failure can result in downregulation of β-adrenergic receptors in neonatal or infant myocardium
- Long-standing decreased ventricular function is often associated with decreased density of β-adrenergic receptors and decreased adenylate cyclase function

Myocardial preconditioning

Myocardial preconditioning refers to the finding that repeated, brief exposures of the myocardium to ischemia, volatile anesthetics, or other stresses induces a protective effect to a later (i.e. 12–24 h), more prolonged ischemic insult resulting in decreased myocardial infarction size and improved myocardial function after the insult [131]. Chronic cyanosis also induces a similar protective effect in the myocardium, although the effect size is smaller and more long-lasting, i.e. beyond 24 h. Another mechanism is remote ischemic preconditioning (RIPC), in which ischemia is produced in a tissue bed remote to the myocardium, for example skeletal muscle of the arm or leg, by repeated inflation of a blood pressure cuff which is thought to liberate as yet uncharacterized neurohumoral or hormonal substances that can protect the myocardium [132]. The mechanisms of myocardial preconditioning are complex but are thought to involve

release of various neurohormonal agents and peptides such as adenosine, bradykinin, and nitric oxide via a cGMP-dependent mechanism, which then triggers a series of signal transduction events within the cardiomyocyte that confer a "memory" effect that protects the myocardium from future ischemic insults. The signal transduction effects include protein kinase C, tyrosine kinases, mitogen-activated protein kinases, glycogen synthase kinase 3β, and other enzymes [133]. This series of events allows activation of mitochondrial and sacrolemmal K-ATP channels, which leads to the preconditioning by elusive mechanisms. One recently discovered candidate for this end effector is the mitochondrial permeability transition pore (MPTP) [133]. This is a nonspecific channel that spans both mitochondrial membranes; when opened for a prolonged period the result is a dissipation of mitochondrial electrical potential, inhibition of ATP synthesis, and ultimately mitochondrial swelling, rupture, failure of cellular energy metabolism, and cell death. Agents and stimuli that confer myocardial preconditioning have been found to keep the MPTP closed, thus possibly elucidating further the subcellular mechanisms involved.

KEY POINTS: MYOCARDIAL PRECONDITIONING

- Myocardial preconditioning is a complex phenomenon by which repeated brief exposure of the myocardium to ischemia or other stresses induces a protective effect to later ischemic insults
- The mitochondrial permeability transition pore is a common pathway for the various forms of ischemic preconditioning, staying closed and preventing mitochondrial failure
- Remote ischemic preconditioning produced by inflation of a blood pressure cuff on a limb before cardiopulmonary bypass will reduce some inflammatory and ischemic cell death markers, but as yet has not improved clinical outcomes.

Acknowledgment

Please note: major portions of this chapter were previously published as Chapter 4: Development of the Cardiovascular System and Nomenclature for Congenital Heart Disease, authors Barry D. Kussman and Wanda C. Miller-Hance; and as Chapter 5: Physiology and Cellular Biology of the Developing Circulation, author Dean B. Andropoulos. Both were published in *Anesthesia for Congenital Heart Disease*, 3rd edition, 2015, John Wiley and Sons, Hoboken NJ.

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CHAPTER 7

Developmental Physiology of the Respiratory System

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Introduction

Aerobic cellular respiration is critical for survival and requires the efficient exchange of oxygen for carbon dioxide at the alveolar surface. The alveolar surface area must be able to accommodate the tremendous range in oxygen consumption – from 250 mL/min at rest to 5500 mL/min at peak exercise [1]. As a result, the gas exchange surface area of the adult lung will attain 50–100 m^2 with a final total lung capacity of 2.5–3.0 L. Lung organogenesis has to expand the lung surface area to meet these needs. This chapter will discuss the development of lung, chest wall, and diaphragm structure, development of the pulmonary vasculature, lung fluid physiology, transition in pulmonary function and circulation at the time of birth, and the postnatal development of lung structure and pulmonary function. Then the developmental pathophysiology of three diseases commonly encountered by the anesthesiologist will be presented: asthma, bronchopulmonary dysplasia, and cystic fibrosis.

Embryology of the lungs, chest wall, and diaphragm

Lung formation begins early in human gestation and growth extends well into childhood [2,3]. Although lung development is organized into stages (embryonic, pseudoglandular, canalicular, saccular, and alveolar), there is considerable temporal overlap of each stage that can be modified by prenatal and postnatal events (Fig. 7.1).

Embryological phase

This phase of lung development is marked by the formation of the lung bud and initial branches of the airways. The primordial lung is a foregut derivative, first recognizable at 25 days in the human fetus as a laryngotracheal groove in the ventral foregut. The more distal aspect of the groove closes, resulting in the only remaining connection between foregut in the region of the developing hypopharynx and larynx. Failure of closure results in a spectrum of tracheoesophageal fistulae, from the most common proximal esophageal pouch with a distal fistula between trachea and esophagus typically at the level of the carina (87%) to the less common isolated esophageal atresia (8%), H-type fistula (4%), and esophageal atresia with either proximal (1%) or proximal plus distal (1%) fistula [4]. Upon closure of the laryngotracheal groove, the lung bud begins a series of dichotomous divisions that give rise to the conducting airways and five primordial lung lobes (two left and three right). Failure of the lung bud to divide can result in pulmonary agenesis, most typically of the right lung.

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

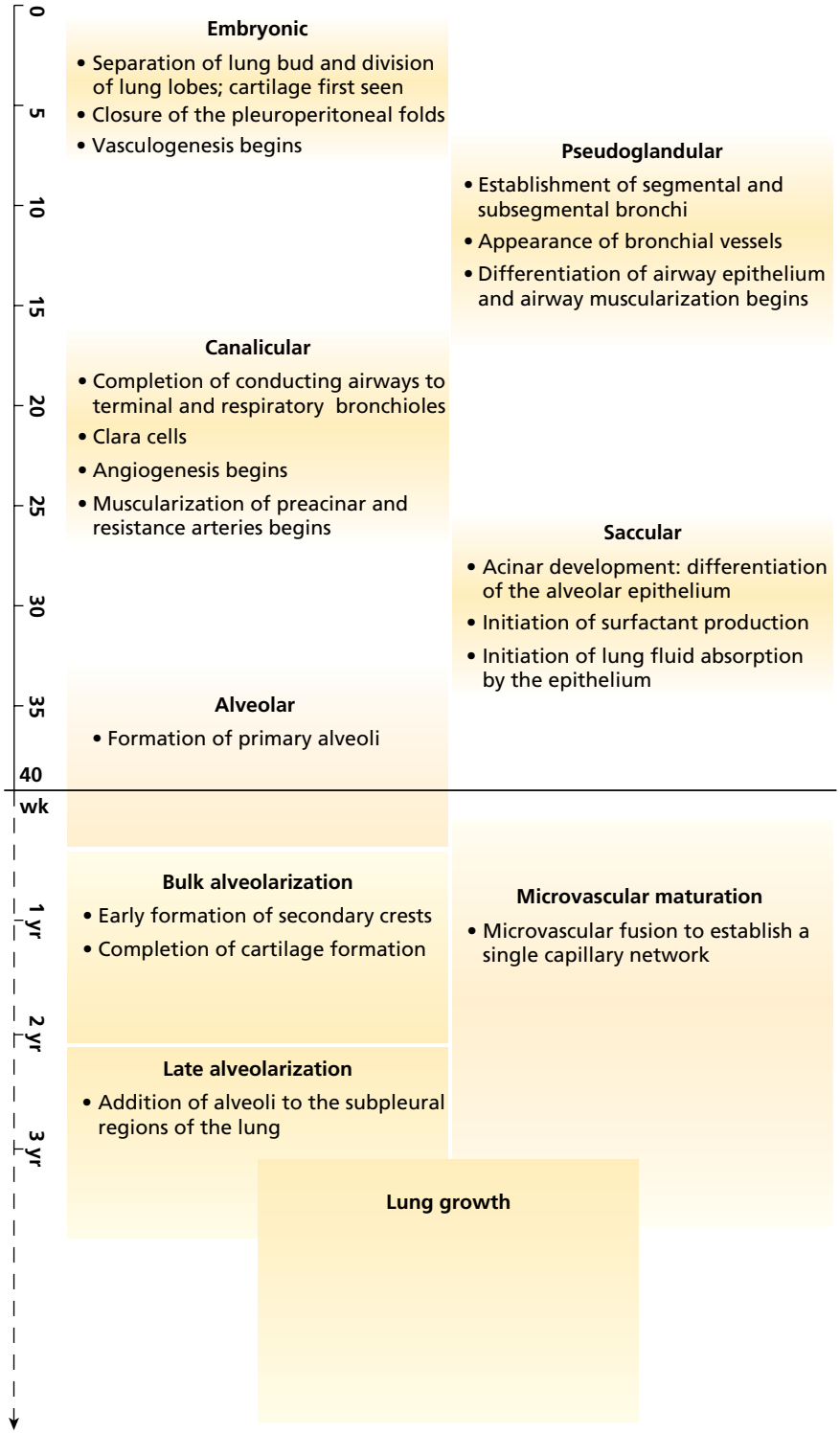


Figure 7.1 Schematic diagram of the fetal and postnatal stages of lung development.

Pseudoglandular phase

This stage of lung development marks the establishment of the large conducting airways of the lung. Divisions that establish the tracheaand segmental and subsegmental bronchi are completed by 7 weeks in the human fetus, and all bronchial divisions are completed by 16 weeks. It is important to remember that although the conducting airways will enlarge as the fetus and newborn grow (airway diameter and length increase 2- to 3-fold between birth and adulthood), large airway branching ceases after 16 weeks of gestation.

Canalicular phase

The canalicular phase of lung development is marked by completion of the small conducting airways through the

level of the terminal bronchioles, the last airways with cartilaginous support. Respiratory bronchioles no longer invested with cartilage mark the beginning of the gas exchange region of the lung. A respiratory bronchiole and all of its associated alveolar ducts and alveoli constitutes an acinus, and is the basic gas exchange unit of the lung. A terminal bronchiole with all its associated acinar structures constitutes a lobule. Branching of the terminal and respiratory bronchioles during the canalicular phase will ultimately result in a total of 23 airway subdivisions and completes the branching of the airways.

Saccular phase

This phase of lung development begins at roughly 24 weeks of human gestation and continues until just prior to term gestation. During this phase there is evolution of the relationships between the airspaces, capillaries, and mesenchyme, although the alveolocapillary membrane (the distance from the luminal surface of the airspace/alveolus to the luminal surface of the capillary) is sufficient to participate in gas exchange (0.6 μm) by approximately 24 weeks. Beyond this point, the efficiency of gas exchange is determined by the available surface area, not by the width of the alveolocapillary membrane. Lengthening and widening of the smooth-walled airspaces of terminal sacs expands the gas exchange surface area, which remains invested with a double capillary network.

Alveolar phase

This phase of lung development is the final stage that is initiated during fetal lung development, but alveolarization will not be completed until much later (see section "Lung development after birth"). While branching morphogenesis establishes the conducting airways of the lung, alveolarization will establish the large surface area involved in gas exchange [5]. This process will result in a 20-fold increase in surface area between birth (with between 0 and 50 million alveoli) and adulthood (>300 million alveoli). Primitive saccules develop low ridges (primary septa) that subdivide the saccule into an alveolar duct containing primary alveoli, and outpouchings between the ridges (secondary septa) that establish secondary alveoli. Regions destined for secondary septation exhibit increased elastin deposition [6], and elastin localizes to the tips of the secondary crests as they form. The septa contain a connective tissue core separating two capillary membranes, suggesting that the septum is formed by the folding of a capillary on itself. Septation also leads to the development of the pores of Kohn, allowing gaseous continuity between acini. Formation of secondary crests and the maturation of the microvasculature are critical elements of this stage of lung development, which only begins at roughly 36 weeks gestation in the human. Thus, the human lung is not fully mature structurally, even at term delivery. The completion of alveolar development is discussed in the section "Development of the pulmonary vasculature and its relationship to alveoli."

Development of the chest wall and diaphragm

Formation of the ventral body wall is initiated in the fourth week post fertilization with the formation of the lateral body wall folds. The folds consist of lateral plate mesoderm and overlying ectoderm, and the folds will move ventrally to meet in the midline of the developing embryo [7]. Failure of closure may occur anywhere along the midline, resulting in congenital malformations of the thoracic body wall (ectopia cordis, sternal cleft), and abdominal body wall (omphalocele, bladder exstrophy). The sternum arises from parallel bands of condensed mesenchyme in the 6th week and will fuse in the 10th week [8]. Formation of cartilage appears in the sternum immediately but ossification will not begin until the 6th month. Ossification of the ribs begins in the 7th week of gestation and will be completed by early adulthood. The diaphragm is critical for separating the developing lung within the thorax from the abdominal cavity with the developing gut and solid organs of the abdomen. Closure of the pleuroperitoneal folds is initiated in the pseudoglandular phase, and is completed by 7 weeks in the human fetus. During this time, the midgut resides within the umbilical cord and returns to the peritoneal cavity at 10 weeks. Thus, failure of diaphragm formation results in continuity between thoracic and peritoneal cavities, allowing peritoneal contents (stomach, intestine, and/or liver) to migrate into the thoracic cavity. This restricts the space into which the lung grows, leading to pulmonary hypoplasia of the lung ipsilateral to the diaphragmatic defect. Pulmonary hypoplasia can also extend to the contralateral lung due to shifting of the mediastinum as abdominal viscera accumulate within the thorax.

KEY POINTS: EMBRYOLOGY OF LUNGS, CHEST WALL, AND DIAPHRAGM

- Lung development passes through five phases that somewhat overlap
- Each developmental phase extends the structure of the lung and eventually produces a lung that is capable of oxygenation and carbon dioxide removal without the placenta
- Alveolarization, while incomplete at birth, is mostly complete by about 3 years of age
- The chest wall is mostly cartilage at birth and therefore very compliant. This chest wall plasticity is necessary to allow vaginal birth

Development of the pulmonary vasculature and its relationship to alveoli

The pulmonary vasculature consists of the vascular supply to the acini and the bronchial circulation [9]. During early fetal life, the airways act as a template for pulmonary blood vessel development. Early pulmonary blood vessels form by vasculogenesis, which is *de novo* differentiation of mesenchymal cells into endothelial cells and then capillaries. As each new airway buds into the mesenchyme, a new plexus forms and

adds to the pulmonary circulation. By 5 weeks of human gestation, a capillary network surrounds each bronchus and circulation of blood between the right ventricle and the left atrium via this network is evident. By the canalicular stage of lung development, new blood vessels form from pre-existing vessels via *angiogenesis* in which endothelial cells proliferate and sprout from established vessels. *Vasculogenesis* is the primary mode of pulmonary vascular development until the 17th week of gestation when all preacinar airways are complete, whereas angiogenesis becomes the predominant mode in the later stages of lung development. Interconnections between vascular networks arising from both angiogenesis and vasculogenesis increase in the saccular phase of lung development.

In the human lung, a second circulatory system, the bronchial circulation, arises from the dorsal aorta supplying systemic blood. The bronchial vasculature develops after the pulmonary circulation, with bronchial vessels first apparent by 8 weeks. The network of bronchial vessels is extensive, with bronchial arteries demonstrated as distal as the alveolar ducts in the adult respiratory tree. The inappropriate branching of bronchial vessels from the dorsal aorta is implicated in the formation of bronchopulmonary sequestration, a space-occupying lung malformation that can result in hypoplasia of the ipsilateral lung.

Vasculogenesis and angiogenesis are the primary mechanisms of vascular development throughout intrauterine life. The human lung at term contains only a small portion of the adult number of alveoli, and the airspace walls are represented by a thick "primary septum" consisting of a central layer of connective tissue surrounded by two capillary beds, each of them facing one alveolar surface [3]. This double capillary network is not present in the adult lung. As alveolar architecture changes with the appearance of secondary septa, folding of one of the two capillary layers occurs within the secondary septa. Microvascular maturation involves fusion of the double capillary network into a single capillary system. The expansion of surface area and luminal volume compresses the interstitium, bringing the capillary networks in close proximity to potential airspaces and thereby promoting both alveolar surface area expansion and capillary bed fusion. By the third postnatal week, lung volume increases by 25% and there is a 27% decrease of the interstitial tissue volume that is believed to promote microvascular fusions. Subsequently, there is preferential growth of fused areas that continues until ~3 years of age. Lung volume increases about 23-fold between birth and young adulthood, while capillary volume expands 35-fold. It has been recently shown that this increase in capillary volume occurs by insertion of capillaries in the absence of capillary sprouting. This new concept in capillary network growth has been named *intussusceptive microvascular growth*, and involves the formation of transluminal tissue pillars within existing vessels that then expand to increase capillary surface area [3].

Muscularization can be detected early in development of the pulmonary arteries [9]. Initially the muscular investment of the vasculature is derived from the migration of bronchial smooth muscle cells from adjacent airways. Muscularization of preacinar and resistance arteries of the pulmonary vasculature begins in the canalicular stage and continues through the remainder of gestation. This second phase of smooth muscle cells investing pulmonary vessels develops from the surrounding mesenchyme. A third phase of vascular muscularization has been described, largely in the very distal lung, in which capillary endothelial cells undergo a process of endothelial–mesenchymal transition that encompasses endothelial cell division, separation and migration from the endothelial layer, and expression of smooth muscle cell markers. Normal muscularization of pulmonary arteries extends down to the level of the terminal bronchiole and is minimal to absent in vessels surrounding respiratory bronchioles. Abnormal extension of smooth muscle along arterioles supplying acinar structures occurs in infants dying from persistent pulmonary hypertension of the newborn and in severe bronchopulmonary dysplasia.

Recent evidence suggests that the pulmonary capillary bed actively promotes normal alveolar development and contributes to the maintenance of alveolar structures throughout life [10]. The observation that combined abnormalities in the airways and vasculature occur in bronchopulmonary dysplasia supports this hypothesis. Intra-acinar arteries and veins continue to develop after birth by angiogenesis as long as alveoli continue to increase in number and size. This may well be a reciprocal process because vascular growth around the distal airspaces suggests an inductive influence from the alveolar epithelial cells.

KEY POINTS: DEVELOPMENT OF THE PULMONARY VASCULATURE

- Development of pulmonary vasculature generally follows development of the airways
- There is a dual system of vessels in the alveoli at birth that disappears with further extrauterine lung growth
- From birth to young adulthood the lung volume increases 23-fold and the capillary volume increases 35-fold
- The pulmonary capillary bed probably actively promotes normal alveolar development and contributes to the maintenance of alveolar structures throughout life

Physiology and anatomy of the upper and lower airways in infants and children

Some aspects of this topic are also covered in Chapter 16. The airway of infants and young children has several anatomical and physiological differences compared to that of older children and adults. Nasal breathing is strongly preferred over oral breathing in the neonatal period. Newborn infants with obstruction of the nasal passage, i.e. with choanal atresia, can present with severe episodes of cyanosis. However, infants can breathe through their mouth in the case of nasal obstruction [11]. Reasons for the preferred nasal route in newborn infants are the relatively large tongue and the more cranially positioned epiglottis which can be in contact with the soft palate and therefore impede oral breathing [12]. The highly positioned epiglottis and larynx move down over the first years of life. The upper airway, including pharynx, larynx, trachea,

and bronchi, shows also a much higher compliance in infants compared to older children and adults. This is due to a decreased upper airway muscle tone and a higher flaccidity of the supporting laryngeal, tracheal, and bronchial cartilage. Infants and young children are therefore at higher risk of upper airway collapse [13]. This can be observed in infants with upper airway obstruction, who can aggravate their obstruction by forceful inspirations leading to upper airway collapse and further obstruction. In lower airway obstruction, forceful expiration can lead to airway collapse due to compressive forces of the thorax and respiratory muscles. This phenomenon of dynamic airway collapse can be observed in agitated and crying infants and young children. It also explains why sedatives can improve their respiratory function, especially by preventing airway collapse due to forceful inspirations and expirations [14].

Airway resistance (R_{aw}) is much higher in newborn infants compared to older children and adults, and small reductions of their airway diameter lead to a much higher increase in R_{aw} than in airways with larger diameters. This is one of the reasons why infants and young children are much more affected by small airway diseases, e.g. bronchiolitis, compared to adults, as up to 50% of R_{aw} in infancy is contributed by the small airways [15,16].

KEY POINTS: PHYSIOLOGY OF THE UPPER AIRWAY IN NEONATES

- Neonates prefer nasal breathing
- The large tongue and more cranial epiglottis make contact with soft palate and make difficult breathing more likely
- Structures of the upper airway are more compliant and, therefore, more prone to collapse during upper airway obstruction
- Airway resistance is higher in neonates and infants due to the small airway. Edema of these airways has a much more profound effect than in older patients

Chest wall and respiratory muscles

Breathing is the result of cycling changes of pressures in the lung and airways generated by a complex interplay between chest wall, diaphragm, airways, and lung parenchyma. Besides developmental changes of lung parenchyma and airways, respiratory muscles and chest wall also undergo specific changes during infancy and childhood.

Diaphragm and intercostal muscles

The diaphragm is a dome-shaped musculo-fibrous septum between thorax and abdomen. It represents the most important respiratory muscle. In infancy, the insertion of the diaphragm is more horizontal, i.e. the costo-diaphragmatic angle is more shallow compared with later in life [17]. This reduces the efficiency of breathing and limits the ability of the diaphragm to increase tidal volumes when required. In young children with high chest compliance and less efficient intercostal muscles, maximal diaphragmatic activity during inspiration can lead to an indrawing of the lower costal margin. This so-called Hoover sign is a common symptom in infants and young children with respiratory distress. The relative muscle mass of the diaphragm in infancy is also lower and contains fewer fatigue-resistant type I muscle fibers than in older children and adults. The external intercostal muscles raise the rib cage upward and outward but contribute little to inspiration in early infancy due to the horizontally placed ribs. Additionally, the external intercostal muscles contribute to stabilization of the ribcage. Anesthetic agents can impair their function and can lead to a loss of functional residual capacity. At the end of the first year of life the contribution of ribcage muscles to tidal breathing has reached characteristics of older children and adults [18].

Chest wall

The configuration of the chest differs markedly in infants compared to older children. The cross-sectional area of the thorax in infants shows a relatively square rather than an elliptic shape as in older children. The ribs in infants are more horizontally placed, which limits the function of the intercostal muscles and thoracic respiration. During childhood and adolescence, the ribs become more downward sloping so that by age 10 years they have reached the adult configuration. This enables older children to increase their thoracic diameter more than younger children. As a result, the contraction of the diaphragm and intercostal muscles, lifting the ribs like a bucket handle, is more effective in increasing intrathoracic volume, and thus negative pressure, in adulthood than it is in infancy. Furthermore, the chest wall in infants is highly compliant and shows a higher deformability than in older children [19]. Respiratory distress in young children can lead to thoracic distortion with waste of energy and reduced efficiency of breathing. During the first years of life, chest configuration gradually changes and chest wall compliance decreases continuously with progressive ossification of the ribs.

KEY POINTS: DIAPHRAGM AND CHEST WALL OF NEONATES AND INFANTS

- The diaphragm of infants inserts more horizontally, which decreases the efficiency of breathing
- The decreased efficiency of the diaphragm decreases the infant's ability to increase tidal volume when needed
- The diaphragm of neonates and young infants has fewer fatigue-resistant type I fibers
- Anesthesia decreases the function of the external intercostal muscles, which reduces functional residual capacity
- The very compliant chest wall of neonates is distorted during airway obstruction, which wastes energy and decreases breathing efficiency

Lung fluid physiology

Fetal lung fluid is a product of the epithelial cells lining the developing lung [20], and averages 4–6 mL/kg/h. Laryngeal abduction creates resistance to passage of lung fluid out into

Table 7.1 Composition of human fetal lung fluid compared to other body fluids

Component	Lung fluid	Interstitial fluid	Plasma	Amniotic fluid
Sodium (mEq/L)	150	147	150	113
Potassium (mEq/L)	6.3	4.8	4.8	7.6
Chloride (mEq/L)	157	107	107	87
Bicarbonate (mEq/L)	3	25	24	19
pH	6.27	7.31	7.34	7.02
Protein (g/dL)	0.03	3.27	4.09	0.10

the amniotic fluid, providing an end-expiratory pressure of approximately 2–4 cmH_2O. As a result, fetal lung fluid accumulates to a total volume of 20–30 mL/kg during gestation. The composition of fetal lung fluid is distinct from both amniotic fluid and plasma, as illustrated in Table 7.1. The increased chloride content of fetal lung fluid, as compared to serum, is the result of active chloride secretion by the tracheal and distal pulmonary epithelium. Fetal lung fluid secretion can be enhanced by prolactin, keratinocyte growth factor, and prostaglandins E2 and F2, while it is inhibited by a variety of mediators, including β-adrenergic agonists, vasopressin, serotonin, and glucagon.

While fetal lung fluid is an essential component of lung development, it presents a significant obstacle to the transition to air breathing upon delivery. Three important events must occur to decrease the amount of fetal lung fluid and its potential impact on alveolar surface tension: absorption, bulk removal, and maturation of pulmonary surfactant. Conversion of the epithelial surface from secretory to absorptive is largely due to enhanced sodium transport across the alveolar epithelium during the third trimester [20]. Much evidence suggests that induction of components of the epithelial sodium channels (ENaC) around the time of birth is a major factor in promoting sodium transport with water passively following the movement of sodium. Induction of ENaC components occurs at a transcriptional level in response to changes in extracellular matrix components, glucocorticoids, aldosterone, and oxygen. By comparison, agents that increase intracellular cyclic adenosine monophosphate (cAMP) levels (i.e. β-agonists, phosphodiesterase inhibitors, and cAMP analogs), while not increasing the number of sodium channels, increase the probability of a channel being open to sodium transport. Glucocorticoids and thyroid hormones play an important role in priming the lung epithelium to the actions of β-adrenergic agonists on sodium transport across lung epithelia near term. Water channels consisting of aquaporins are also induced during the late fetal period to facilitate fluid movement, but their importance remains unclear.

Conversion to an absorptive surface is not sufficient to minimize the fetal lung fluid at the time of term delivery. The absence of uterine contractions is associated with an increased incidence of retained fetal lung fluid in infants delivered by cesarean section without the benefit of labor. Upon delivery of the head and neck, continued uterine contractions on the fetal thorax promote expulsion of bulk fluid from the fetal lung. However, animal studies have shown that the magnitude of the benefit of thoracic compression during labor is only modest [21]. The primary mechanism by which labor facilitates clearance of lung fluid is through hormonal effects on fluid clearance, especially through catecholamine-induced changes in the open probability of ENaC. The onset of air breathing with increased intrathoracic negative pressure assists in the clearance of residual fetal lung fluid into the loose interstitial tissues surrounding alveoli. Fluid is then reabsorbed via lymphatics and pulmonary blood vessels. The amount of residual liquid in the lung after transition is approximately 0.37 mL/kg bodyweight.

KEY POINTS: LUNG FLUID PHYSIOLOGY

- The lungs of fetuses produce 4–6 mL/kg/h of fluid, which is necessary for lung growth
- Near birth the volume of fluid in the lungs is 20–30 mL/kg, similar to the functional residual capacity after birth
- Fetal lung fluid is removed at or near birth by absorption, bulk removal, and maturation of surfactant

Pulmonary cell types, development, and release of surfactant

Proximal airways

The proximal airway epithelium is tall and columnar, decreasing to a more cuboidal appearance distally [22,23]. The endodermal epithelial lining cells of the trachea and bronchi partition into four cell types: undifferentiated columnar, ciliated, secretory/goblet, and basal cells. Ciliated cells critical to the process of mucous clearance are first apparent between 11 and 16 weeks of human gestation and become less prevalent in more distal airways. Three types of secretory cells – those with largely mucous granules, those with serous granules, and some with both types of granules – can be seen as early as 13 weeks. The number of mucin-producing goblet cells in airways peaks at mid-gestation in the fetus and declines into adulthood. Finally, immature basal cells expressing epidermal keratin have been noted as early as 12 weeks of gestation.

Cartilaginous support of the tracheobronchial tree proceeds in a centrifugal fashion beginning in the primitive trachea at 4 weeks of human gestation, reaching the main bronchi by 10 weeks, and proceeding to the most distal terminal bronchioles by approximately 25 weeks of gestation. Cartilaginous investment of airways is complete by the second month postnatally. Submucosal glands are found in the interstitium between the cartilaginous tissue and surface epithelium, and play a major role in airway host defense. The airways of infants and children contain relatively more submucous glands than adults. The glands are lined by mucous cells proximally and serous cells more distally, the latter comprising 60% of the total epithelial cell content of the glands. Serous cells secrete water, electrolytes, and proteins with antimicrobial, anti-inflammatory, and antioxidant properties, while the mucous cells produce primarily mucins. In addition to this host defense role, submucosal glands also contain a population of basal cells that respond to injury of the airway by replenishing the airway epithelium.

Muscular investment of the airways begins as early as 6–8 weeks of gestation as smooth muscle cells are identifiable around the trachea and large airways. Fetal airway smooth muscle is innervated and able to contract during the first trimester. It is also responsive to methacholine challenge that is reversible with β-adrenergic agonists. Muscularization increases through fetal life and childhood such that there is an increase in the amount of smooth muscle relative to airway size compared to adults. Furthermore, there is a rapid increase in bronchial smooth muscle immediately after birth, whether at term or prematurely.

Pulmonary neuroendocrine cells (PNEC) are found throughout the airways, often in innervated clusters known as pulmonary neuroendocrine bodies (NEB) located at branch points in the bronchial tree [24]. Solitary PNEC are sensitive to stretch- and hypoxia-mediated secretion, producing both amines (i.e. serotonin) and peptides (i.e. bombesin) that are important in regulating bronchial tone. Pathological conditions recently associated with PNEC/NEB, most often characterized by hyperplasia, include bronchopulmonary dysplasia, disorders of respiratory control (congenital central hypoventilation syndrome and sudden infant death syndrome), cystic fibrosis, and pulmonary hypertension. Neuroendocrine hyperplasia of infancy (NEHI) is a rare form of interstitial lung disease of infancy associated with expansion of the number of PNEC and NEB, yet little is known about the mechanism of disease.

Distal airways

The bronchiolar epithelium differs from the more proximal airway epithelium. The bronchiolar epithelium contains progressively fewer ciliated cells and goblet cells, which are ultimately absent from the terminal bronchioles. Clara cells are found in increasing numbers and density down the conducting airways, such that it is the most abundant cell of the terminal bronchiole [22]. Clara cells are first evident by 16–17 weeks of human gestation, initially exhibiting large glycogen stores that are replaced by secretory granules. Between 23 and 34 weeks there is a dramatic increase in Clara cell numbers in distal bronchioles. Clara cells play an important role in host defense and in the detoxification of gaseous components of the air we breathe. This specialized cell produces the highest levels of cytochrome P450 and flavin mono-oxygenases in the lung. While critically important in detoxification, these enzymes participate in the bioactivation of procarcinogens as well, placing the Clara cell at risk as a target of toxic metabolites. The Clara cell also plays an important role in immunoregulation in the distal airways. Important host defense products of the Clara cell include Clara cell secretory protein (CCSP or CC10), surfactant proteins A and D, leukocyte protease inhibitor, and a trypsin-like protease. The secretion of antiproteases from Clara cells suggests that they modulate the protease–antiprotease balance in the distal lung.

Alveoli

During the 4th through 6th months of gestation the epithelial cells lining the acini begin to differentiate further [25]. The cuboidal epithelial cells accumulate large glycogen stores and develop small vesicles containing loose lamellae. The large glycogen pools provide a ready source of substrate required for the production of increasing amounts of surfactant phospholipids, and they decrease in size as surfactant production advances in the fetal lung. In cells destined to become type 2 cells, lamellar bodies become larger, more numerous, and more densely packed with surfactant phospholipids and proteins, whereas those cells destined to become type 1 cells, upon losing their relationship to mesenchymal fibroblasts, lose the prelamellar vesicles and become progressively thinner, thereby adopting a phenotype more suitable for gas exchange. Alveolar type 1 and 2 cells are readily identified early in the saccular stage of fetal lung development. There remains considerable controversy regarding the origin of type 1 cells. In culture these cells demonstrate very slow turnover, with a doubling time estimated to be between 40 and 120 days, suggesting that *in vivo* they are functionally terminally differentiated. In response to epithelial damage, type 2 cells proliferate to re-establish epithelial continuity, and then lose phenotypic features such as lamellar bodies while acquiring markers of type 1 cells, suggesting that rapid repopulation of type 1 cells requires a type 2 cell intermediary.

There is increasing appreciation for the alveolar type 1 cell as more than a passive membrane for gas exchange [26]. The large surface area and small cytoplasm:nucleus ratio provides for a thin alveolocapillary membrane to facilitate gas exchange. However, this large surface area also provides a large absorptive surface in the lung. The presence of water and ion channels, some distinct from those in type 2 cells, helps to ensure that the alveolus remains relatively dry. Type 1 cells may also regulate cell proliferation locally, signal macrophage accumulation, and modulate the functions of local peptides, proteases, and growth factors.

While most notable for its role in surfactant production, the alveolar type 2 cell provides additional important functions in the alveolus [27]. Alveolar type 2 cells are local progenitor cells, as mentioned previously. Like type 1 cells, alveolar type 2 cells contain specialized ion and water channels as well as ion pumps in both the apical and basal membranes that contribute to the movement of water and ions across the epithelium. Type 2 cells also produce important antioxidants (SOD-1, -2, -3, glutathione) and molecules of innate host defense (SP-A, SP-D, lysozyme) to participate in detoxification and sterilization of the alveolar microenvironment.

More recently, it is becoming clear that alveolar type 2 cells may also play a part in exacerbating alveolar pathology. The type 2 cell participates in the coagulation–fibrinolysis cascade through the production of fibrinogen, urokinase-type plasminogen activator, and tissue factor, especially under pathological circumstances. Type 2 cells are increasingly recognized as a source of cytokine and chemokine production in the lung, as well as growth factors that can promote fibrosis. Finally, crosstalk between epithelial cells, cell matrix, interstitial cells, and local inflammatory cells can foster the resolution of injury and inflammation, or prolong lung remodeling after injury with detrimental effects, such as lung destruction and fibrosis. Therefore, while previously heralded as the defender of the alveolus, the alveolar type 2 cell plays a much more complex role in alveolar health and disease.

KEY POINTS: PULMONARY CELL TYPES AND SURFACTANT RELEASE

- Ciliated epithelial cells are present by 10–16 weeks of gestation and are important for clearing mucus from the lung
- Mucus-producing goblet cells are present by 13 weeks of gestation and are important for proteting the lung from foreign material
- Cartilage is found early in the trachea and is in the distal terminal bronchioles by 25 weeks of gestation
- Clara cells in the distal airways are important for host defenses
- Type 2 cells are the eventual source of surfactant but also produce cytokines and chemokines

Surfactant

Pulmonary surfactant is essential to alveolar health. A thin layer of liquid is constantly secreted into the alveolar lumen to protect the delicate alveolar epithelium. The surface tension generated by this aqueous layer opposes alveolar inflation and promotes alveolar collapse at the end of expiration owing to the law of Laplace, which states that the collapsing pressure on the alveolus is directly proportional to the surface tension while inversely proportional to the radius of curvature of the alveolus. The presence of pulmonary surfactant at the air–liquid interface lowers surface tension as alveolar surface area decreases, thereby preventing end-expiratory atelectasis, maintaining functional residual capacity, and lowering the force required for subsequent alveolar inflations.

Pulmonary surfactant is a complex mixture of phospholipids (80% by weight), neutral lipids (10%), and proteins (10%) that is synthesized, packaged, and secreted by alveolar type 2 cells [28]. Storage of surfactant occurs in the lamellar body, a lysosome-derived membrane-bound organelle that undergoes regulated secretion in response to a variety of stimuli, including stretch. In the alveolus, surfactant phospholipids transition through an extracellular storage form, tubular myelin. Phospholipid and protein components are recycled out of the surfactant monolayer at the air–liquid interface and taken back into the alveolar type 2 cell where they can be repackaged into lamellar bodies. Alveolar macrophages engulf and degrade surfactant components as well.

Saturated phosphatidylcholine makes up 45% of surfactant by weight, with unsaturated phospholipids accounting for 25%, and other phospholipids (most notably phosphatidylglycerol at 5%) contributing 10%. The predominant saturated surfactant phospholipid is dipalmitoyl phosphatidylcholine, or DPPC. DPPC is the only surface-active component of lung surfactant, capable of lowering surface tension to nearly zero. The presence of unsaturated phospholipids and other lipid components like cholesterol enables the monolayer to remain fluid at body temperature during the respiratory cycle. The phospholipid content of the developing fetal lung increases with advancing gestation due to increased activity of enzymes responsible for phospholipid synthesis within alveolar type 2 cells. The expression and activity of enzymes of the choline incorporation pathway, the predominant pathway for surfactant phospholipid synthesis, are not only developmentally regulated but are also induced by hormones. The inductive hormones that have direct clinical relevance are glucocorticoids and agents that increase intracellular cAMP, such as the β-adrenergic agonist (and tocolytic) terbutaline.

Surfactant contains a group of specific proteins with importance to surfactant function and host defense that contribute up to 5% of surfactant by weight; the remaining 5% of the protein content of surfactant comes largely from serum proteins. The four surfactant proteins, SP-A, -B, -C, and -D, are subdivided based upon their physical characteristics into either hydrophobic (SP-B and -C) or hydrophilic (SP-A and -D) proteins. The hydrophobic surfactant proteins play a major role in the surface-active properties of surfactant, whereas the primary roles of the hydrophilic surfactant proteins are in host defense, immunomodulation, and surfactant clearance and metabolism.

Together, the hydrophobic proteins facilitate the mobilization of surfactant phospholipid from tubular myelin to the surface monolayer, promote spreading of phospholipids in the surfactant film, and assist in film stability at end-expiration [28]. SP-B plays a central role in alveolar health due to its critical function in surfactant homeostasis. It is a secretory protein that exhibits strong association with membranes, unlike SP-C which contains a membrane-spanning domain and covalently attached fatty acids (palmitate) that render it integral to phospholipid membranes [29]. Both SP-B and SP-C are synthesized as large precursor proproteins that undergo extensive post-translational processing as they pass through the secretory pathway, ultimately reaching the lamellar body. SP-B is essential for the process of lamellar body formation, and the alveolar type 2 cells of infants with inherited deficiency of SP-B are devoid of lamellar bodies. Because the lamellar body is where SP-C processing is completed, infants with inherited deficiency of SP-B are also deficient in mature SP-C, instead accumulating a larger, non-functional precursor of SP-C. Thus, patients with inherited deficiency of SP-B, despite having relatively normal surfactant phospholipid profiles, make a pulmonary surfactant with very poor surface tension properties due to the absence of both SP-B and SP-C. Conversely, because SP-C does not play either a direct or indirect role in SP-B protein processing, animals with SP-C deficiency have normal SP-B, normal lamellar bodies, relatively normal surfactant function, and exhibit no perinatal lethality due to surfactant dysfunction.

Like the enzymes of surfactant phospholipid production, SP-B and SP-C exhibit developmental and hormonal regulation of expression [30]. In human fetuses, SP-C mRNA is detected as early as 12 weeks of gestation and SP-B mRNA by 14 weeks, yet the mature proteins are not detectable in fetal lung tissue until after 24 weeks. SP-B protein is not detectable in amniotic fluid until after 30 weeks of gestation, increasing towards term [31]. This is due to developmental regulation of post-translational events in the proteolytic processing of proSP-B and proSP-C [32]. Consequently, infants delivered prematurely have reduced levels of both surface-active components of surfactant, phospholipid and hydrophobic surfactant proteins, due to the developmental regulation of surfactant proteins and the enzymes of phospholipid production in alveolar type 2 cells. The rate of type

2 cell differentiation, and secondarily surfactant production by the fetal lung, is modulated by levels of endogenous corticosteroids and is accelerated by administration of antenatal glucocorticoid to women in preterm labor. The response of the surfactant system to glucocorticoid involves all the lipid and protein components, and occurs primarily through increased gene expression, thus representing precocious maturation mimicking the normal developmental pattern. Endogenous thyroid hormones, prostaglandins, and catecholamines also have stimulatory effects on type 2 cell maturation as well as on clearance of lung fluid at birth. Certain proinflammatory cytokines (e.g. tumor necrosis factor and TGF-β) inhibit surfactant production in experimental systems and may downregulate surfactant in conditions such as sepsis and inflammation.

KEY POINTS: SURFACTANT

- Surface-active material improves lung function by lowering the surface tension of alveoli at end-expiration and preventing alveolar collapse
- Surface-active material is made up of phospholipids, lipids, and proteins
- Surfactant proteins are important for surfactant function and for host defenses
- The rate of type 2 cell differentiation is modulated by levels of endogenous corticosteroids and is accelerated by administration of antenatal glucocorticoid to women in preterm labor

Physiological changes in lung liquid and pulmonary blood flow at birth

Two critical events in fetal development play a major role in the adaptation to air breathing that occurs at birth: removal of fetal lung liquid and changes in fetal circulation. Each is considered separately here but they are interdependent in the process of neonatal transition.

While fetal lung fluid is critical for early lung development, it is essential that fluid is cleared in preparation for the onset of air breathing [33]. Because fluid reabsorption depends largely upon regulation of the sodium channel, management options during labor and delivery that impair the catecholamine-induced maturation of ENaC (i.e. cesarean section without the benefit of labor) can impair lung fluid clearance, resulting in retention of fetal lung fluid, known as transient tachypnea of the newborn. Transient tachypnea of the newborn is a relatively benign condition generally requiring supportive care in the form of supplemental oxygen to allow for drainage of the excess fluid via lymphatics, or continuous positive airway pressure (CPAP) to facilitate clearance of lung fluid from the alveoli. It is important to recognize that retained fetal lung fluid can complicate other neonatal respiratory conditions such as meconium aspiration syndrome and bacterial and viral pneumonias. Furthermore, retained fetal lung fluid may complicate the transition from fetal to adult circulatory physiology and thereby contribute to the development of persistant pulmonary hypertension of the newborn.

The other critical event during neonatal transition is the adaptation of the circulatory pattern. During fetal life, the organ of gas exchange is the placenta. Thus, the circulatory pattern of the fetus is adapted to optimize blood flow to/from the placenta and minimize blood flowing to/from the lungs to between 5% and 10% of cardiac output. This is achieved through the low resistance/high capacitance of the placenta, the high resistance of the pulmonary vasculature, and the ductus arteriosus. The large surface area and lacunar structure of the placenta contribute to the low resistance/high capacitance of this organ. The low partial pressure of oxygen in the fetal lung and circulating vasoconstrictors, such as endothelin-1, leukotrienes, and Rho kinase, in the face of low production of vasodilators, including nitric oxide and prostacyclin, contribute to high pulmonary vascular tone [34]. As a result, pulmonary and systemic pressures are roughly equivalent. The high pulmonary vascular resistance and equivalent pulmonary and systemic pressures together favor the flow of oxygenated blood returning from the placenta (via the umbilical vein and ductus venosus) to the right atrium across the foramen ovale to the left atrium and out to the systemic circulation. The ductus arteriosus, a blood vessel developing from the 6th aortic arches, bridges between the pulmonary artery and the aorta at the bifurcation of the left pulmonary artery, and approximately at the level of the left subclavian artery as it branches from the aortic arch. The high pulmonary vascular resistance and low systemic vascular resistance *in utero* favor flow of oxygenated blood passing from right atrium to right ventricle and pulmonary artery, through the ductus arteriosus, and into the aortic arch to supply the systemic circulation. In addition to optimizing flow of oxygenated blood systemically, the combination of atrial and ductal level shunts allows for sufficient blood flow to all of the chambers of the heart facilitating their development during fetal life, and this explains the greater muscularization of the right ventricle in the newborn period relative to the left ventricle.

In the transition to air breathing, the circulatory pattern must undergo change to establish the lung as the organ of gas exchange [35]. Clamping and transection of the umbilical cord at delivery removes the placenta from the systemic circulation, resulting in a precipitous increase in systemic vascular resistance. This has at best a modest effect on changing blood flow centrally, instead improving blood flow to the lower body. Initiation of air breathing inflates the lungs and increases oxygen tension across the alveolar capillary bed, facilitating a precipitous drop in pulmonary vascular resistance. Pulmonary stretch receptors elicit reflex dilatation of the pulmonary vasculature independently of the effects of enhanced oxygen tension. The net effect of these events is that left atrial pressure becomes higher than right atrial pressure, leading to functional closure of the foramen ovale. These changes also reduce flow through the ductus arteriosus by 24% soon after birth, but are not sufficient to eliminate ductal flow for 48 hours after birth. Cessation of ductal blood flow and ultimately scarring of this structure, which becomes the ligamentum arteriosum, occurs over the first 2–3 weeks of life. Increasing hypoxemia of the muscle media of the ductus due to reduced blood flow through the ductal lumen promotes

vasoconstriction of the ductus. Ductal constriction enhances muscle media hypoxia by collapsing the vasa vasorum, the other source of oxygen to the ductus. Together, these adaptations lead to the adult circulatory pattern with the lung in series with the systemic circulation, enabling efficient oxygenation.

These physiological changes are dynamic and capable of reverting to a fetal pattern over the first days of life. While pulmonary vascular resistance decreases precipitously in the first minutes to hours of life, it does not achieve adult levels for weeks to months postnatally, and the pulmonary vasculature is prone to vasoconstriction in response to hypoxia and acidosis during that time. In addition, events associated with reduced systemic vascular resistance, such as septicemia, can lower systemic vascular resistance to the extent that even the normal pulmonary vascular tone in the first days of life can lead to pulmonary pressures becoming suprasystemic, leading to enhanced right-to-left blood flow.

Persistent pulmonary hypertension of the newborn (PPHN), also known as persistent fetal circulation, can occur in association with other neonatal diseases such as septicemia or meconium aspiration, or can be idiopathic in nature [34]. The disorder is characterized by suprasystemic right ventricular pressure, right-to-left flow of deoxygenated blood through the ductus arteriosus, and severe hypoxemia. PPHN can result from lung parenchymal disease leading to pulmonary vasoconstriction, from pulmonary vascular remodeling in the absence of lung parenchymal disease, or from primary or secondary pulmonary hypoplasia. Animal studies have elucidated pathways for targeted therapies such as nitric oxide/cGMP, prostacyclin/cAMP, and endothelin to lower pulmonary vascular resistance. Optimization of oxygenation and ventilation while providing specific pulmonary vasodilatation with nitric oxide has lowered the morbidity and mortality of this disorder and reduced the need for more aggressive therapies such as extracorporeal membrane oxygenation (ECMO).

Ductal patency can also complicate the management of prematurely born infants [36,37]. The ductus arteriosus of premature infants is thin-walled and thus depends only on luminal blood flow for oxygenation. As a consequence, the ductal muscle media does not become as hypoxic with constriction of the premature ductus, thus contributing to a prolonged delay in anatomical closure. As pulmonary vascular resistance decreases in preterm infants in response to lung inflation and surfactant administration, the high systemic vascular resistance favors left-to-right flow across a patent ductus arteriosus, resulting in pulmonary edema. Both are responsive acutely to elevated positive end-expiratory pressure. The pulmonary overcirculation can also be associated with vascular steal from the cerebral and mesenteric vasculatures, increasing the risk of intraventricular hemorrhage and intestinal ischemia. Closure of a patent ductus arteriosus can be achieved by treatment with agents that reduce prostaglandin synthesis, such as indomethacin and ibuprofen, but success is inversely related to gestational age. When repeated indomethacin therapy fails and the patent ductus arteriosus is felt to be a major factor in pulmonary symptoms, surgical ligation through a left thoracotomy approach is possible. There is some controversy regarding the long-term morbidity of surgical ligation of a patent ductus arteriosus.

KEY POINTS: LUNG FLUID AND PULMONARY CIRCULATION CHANGES AT BIRTH

- Critical events at birth include exchange of lung fluid for air and conversion of the parallel fetal circulation to the adult series circulation
- Retained lung fluid (as with cesarean section) causes transient tachypnea of the newborn and a need for additional oxygen and occasionally for nasal CPAP (nCPAP)
- Fetal type circulation (right-to-left shunting) can be re-established in the first few days of life with resultant hypoxemia
- The right heart pressures of patients with persistent pulmonary hypertension can re-establish fetal type circulation and cause severe hypoxemia
- The ductus arteriosus of premature infants often remains open, worsening lung disease

Lung development after birth

As with fetal lung development, postnatal lung development can be subdivided into several stages, also illustrated in Figure 7.1 [3]. True alveoli containing secondary septa (described previously) become evident as early as 36 weeks in the human fetus, initiating the alveolar phase of fetal lung development that extends to 1–2 years of age. Postnatal alveolarization begins with a phase of bulk alveolarization occurring within the first 6 months, with a more modest addition of secondary alveoli through the remainder of this period. The alveoli of the infant lung are different from adult alveoli. These immature secondary alveoli contain a double capillary bed, whereas adult alveoli are invested by a single capillary bed. Microvascular maturation, the next phase of postnatal lung development, occurs from the first few postnatal months of life through 3 years of age (discussed previously). Alveolar addition continues throughout childhood well into adolescence. It has been even observed that alveolar expansion can occur in response to pneumonectomy in adult animals and humans. The acquisition of alveoli after the maturation of the microvasculature has been termed late alveolarization. This activity has been most often demonstrated in subpleural regions of the lung and likely invokes mechanisms similar to the formation of secondary alveoli. Alveolarization is accompanied by increasing content of elastic fibers in the alveolar septa that prevents alveolar and small airways from collapsing by increasing the elastic recoil properties of the lung parenchyma. Interalveolar pores of Kohn and bronchoalveolar canals of Lambert develop at 3–4 years of age during the process of thinning of alveolar septa. Absence of these connections in newborn infants predisposes them to lung atelectasis.

The addition of alveoli is not the only means of expanding the surface area of the lung. While alveolarization wanes over the first 3 years of life in the human, growth of the lung continues to expand the gas exchange surface. Between

2 years of age and adulthood, lung tissue expands with lung volume roughly proportionately to the increase in bodyweight of the child. Alveolar diameter increases from 50–100 µm in newborn infants to 200–300 µm in adults. Thus, owing to the combined processes of prenatal lung development, postnatal lung development, and lung growth, there is tremendous potential for expansion of the gas exchange surface area that is developmentally programmed into the fetal lung to account for the growing needs of the infant, child, and adult for aerobic cellular respiration. The extent to which these developmental mechanisms can be harnessed after premature birth, with or without superimposed lung injury, is a topic of active investigation.

KEY POINTS: LUNG DEVELOPMENT AFTER BIRTH

- The alveolar phase of lung development extends to the first 2 years of life but continues to a lesser extent into teenage years
- Bulk alveolarization occurs during the first 6 months of extrauterine life
- Microvascular maturation continues up to 3 years of age
- After 3 years of age, the increase in lung surface area is due to increase in size of the alveoli

Control of breathing

The development of respiratory control starts prenatally but continues to mature for several weeks and months after birth [38]. Preterm and term infants can present with immature breathing patterns characterized by irregular and periodic breathing. Several components of the respiratory control system can still be immature including peripheral and central chemoreceptor responses, brainstem respiratory rhythmogenesis, and other parts of the network. The risk of severe and life-threatening apneas is therefore increased in young infants compared to older children. The ventilatory response to carbon dioxide and oxygen is impaired in newborn infants [39]. Whereas hypercapnia leads to increased tidal volumes and respiratory rates in term infants, children, and adults, the response is often diminished in preterm neonates. Preterm infants show a biphasic response to hypoxia. After an initial period of increased ventilation for approximately 1 minute, ventilation subsequently decreases with an increased risk of apneas. Other important mechanisms contributing to apneas in neonates are an exaggerated inhibitory response to either an afferent laryngeal stimulation or excessive lung inflation. Apneic response to the latter due to stimulation of pulmonary stretch receptors is also known as the Hering–Breuer inflation reflex, which is more pronounced in infants compared with older children. Apneas are defined periods of absence of airflow for more than 20 s and classified as either central apneas in the absence of breathing efforts or obstructive apneas in the presence of breathing efforts. Clinically, in infants most apneas occur as mixed apneas, i.e. a combination of absent respiratory drive (central apnea) and failure to maintain a patent airway (obstructive apnea). Central apneas as well as obstructive apneas result from a decreased respiratory center output due to the immaturity of the respiratory control system. The predominant site of airway obstruction in obstructive apneas is the pharynx, which shows reduced muscle tone during this period [40]. Poor respiratory control, especially in very preterm infants, might require the use of respiratory stimulants (e.g. caffeine), CPAP, or mechanical ventilation.

KEY POINTS: CONTROL OF BREATHING

- Respiratory control starts prenatally and continues to mature for several weeks and months after birth
- Preterm infants continue to have immature breathing patterns characterized by irregular and periodic breathing
- Peripheral and central chemoreceptor responses and brainstem respiratory rhythmogenesis are still immature, making neonates prone to apnea
- The Hering–Breuer inflation reflex is more pronounced in infants compared with older children
- Preterm infants are prone to both central and obstructive apnea

Normal values for pulmonary function with age

In neonates and children, the developmental changes discussed previously lead to rapid transformations in the mechanical properties of the respiratory system and influence pulmonary function. Unlike many physiological parameters that do not vary with age (i.e. arterial pH), predicted values of pulmonary function depend upon age, height, gender, and race [41]. Consistent normalization of pulmonary function test results – based on weight or height – is important to the interpretation of results and for comparison to reference values. When tests rely on the subjective effort of an infant or young child, technique can have profound effects on measurements and efforts to standardize pulmonary function testing. For example, several studies have compared compliance measurements from preterm infants with and without bronchopulmonary dysplasia (BPD) to term infants to determine their diagnostic or prognostic value. However, there was a large overlap between the groups, with the majority of infants with BPD having compliance measurements within the 95% confidence interval of the control group [42]. This observation suggests that in particular single point measurements in individual infants are of limited value as a diagnostic or prognostic tool. In a research setting, consistency can best be obtained in a pulmonary function laboratory, although infant and pediatric ventilators now provide opportunities to make measurements in the intensive care setting. The discussion that follows presents an outline of basic parameters and descriptions of how pulmonary function changes with age where applicable, including normal references only where they are considered consistent standards (Table 7.2).

KEY POINTS: NORMAL VALUES FOR PULMONARY FUNCTION WITH AGE

- Predicted values of pulmonary function depend upon age, height, gender, and race
- Tests that rely on the subjective effort of an infant or young child can have profound effects on measurements because the child cannot perform them effectively
- Single point measurements in individual infants are of limited value as a diagnostic or prognostic tool

Compliance

The elastic properties of the lung are described by the changes in volume (V) per unitary change in transpulmonary pressure (P_L) under the conditions of zero flow, or lung compliance ($C_L = \Delta V/\Delta P_L$). The systematic change in both pressure and volume during inflation and deflation allows a static pressure–volume curve of the lungs to be plotted. Compliance of the respiratory system is the combination of lung (C_L) and chest wall compliance (C_W) and changes throughout childhood and adolescence. It ranges from 1.5 to 2 mL/cmH_2O/kg in newborns to 2.5–3 mL/cmH_2O/kg in children and adults [43]. Both chest wall and lung tissue are characterized by specific elastic properties. Whereas the chest wall tends to expand, especially at low lung volumes, the lung tissue has the tendency to recoil and collapse due to its elastic fibers and the surface tension at the alveolar air–fluid interface.

Compliance of the lung

Lung compliance is proportional to its volume and increases with growth throughout childhood. However, specific compliance, which is the lung compliance divided by functional residual volume (C_L/FRC), remains relatively constant in children and adults. The elastic recoil properties of the lung tissue increase from birth into adolescence before they decline in adulthood; they seem to be mainly associated with the pulmonary content of elastic fibers. The compliance of the lung is also dependent on the content and quality of pulmonary surfactant. The function of surfactant is to stabilize alveoli in their size and to prevent them from collapse.

Compliance of the chest wall

Chest wall compliance (C_W) is high in infants and can contribute to ineffective breathing in the presence of lung disease, visible by ribcage recessions. C_w progressively decreases as the ribcage gradually ossifies throughout infancy and childhood into adulthood.

Closing volume and dynamic elevation of functional residual capacity

C_W in infants is 2–6 times higher than the compliance of the lung tissue, even more so in preterm infants, but will decrease to nearly equal to lung tissue compliance in childhood and adulthood. FRC is determined by the tendency of the chest wall to expand and the lungs to collapse and reflects the elastic equilibrium of C_W and C_L. The chest wall in newborns and infants is less stiff than in older children and adults and has therefore a higher C_W which results in a lower FRC.

The increased compliance in infants leads to an FRC that is near the infant's closing capacity, the volume in the lungs at which alveoli and small airways can collapse [44]. Infants can counteract the collapse by dynamically elevating their FRC. Several mechanisms contribute to increase of the FRC:

- Activation of the respiratory muscles: in inspiration as well as in expiration there is an activation of the respiratory muscles including the diaphragm, which brakes at expiration.
- High breathing frequency: less time for expiration and lung emptying.
- Vocal cord adduction: especially in expiration, vocal cord adduction leads to a higher respiratory resistance and a lower expiratory flow. Expiratory grunting can be observed in newborn infants with lung disease.

These mechanisms are being used mainly in the first year of life. As the chest wall gradually stiffens, C_W decreases and matches C_L at resting volume of the respiratory system.

KEY POINTS: LUNG AND CHEST WALL COMPLIANCE

- The elastic properties of the lung are described by the changes in volume (V) per unitary change in transpulmonary pressure
- Compliance of the respiratory system is the combination of lung (C_L) and chest wall compliance (C_W) and changes throughout childhood and adolescence
- The specific compliance (lung compliance divided by functional residual volume (C_L/FRC)) remains relatively constant in children and adults
- Chest wall compliance (C_W) is high in infants and can contribute to ineffective breathing in the presence of lung disease, visible by ribcage recessions
- Increased chest wall compliance in infants leads to an FRC that is near the infant's closing capacity, the volume in the lungs at which alveoli and small airways can collapse

Resistance

Airway resistance (R_{aw}) reflects the non-elastic airway and tissue forces resisting gas flow. Lung resistance is determined predominantly by frictional resistance to inspiratory and expiratory airflow in the larger airways (80%), while tissue resistance (19%) and inertial forces (1%) also contribute [43]. By definition, resistance to airflow is equal to the resistive component of driving pressure (ΔP) divided by the airflow (Q), $R_{aw} = \Delta P/Q$ with units of cmH_2O/L/s. Poiseuille's law states that resistance to flow increases by a power of 4 with any decrease in airway diameter ($R_{aw} = 8\eta L/\pi r^4$, where η is the gas viscosity, L is length, and r the radius of the airway). Compared to an adult the airways in children are relatively large. However, in actual size the diameter of airways in infants and children is much smaller than that in adults, resulting in increased R_{aw}. Therefore, minor changes in the

Table 7.2 Standards for lung mechanics and pulmonary function in infants, children, and adults

	Infant	Child	Adult
Compliance	1.5–2.0 mL/cmH_2O/kg	2.5–3.0 mL/cmH_2O/kg	0.1 L/cmH_2O *note different units
Resistance	20–40 cmH_2O/L/s	20–40 cmH_2O/L/s *up to 2 years	1–2 cmH_2O/L/s
Functional residual capacity	20–25 mL/kg	20–25 mL/kg *up to 18 months	1.9–2.4 L *note different units
Tidal volume	4–8 mL/kg *preterm 3–5 mL/kg	4–8 mL/kg	6–8 mL/kg
Respiratory rate	20–60 breaths/min	20–30 breaths/min	12–20 breaths/min
Minute ventilation	240–480 mL/kg/min		5–8 L/min *note different units

airway diameter lead to much larger increases in R_{aw} in infants compared to adults [45]. Resistance is also dependent on the number of airways, lung volume, and respiratory rate. In adults about 80% of R_{aw} is attributed to airways larger than 2 mm in diameter and only about 20% to small peripheral airways as the cross-sectional area is much larger than in infants. In infants the small peripheral airways account for up to 50% of R_{aw} which explains their vulnerability to small airway diseases, e.g. bronchiolitis [16]. Airway resistance in normal healthy infants up to 2 years of age ranges from 20 to 40 cmH_2O/L/s, whereas R_{aw} in adults is 1–2 cmH_2O/L/s.

KEY POINTS: AIRWAY RESISTANCE

- Airway resistance (R_{aw}) reflects the non-elastic airway and tissue forces resisting gas flow
- The diameter of the airways in infants and children is much smaller than in adults, resulting in increased airways resistance

Tidal volume

Tidal volume is the volume of each breath and is measured during inhalation or exhalation, or averaged for the entire respiratory cycle. The value should be normalized to bodyweight or length. Very small preterm infants may have spontaneous breathing tidal volumes as low as 3–5 mL/kg. During spontaneous breathing, normal values in healthy infants are approximately 7–8 mL/kg (range from 4.3 to 11.8 mL/kg) [46] and are similar to the tidal volumes in older children and adults.

Gas exchange

The pulmonary gas exchange takes place in the terminal respiratory units of the lung, i.e. alveoli, by diffusion. The diffusion process of oxygen and carbon dioxide across the alveolar–capillary membrane is similar in infants and older subjects. The thickness of the alveolar–capillary membrane is similar for all ages but its surface area increases markedly throughout childhood. The increasing surface area is also associated with an increase of the diffusion capacity. The reserve of diffusion capacity seems therefore to be lower in newborn infants compared to older children and adults. The development of interalveolar (pores of Kohn) and bronchoalveolar connections (canals of Lambert) in the first years of life improves gas exchange within the lungs. Its absence predisposes infants to lung atelectasis, ventilation–perfusion mismatch, and intrapulmonary shunting. Gas exchange depends on the amount of gas that reaches the alveolar–capillary membrane. A certain amount of gas does not reach the alveolar–capillary membrane but remains in the conducting airways and therefore does not participate in gas exchange. This is referred to as anatomical dead space. Another portion of the inspired gas might reach alveoli that are not perfused or poorly perfused, which is referred to as alveolar dead space. Dead space in infants is markedly higher than that in older children and adults. This is mainly due to the relatively larger extrathoracic component of the anatomical dead space in infants, which is 50% greater than in older subjects [47]. The dead space to tidal volume ratio (V_D/V_T) in adults is considerably lower than in newborn infants (approximately 0.2–0.3 versus 0.4–0.5 respectively). This explains to some degree the need for a higher minute ventilation/kg bodyweight in infants compared to older children and adults as some portion of the inspired gas is "wasted" and does not participate in alveolar ventilation [48].

Minute ventilation

Minute ventilation is the product of tidal volume and respiratory rate. Respiratory rates of most preterm and term infants are 20–60 breaths/min, and the normal range for minute ventilation is from 240 to 480 mL/kg/min [49].

KEY POINTS: TIDAL VOLUME, DEAD SPACE, AND MINUTE VENTILATION

- Normal values for tidal volume in healthy spontaneously breathing infants are approximately 7–8 mL/kg, similar to those of older patients
- The thickness of the alveolar–capillary membrane is similar for all ages, but its surface area increases markedly throughout childhood
- The increasing surface area is also associated with an increase of the diffusion capacity
- Absence of the pores of Kohn and the canals of Lambert predisposes infants to lung atelectasis, ventilation–perfusion mismatch, and intrapulmonary shunting
- The dead space in infants (0.4–0.5) is markedly higher than that of older children and adults (0.2–0.3)

Pathophysiology of important respiratory diseases affecting infants and children

Asthma

Asthma is a chronic, recurrent disease; its prevalence is 1–20% and is higher in countries with a Western lifestyle and higher rates of obesity (e.g. Scotland 18%, Australia 15%, USA and Brazil 11%) [50]. The characteristics of bronchial asthma include a variable and often reversible airflow obstruction and bronchial hyperreactivity. Patients with bronchial hyperreactivity have an increased tendency for and higher degree of airway narrowing in response to stimulation. This makes children with asthma or other diseases associated with airway inflammation (e.g. upper respiratory tract infection) more prone to the development of respiratory adverse events in the perioperative setting, particularly with regards to the incidence of bronchospasm and laryngospasm. Asthmatic patients have varying degrees of airway inflammation, bronchial hyperreactivity, wheeze, and remodeling [51], which can also be found in children with recurrent respiratory tract infections, cystic fibrosis, and BPD.

Asthma is characterized by reversible bronchoconstriction, wheezing, and cough accompanied by inflammation and increased and more viscous mucus production in the small airways that can lead to airway plugging. A child's smaller airway diameter causes increased airflow obstruction and puts it at a significantly increased risk for asthma-related morbidity and mortality [50].

Hypoxemia during an acute asthma exacerbation is mainly caused by the perfusion of hypoventilated airways leading to a ventilation–perfusion (V/Q) mismatch [52]. Children with mild airflow obstruction will hyperventilate to improve gas exchange while at the same time increasing their risk of lung hyperinflation, placing the diaphragm at a mechanical disadvantage and leading to an increased work of breathing [53].

While expiration in healthy children is usually passive, increased airflow obstruction forces the child to actively support expiratory efforts by using accessory respiratory and abdominal muscles, which may lead to fatigue, particularly in young infants, causing carbon dioxide retention. In addition, greater inspiratory effort will be required to overcome the positive intrathoracic pressures as a result of trapped gas. Hypercapnia is a warning sign that the child may require ventilatory support.

Many infants are labeled "asthmatic" in infancy because of wheeze with viral upper and lower respiratory tract infections, particularly with respiratory syncytial virus (RSV) and rhinovirus. Many of these children will only wheeze during their preschool years, and thus do not develop chronic asthma. In some children, RSV infection is felt to increase the risk of developing chronic asthma, through a combination of genetic, environmental, and immune response mechanisms that are not clearly elucidated. Those who have recurrent bronchospasm events after age 6 years are diagnosed with asthma; many of these patients will have their disease resolve completely or greatly diminish after adolescence. Those with asthma persisting into adolescence often have an atopic/allergic component to their disease. Up to 75% of young children who wheeze with viral respiratory tract infections will have complete resolution of symptoms by adulthood [54–57].

The inciting events for an episode of bronchospasm are myriad. As noted previously, viral respiratory infections, especially with RSV, are a frequent inciting event in children. Other viruses known to be associated with asthma exacerbations include rhinovirus, influenza, parainfluenza, and coronavirus. Allergic sensitization and innate immune response to the virus exposure play a role in these exacerbations [54]. Other infections, such as chlamydia, mycoplasma, and bacterial infections of the respiratory tract, can provoke asthma exacerbations. Allergic responses with antigen-specific IgE antibodies to aeroallergens are another important mechanism that usually does not occur until at least 2–3 years of age. This mechanism increases during later childhood and adolescence and peaks in the second decade of life. Dust mites, animal dander, tree and grass pollens are among the most frequent underlying factors for allergic asthma. Another very important risk factor for childhood asthma is exposure to tobacco smoke, which is thought to be the single most important environmental factor for asthma exacerbation in infants and children [57]. Other factors for asthma exacerbation, particularly in older children, include exercise, gastroesophageal reflux, and psychosocial stressors. The genetic components of asthma are complex and multifactorial, and although the atopic phenotype has a familial component, recent genomewide association studies and other gene candidate studies have had limited success in elucidating the genetic origins of asthma. Several groups have reported markers on chromosome 17q21 that were reproducibly associated with childhood-onset asthma in families from the UK and Germany and other populations. This association appears to be strongest in young children with tobacco smoke exposure. There are several candidates identified, but as yet no definitive asthma genes have been designated [58].

The pathophysiology of an asthma exacerbation is complex, keeping in mind that it is an acute episode superimposed upon an abnormal airway with chronic changes of inflammation, increased airway smooth muscle that results in airway remodeling and chronic loss of lung function, and increased mucus production. In addition, the asthma phenotype has been divided into a number of subphenotypes. Airway inflammation is a fundamental abnormality in asthma pathogenesis, with mast cells, eosinophils, neutrophils, and $CD4^+$ T lymphocytes all playing a role. In allergic asthma, antigen exposure in the airway to IgE specific antibodies incites a T-helper cell 2 (Th2) type lymphocyte response, which in turn generates a cytokine response. The cytokine response attracts mast cells, eosinophils, and basophils, which in turn are activated and release mediators of airway smooth muscle tone, including histamine, leukotrienes (including slow-reacting substance of anaphylaxis), and prostaglandins, resulting in acute bronchospasm [59]. The effects of chronic inflammation on the airway epithelium are known to be crucially important to asthma pathogenesis. Bronchial biopsies in moderate to severe asthma show areas of epithelial metaplasia, thickening of the subepithelial basal membranes, increased numbers of myofibroblasts, and evidence of airway remodeling, including hypertrophy and hyperplasia of airway smooth muscle, mucous gland hyperplasia, angiogenesis, and an altered deposition and composition of extracellular matrix proteins

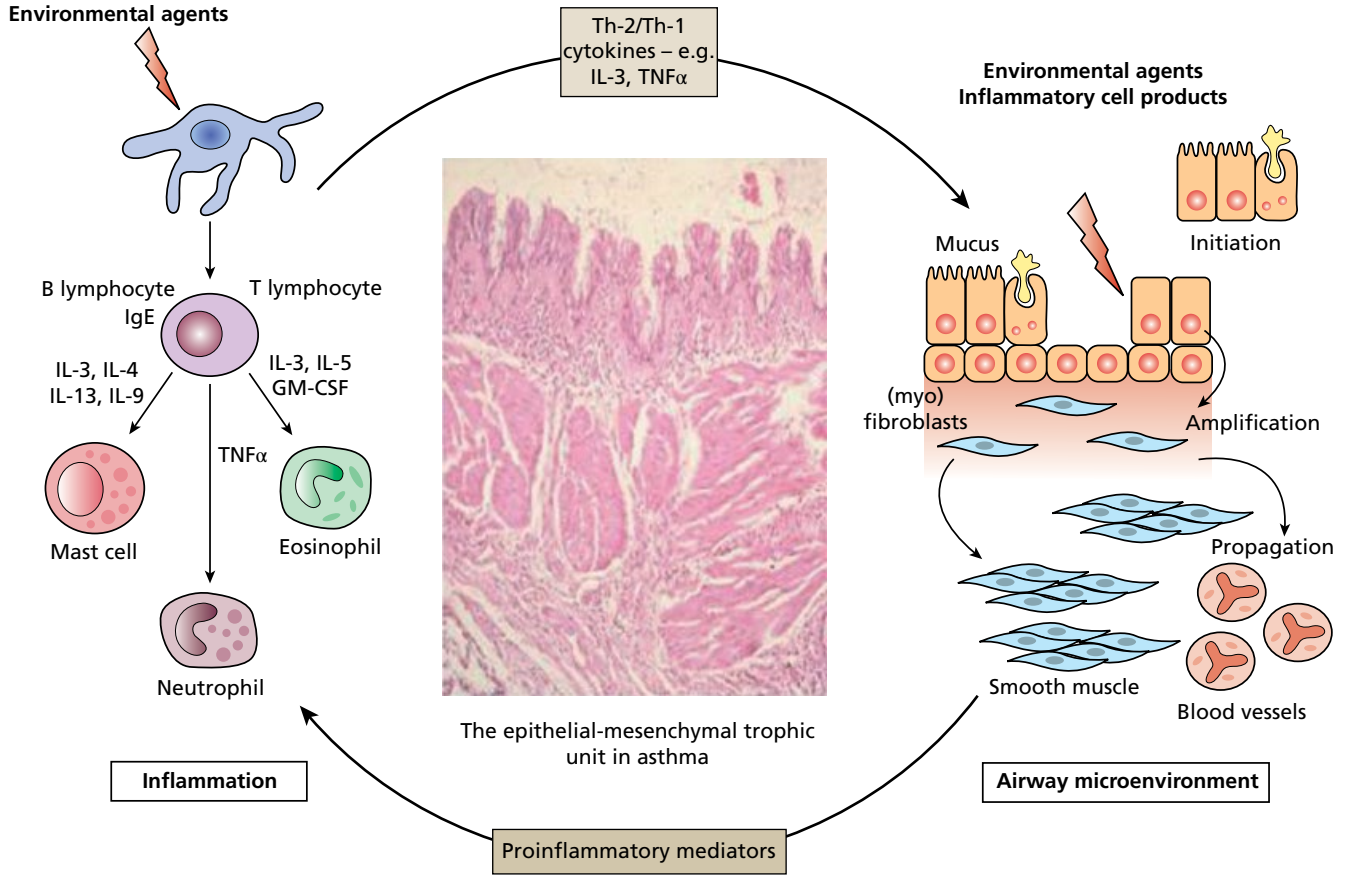


Figure 7.2 Inflammatory and remodeling responses in asthma with activation of the epithelial–mesenchymal trophic unit. Epithelial damage alters the set point for communication between bronchial epithelium and underlying mesenchymal cells, leading to myofibroblast activation and increase in mesenchymal volume, and induction of structural changes throughout the airway wall. GM-CSF, granulocyte–macrophage colony stimulating factor; IL, interleukin; Th, T helper; TNF, tumor necrosis factor. *Source:* Reproduced from Holgate and Polosa [60] with permission of Elsevier.

[59,60] (Fig. 7.2). This means, a chronically abnormal airway characterized by increased smooth muscle, an immune system primed to respond to allergen exposure, and airways chronically narrowed by this inflammation and mucus production will constrict further with acute airway smooth muscle constriction. Particularly in small pediatric patients, the narrow small airways diameter means that a relatively small degree of airway smooth muscle constriction can result in more severe bronchospasm symptoms, given that resistance to airflow is inversely proportional to the fourth power of the airway radius with laminar flow, and the fifth power of the radius with turbulent flow.

Preoperatively, it is important to assess whether the patient has undiagnosed and/or uncontrolled asthma. If possible, surgery should be delayed until asthma symptoms are well controlled. There is no standardization of findings required to confirm an asthma diagnosis. However, most definitions will include some degree of wheeze and bronchial hyperreactivity [50]. Further common symptoms include coughing, difficulty breathing, and chest tightness. Children with frequent or recurrent (nighttime or early morning) wheezing, exercise or allergy induced wheeze, or wheeze in absence of a respiratory tract infection, as well as those with clinical improvement following the administration of a β_2-agonist and/or a (family) history of atopic disease have a high likelihood to have asthma [61].

Therefore, the evaluation of asthma in young children involves a careful history of frequency and severity of episodes and response to treatment, and ascertaining environmental allergens and exposures. Clinical examination is important; active wheezing in the preanesthetic period is cause for concern and should merit cancellation of elective surgery. However, preoperative blood testing or chest X-rays are rarely necessary [62]. While patients with allergy-triggered asthma may present with positive skin prick testing, eosinophilia, and/or specific IgE, these tests do not improve the prediction of perioperative respiratory adverse events [61]. Pulmonary function testing is not well correlated with clinical severity of asthma in children with well-controlled asthma [63]. Due to the reversible nature of the airflow obstruction in asthma, normal lung function values also do not exclude the presence of asthma. Only a metacholine challenge has a high negative predictive value in this setting; however this is not indicated routinely preoperatively [63].

It is of extreme importance to continue all asthma medications throughout the perioperative period. Additional preoperative β_2-agonists may be advantageous in asthmatic children [64] although they maybe of lesser importance in older children without respiratory symptoms undergoing low risk surgery [65]. However, children with active respiratory symptoms benefit slightly from premedication with salbutamol [65]. Treatment of asthma depends on the

age of the patient, and the severity of the asthma. Acute exacerbations of asthma are usually treated with a short-acting β-agonist by inhalation route (nebulized or metered dose inhaler), such as levalbuterol or salbutamol, which will enhance the action of cyclic AMP and thus relax airway smooth muscles. Halogenated inhaled anesthetics are well known to relax airway smooth muscle via inhibition of Ca^{2+} influx. (See Chapter 10 for a complete discussion of the pharmacology of inhaled anesthetics.) In the rare case of acute severe bronchospasm with general anesthesia, where gas exchange is so compromised that any inhaled agent does not reach the airways, intravenous β-agonists (epinephrine, isoproterenol), as well as intravenous magnesium sulfate, can acutely relax airway smooth muscle and allow inhaled agents to reach the airways. The US National Institutes of Health as well as the British Thoracic Society published evidence-based asthma evaluation and treatment guidelines [61]. For intermittent asthma, episodic treatment with short-acting β-agonists as needed is recommended. As the severity and chronicity of asthma increases, additional chronic treatments such as inhaled corticosteroids, cromolyn (mast cell stabilizer), montelukast (leukotriene receptor inhibitor), longer-acting β-agonists, or oral corticosteroids, are added (Fig. 7.3).

Non-steroidal anti-inflammatory drugs (NSAIDs) are often avoided in asthmatic patients, however the basis for this is not very strong and rather more theoretical than a real concern [61,66,67]. However, more recent studies have shown that paracetamol (acetaminophen) may be of more concern [68]. Short-term NSAIDs are associated with a very low risk of adverse effects in asthmatic children and should be preferred as analgesic agents, with the exception of children with asthma and nasal polyps who have a higher likelihood for NSAID-induced bronchospasm.

KEY POINTS: ASTHMA

- The characteristics of bronchial asthma include a variable and often reversible airflow obstruction and bronchial hyperreactivity
- Children with asthma or other diseases associated with airway inflammation (e.g. upper respiratory tract infection) are more prone to the development of respiratory adverse events (bronchospasm and laryngospasm) in the perioperative setting
- Airway inflammation is a fundamental abnormality in asthma pathogenesis
- Evaluation of asthma in young children involves careful history of frequency and severity of episodes, response to treatment, and ascertaining environmental allergens and exposures. Active wheezing in the preanesthetic period is cause for concern and should merit cancellation of elective surgery
- It is of extreme importance to continue all asthma medications throughout the perioperative period
- Children with asthma and nasal polyps have a higher likelihood for NSAID-induced bronchospasm

Bronchopulmonary dysplasia

More than 1 in 10 births worldwide is a premature delivery (<37 weeks of gestational age), accounting for over 15 million premature infants every year with 2.4 million infants born prior to 32 weeks of gestation [69,70]. Bronchopulmonary dysplasia (BPD) was described in 1967 by Northway et al in a series of 32 preterm infants following mechanical ventilation for respiratory distress syndrome (RDS). The disease featured prominent interstitial fibrosis, alveolar overdistention alternating with regions of atelectasis, and airway abnormalities, including squamous metaplasia and excessive muscularization [71]. In those early days of survival of preterm infants, ventilator therapy often included high FiO_2 and high ventilating pressures and volumes – features now known to cause significant lung injury and which contributed to the severe chronic lung disease in many early BPD patients. In recent years, with survival of more and more premature infants, and recognition of pulmonary oxygen toxicity and the adverse effects of excessive pressures and volumes with mechanical ventilation, the BPD phenotype has changed to a histological pattern of arrest of airway and alveolar development: alveolar numbers are reduced and the alveoli are larger than normal in diameter; the more severe changes are absent [72,73] (Fig. 7.4). However, in spite of the improved treatment strategies in preterm infants, BPD is the most common complication of prematurity, with up to two-thirds of children born before 29 weeks being affected [74]. BPD is associated with increased mortality, poor neurodevelopmental outcomes, and chronic respiratory disease [75]. The most common current definition of BPD is a premature infant who had a diagnosis of RDS with a requirement for supplemental oxygen for more than 28 days (independent of the need for mechanical ventilation), with a further classification at 36 weeks of postconceptional age into mild, moderate. or severe BPD [76]. A joint US National Institute of Childhood Health and Development–National Heart Lung and Blood Institute workshop further classified mild BPD as the need for supplemental oxygen at ≥28 days but not at 36 weeks of postconceptional age; moderate BPD was defined as the need for supplemental oxygen at 28 days, in addition to supplemental oxygen at FiO_2 ≤0.30 at 36 weeks of postconceptional age; and criteria for severe BPD included the need for supplemental oxygen at 28 days and at 36 weeks of postconceptional age, the need for mechanical ventilation and/or FiO_2 >0.30 [72].

The incidence of BPD varies by center, but in recent studies of infants born at 24–31 weeks of gestation at 500–1500 g, BPD rates average 25–30% using the definition of oxygen requirement at 36 weeks; however intercenter variability means these rates vary from about 5% to 60% [72]. The overall incidence of BPD is stable or actually increasing slightly, presumably due to increasing survival of more premature infants. Risk factors for BPD include lower gestational age and birthweight, intrauterine growth retardation, male sex, family history of asthma, not receiving antenatal glucocorticoids, and likely a genetic component that is not yet fully elucidated.

Theories about pathogenesis of the new BPD include lung injury in very preterm infants at critical stages of lung development during the late canalicular and saccular phases, resulting in arrested development of lung structures and disrupted repair at critical stages [77]. Proposed risk factors for

Components of severity		Classification of asthma severity (0–4 years of age)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	0	1–2x/month	3–4x/month	>1x/week
	Short-acting β_2-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2 Exacerbations in 6 months requiring oral systemic corticosteroids, or ≥4 wheezing episodes/1 year lasting >1 day AND risk factors for persistent asthma		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time. → Exacerbations of any severity may occur in patients in any severity category.			
Recommended step for initiating therapy (See Fig. 6.3C for treatment steps.)		Step 1	Step 2	3 and consider short course of oral systemic corticosteroids	
		In 2–6 weeks, depending on severity, evaluate level of asthma control that is achieved. If no clear benefit is observed in 4–6 weeks, consider adjusting therapy or alternative diagnoses.			

Key: EIB, exercise-induced bronchospasm

Notes

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past 6 months, or ≥4 wheezing episodes in the past year, and who have risk factors for persistent asthma may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

(A)

Figure 7.3 (A and B) Classifying asthma severity and initiating treatment in children who are not currently taking long-term control medication: (A) children 0–4 years of age; (B) children 5–11 years of age. (C and D) Stepwise approach for managing asthma in: (C) children 0–4 years of age; (D) children 5–11 years of age. *Source:* Reproduced from [86] with permission of National Heart, Lung, and Blood Institute; National Institutes of Health; US Department of Health and Human Services.

this lung injury include chorioamnionitis and fetal inflammatory response, ventilator-induced lung injury (volutrauma, barotrauma, atelectotrauma), oxygen toxicity (oxygen free radical production and lipid peroxidation), lack of surfactant, and disruption of vasculogenesis (inhibition of vascular endothelial growth factor (VEGF) pathways) [77].

Strategies to reduce the incidence and severity of BPD include non-invasive forms of ventilation, in lieu of endotracheal intubation in premature infants with RDS. Both nCPAP and nasal intermittent positive pressure ventilation (NIPPV), delivered via specially designed nasal prongs, have been used for this purpose. As a primary treatment for respiratory

Components of severity		Classification of asthma severity (5–11 years of age)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting β_2-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC >85%	• FEV_1 = >80% predicted • FEV_1/FVC >80%	• FEV_1 = 60–80% predicted • FEV_1/FVC = 75–80%	• FEV_1 <60% predicted • FEV_1/FVC <75%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← Consider severity and interval since last exacerbation. → Frequency and severity may fluctuate over time for patients in any severity category.			
		Relative annual risk of exacerbations may be related to FEV_1.			
Recommended step for initiating therapy (See Fig. 6.3D for treatment steps.)		Step 1	Step 2	Step 3, medium-dose ICS option and consider short course of oral systemic corticosteroids	Step 3, medium-dose ICS option, or step 4 and consider short course of oral systemic corticosteroids
		In 2–6 weeks, evaluate level of asthma control that is achieved, and adjust therapy accordingly.			

Key: EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids

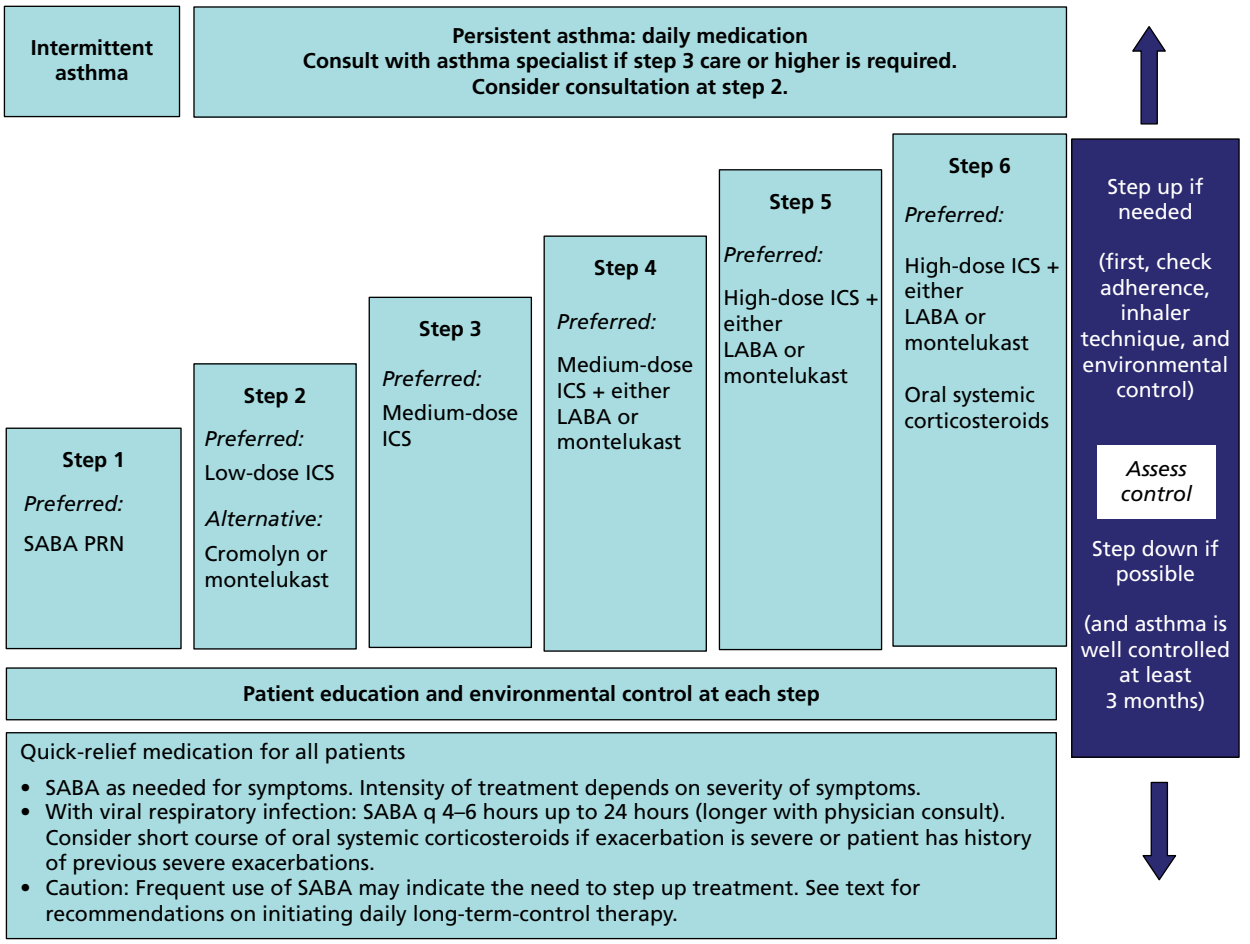
Notes

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of the previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g. requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

(B)

Figure 7.3 (*Continued*)

failure secondary to RDS, non-invasive ventilation may avoid tracheal intubation in some infants, but so far trials have not shown a consistent ability to reduce the incidence of BPD with these modalities. Non-invasive ventilation is well established as a postextubation therapy to reduce the duration of tracheal intubation and mechanical ventilation. However, these modalities used after extubation have not been conclusively demonstrated to reduce the incidence of BPD [73]. Modern conventional mechanical ventilation techniques employ microprocessor technology, allowing patient-triggered synchronized ventilation, volume-targeted ventilation, and flow-cycled ventilation, all of which are proving to have advantages in preventing ventilator-induced lung injury. Volume-targeted ventilation is associated with a lower incidence of BPD as compared with pressure-controlled ventilation modes [16]. Permissive hypercapnea reduces the duration of mechanical ventilation; however, the incidence of BPD with this technique is unchanged. High-frequency oscillatory ventilation is



Key: Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy. ICS, inhaled corticosteroid; LABA, inhaled long-acting β_2-agonist; SABA, inhaled short-acting β_2-agonist

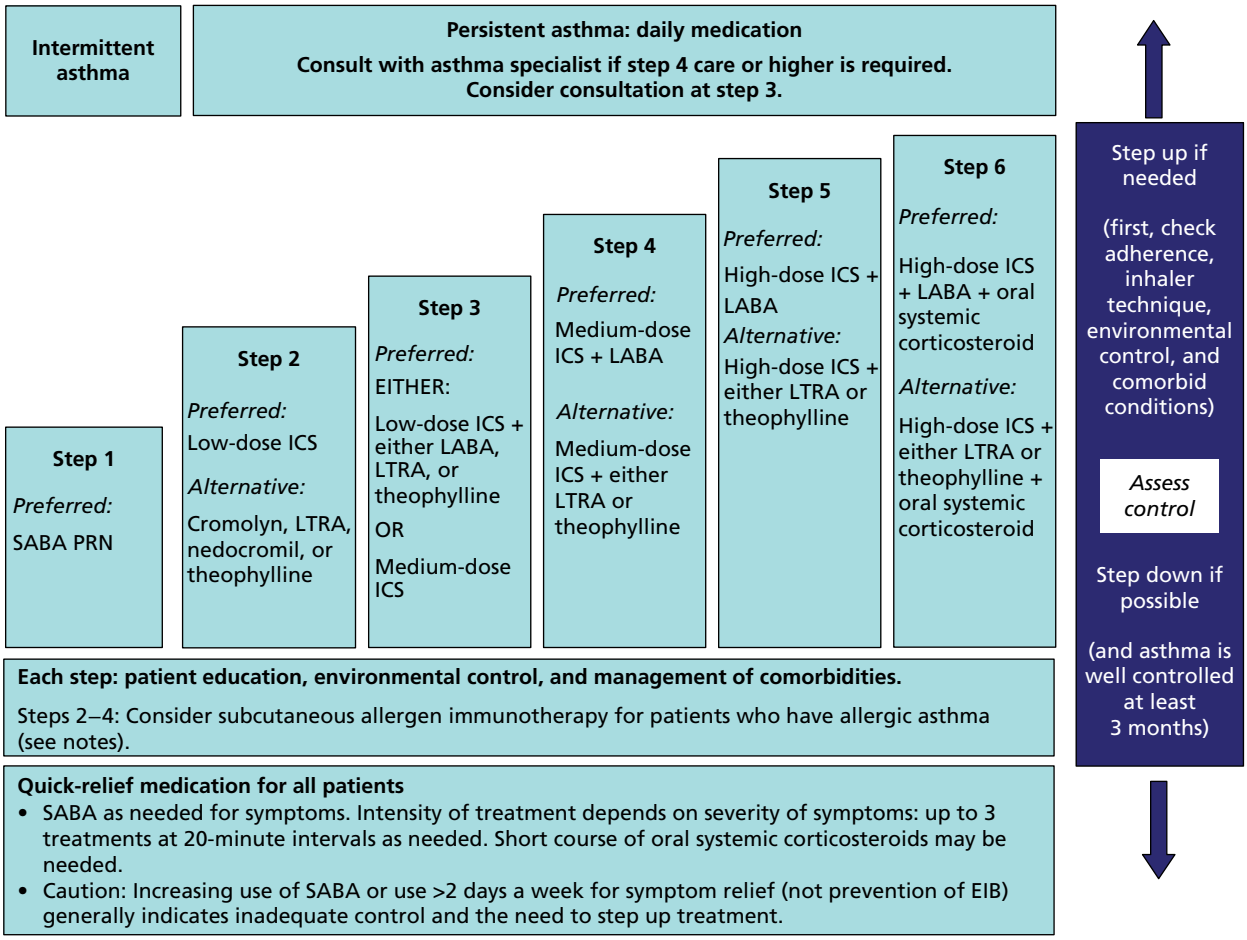
Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- If clear benefit is not observed within 4–6 weeks and patient/family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis.
- Studies on children 0–4 years of age are limited. Step 2 preferred therapy is based on Evidence A. All other recommendations are based on expert opinion and extrapolation from studies in older children.

(C)

Figure 7.3 (*Continued*)

often used in preterm infants with RDS; this strategy has been found to reduce the incidence of BPD in some studies [73]. Oxygen toxicity has been postulated to have an important role in the pathogenesis of worsening RDS and BPD, and in recent studies, targeting an SpO_{2in} the 85–89% range, rather than the 94–97% range, appears to have some effect in reducing the severity of lung injury and of BPD; meta-analysis of combined trials is underway to further elucidate the magnitude of this effect [78]. Drug therapies used to reduce the severity of RDS include a single course of antenatal glucocorticoids (dexamethasone or betamethasone) to accelerate the maturation of surfactant system in the fetal lung; there is no evidence that this intervention reduces the risk of BPD, probably because of an increase in survival. Surfactant therapy significantly reduces the incidence and severity of RDS, but again does not reduce the incidence of BPD, likely because of the survival benefit. Caffeine therapy, originally used to reduce apnea of prematurity, also reduces the incidence of BPD. Inhaled nitric oxide (iNO), the potent pulmonary vasodilator, has been used in premature infants with hypoxemic respiratory failure, but in randomized controlled trials has demonstrated an inconsistent effect on survival and incidence of BPD and is not recommended as routine therapy in RDS. Other drug therapies that have been used in infants with RDS and evaluated to reduce the incidence of BPD include inhaled corticosteroids, furosemide, β-receptor agonist or



Key: Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy. EIB, exercise-induced bronchospasm; ICS, inhaled corticosteroid; LABA, inhaled long-acting β_2-agonist, LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting β_2-agonist

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Theophylline is a less desirable alternative due to the need to monitor serum concentration levels.
- Step 1 and step 2 medications are based on Evidence A. Step 3 ICS + adjunctive therapy and ICS are based on Evidence B for efficacy of each treatment and extrapolation from comparator trials in older children and adults—comparator trials are not available for this age group; steps 4–6 are based on expert opinion and extrapolation from studies in older children and adults.
- Immunotherapy for steps 2–4 is based on Evidence B for house-dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults. Clinicians who administer immunotherapy should be prepared and equipped to identify and treat anaphylaxis that may occur.

(D)

Figure 7.3 (*Continued*)

anticholinergic inhaled drugs, indomethacin and ibuprofen, vitamin E, and superoxide dismutase; these agents have not reduced the incidence of BPD. Therapies shown to be effective at reducing BPD incidence include, besides caffeine, postnatal corticosteroids, vitamin A, and inositol supplementation in the diet [78].

Most longitudinal studies on BPD after preterm birth find abnormal lung function, which is worsened in extremely premature infants, those with higher severity of BPD, and those with intrauterine growth restriction. Generally, this encompasses varying degrees of airway obstruction, bronchial hyperreactivity, pulmonary hyperinflation, and impaired gas-diffusing capacity [79]. The underlying causes of the bronchial hyperreactivity in children with BPD are still poorly understood, and it is controversial whether it is due to structural changes or neutrophilic airway inflammation.

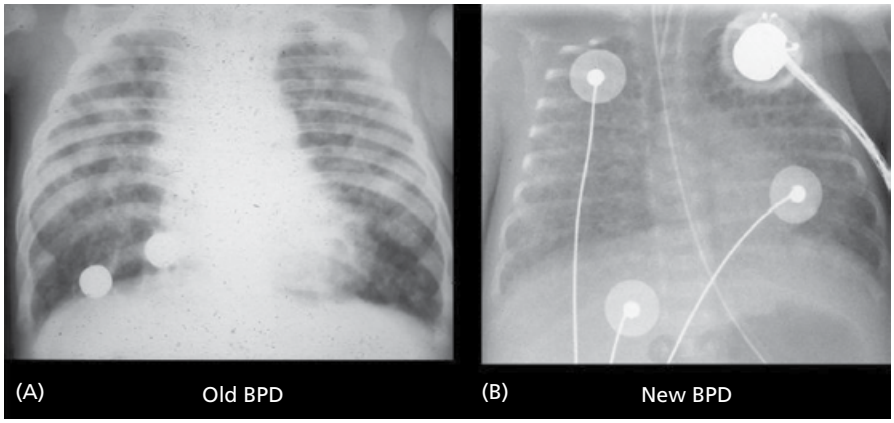


Figure 7.4 Radiographic picture of bronchopulmonary dysplasia (BPD). (A) Old BPD: areas of atelectasis and hyperinflation. (B) New BPD: diffuse opacification of lung fields. *Source:* Reproduced from Gupta et al [73] with permission of Elsevier.

When caring for a patient with a diagnosis of BPD, the anesthesiologist must thoroughly review the history and current chest radiographs if available. The severity of BPD, according to the criteria noted previously, should be assessed. Examination often reveals an infant receiving supplemental oxygen with varying degrees of tachypnea, intercostal and subcostal retractions, and signs of increased lung water or bronchial reactivity, such as fine rales and expiratory wheezing. It is important to understand the patient's baseline oxygen saturation and $PaCO_2$, often available from capillary or venous blood gases. Ventilatory strategies in the operating room should be designed to minimize barotrauma, volutrauma, and oxygen toxicity, and allow permissive hypercapnea to the patient's normal $PaCO_2$. Decreases in lung compliance, increases in resistance, and the increased risk for postoperative mechanical ventilation must all be anticipated and planned for in the infant with BPD. Additional doses of diuretics, or bronchodilators may be needed to optimize perioperative pulmonary outcomes.

Of particular importance for the anesthetist is the presence of bronchial hyperreactivity, particularly in the context of the mechanical stimulation due to airway manipulations. Often the respiratory symptoms in ex-preterm children are classified as asthma, even though the underlying pathophysiological causes seem to be different with no eosinophilic inflammatory pathways observed in children with BPD [79]. This also suggests that routine asthma treatments may not be effective in these children. Additionally, pulmonary hypertension has been recognized as a significant co-morbidity in children with BPD and patients should be screened for pulmonary hypertension preoperatively [75]. Amongst other factors found in the perioperative period, hypothermia, pain, and acidosis can lead to pulmonary vasoconstriction. This can pose a significant risk of hypoxemia due to an increase in ventilation–perfusion inequalities in a child with BPD who already has a limited respiratory reserve [62]. Furthermore, potential right ventricular function impairment may be further increased by anaesthesia.

Although symptoms often decrease with increasing age and the children may seem asymptomatic at preoperative assessments, the rate of bronchial hyperreactivity is still increased, increasing the risk of perioperative respiratory adverse events.

KEY POINTS: BRONCHOPULMONARY DYSPLASIA

- The BPD phenotype has changed to a histological pattern of arrest of airway and alveolar development: alveolar numbers are reduced and the alveoli are larger than normal in diameter; the more severe changes are absent
- The new BPD includes lung injury in very preterm infants during the late canalicular and saccular phases, resulting in arrested development of lung structures and disrupted repair
- Permissive hypercapnea reduces the duration of mechanical ventilation but not the incidence of BPD
- Targeting an SpO_{2in} the 85–89% range, rather than the 94–97% range, appears to somewhat reduce the severity of lung injury and of BPD
- BPD includes varying degrees of airway obstruction, bronchial hyperreactivity, pulmonary hyperinflation, and impaired gas-diffusing capacity
- Pulmonary hypertension is a recognized significant co-morbidity in children with BPD
- Perioperative hypothermia, pain, and acidosis can cause pulmonary vasoconstriction

Cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive disorder caused by a defect in the cystic fibrosis transmembrane conductance regulator (CFTR) gene with an incidence of 1 in 2000 births in Caucasian populations. It is present in approximately 30,000 children and adults in the United States, and more than 70,000 worldwide [80]. The clinical presentation of children with CF, even those with identical CF mutations, is variable. With improvements in early diagnosis and care, life expectancy has increased markedly over the past several decades, with median life expectancy close to 40 years [81]. CFTR is an adenosine triphosphate (ATP)-binding protein that regulates chloride and bicarbonate transport across epithelial cells via cAMP. CFTR also regulates the airway surface liquid depth through regulation of other proteins, most prominently the epithelial sodium channel. Absent or dysfunctional CFTR results in abnormal electrolyte and fluid content on the

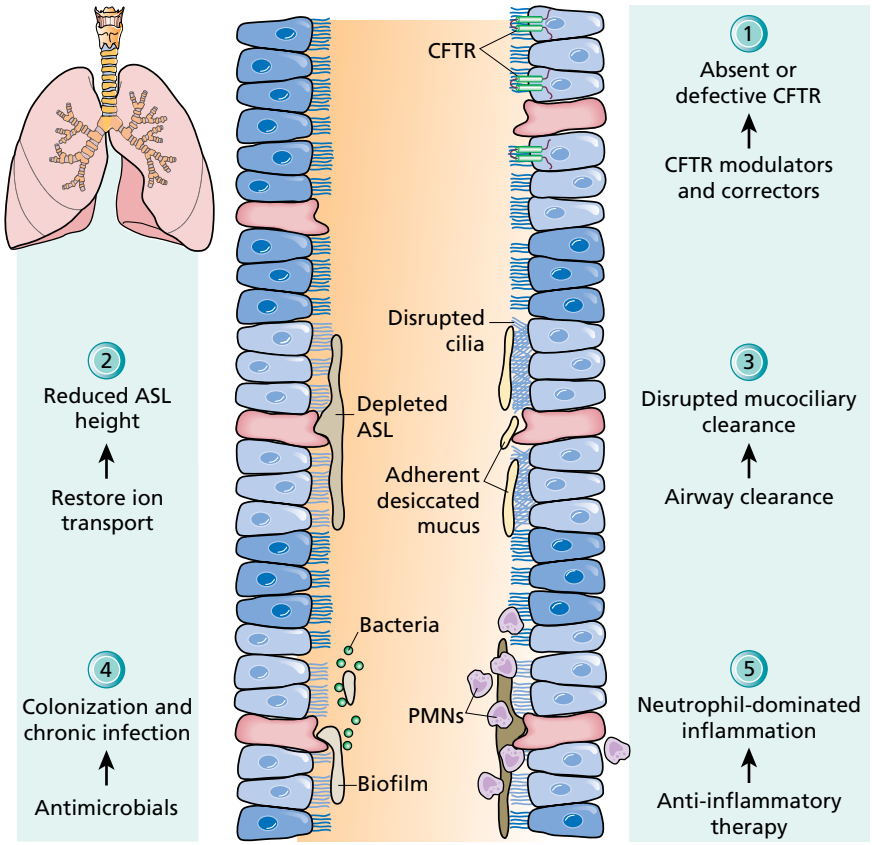


Figure 7.5 The pathogenesis of cystic fibrosis lung disease is characterized by absent or dysfunctional cystic fibrosis transmembrane conductance regulator (CFTR) at the epithelial surface (1), resulting in disordered ion transport and a depleted airway surface liquid layer (2). This contributes to delayed mucociliary clearance (3), setting the stage for colonization and chronic infection with bacterial pathogens (4) and a robust inflammatory response (5). Therapeutic approaches to each feature are indicated. ASL, airway surface liquid; PMN, polymorphonuclear cell. *Source:* Reproduced from Rowe and Clancy [81] with permission of Wolters Kluwer.

epithelia of the lung, pancreas, intestine, hepatobiliary tract, sweat gland, and vas deferens. CF patients have thick, dehydrated, hyperviscous mucus that severely deters effective mucus clearance (Fig. 7.5).

Recent research findings show that the irreversible, progressive lung disease starts to develop early in life even though active symptoms may still be lacking [82]. One of the main underlying factors is the intense inflammation that sets in within the first few weeks of life, even in asymptomatic, culture-negative infants [83]. Similarly, structural changes of the lung also start occurring in infancy and preschool years; mild bronchiectasis, air trapping, and bronchial wall thickening can often be found in asymptomatic infants with the majority of patients having bronchiectasis by age 5. CF patients are susceptible to chronic infection with pathogens such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae* that may be difficult to eradicate. Inflammation occurs both secondary to chronic infection and independent of microbial disease. Chronic infection and inflammation precipitate a cycle of tissue destruction, bronchiectasis, and airway obstruction, a process that eventually leads to respiratory failure. Slowly progressive lung injury is often accompanied by episodic pulmonary exacerbations, followed by periods of relative disease stability [84] (Fig. 7.6).

Standard therapies for CF include daily airway clearance maneuvers with chest physiotherapy by vibropercussion, hand-administered therapy, or specially designed vests that assist with mucus clearance. Inhaled nebulized recombinant human DNase thins excessive DNA debris in sputum that accumulates due to the bacterial burden and the large influx of neutrophils into the airway lumen. This therapy improves pulmonary function, decreases the frequency of CF exacerbations, and improves quality of life [81]. Nebulized hypertonic saline has also been shown to be effective in some trials. Early and aggressive antimicrobial therapy targeted at the patient's specific organisms and susceptibilities is believed to be responsible for a large component of the improvement in quality of life and reduction in exacerbations in CF patients in recent years. Regular parenteral antibiotic therapy (i.e. every 3 months) is used in some centers, with agents including aminoglycosides, ceftazidime, and meropenem. Antibiotic resistance is a major problem, especially with resistant *Pseudomonas* species and other resistant organisms such as *Burkholderia cepacia*. Inhaled nebulized tobramycin has been shown to be effective at preventing CF exacerbations. Anti-inflammatory therapy with low-dose corticosteroids, or NSAIDs, is also used in some patients [81]. CFTR-modulating drugs are under development and in some clinical trials; gene transfer therapy would be the ideal treatment but faces significant obstacles and clinical use is not imminent. Lung transplantation is reserved for patients with severe CF and a life expectancy of 2 years or less.

CF patients present to the anesthesiologist for a variety of procedures, including diagnostic imaging, vascular access

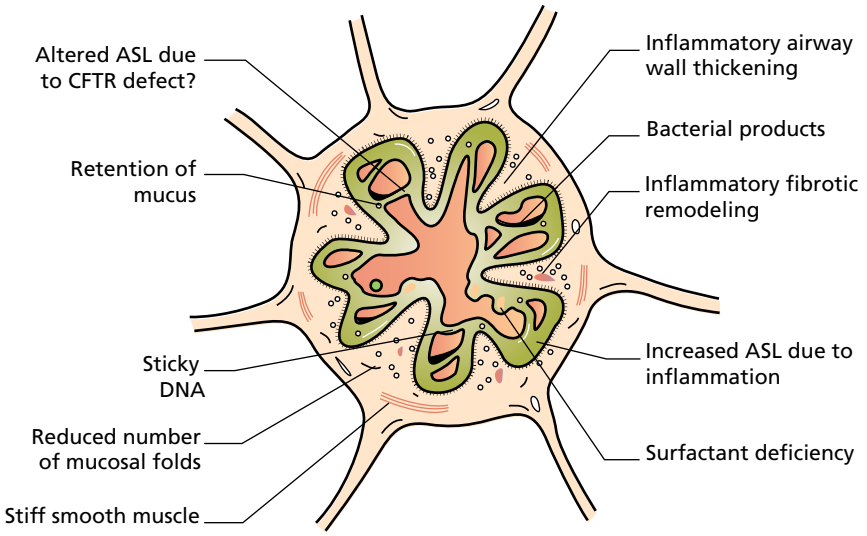


Figure 7.6 Factors that may contribute to small airways obstruction in early CF lung disease. Multiple factors can contribute to filling of the interstices between the folds. ASL, airway surface liquid; CFTR, cystic fibrosis transmembrane conductance regulator. *Source:* Reproduced from Tiddens et al [84] with permission of John Wiley and Sons.

procedures, lung biopsies, bronchoscopy, feeding gastrostomy, endoscopic sinus surgery, and lung transplantation. A very thorough review of history, medications, diagnostic testing, and physical examination is important. Since all children with CF are at a particularly high risk for perioperative respiratory adverse events, anesthesiologists optimize the anesthesia management by considering techniques such as intravenous rather than inhalational induction, noninvasive airway devices and deep removal of airway devices if possible [85].

KEY POINTS: CYSTIC FIBROSIS

- Cystic fibrosis (CF) is an autosomal recessive disorder caused by a defect in the cystic fibrosis transmembrane conductance regulator (CFTR) gene
- Median life expectancy is close to 40 years
- Structural changes of the lung also start occurring in infancy and preschool years; mild bronchiectasis, air trapping, and bronchial wall thickening can often present in asymptomatic infants with the majority of patients having bronchiectasis by age 5
- Chronic infection and inflammation precipitate a cycle of tissue destruction, bronchiectasis, and airway obstruction, a process that eventually leads to respiratory failure

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A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 8

Developmental Physiology of the Central Nervous System

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Introduction

The child is not merely a small adult. Incompletely developed at birth, the central nervous system (CNS) continues to mature until the end of the second year of life. Because of this delay in maturation, several specific pathophysiological and psychological differences ensue. Neurodevelopment follows a complex interplay between timed genetic events and activity-dependent structural modifications. The unforgiving metabolic vulnerability that occurs with conditions of substrate deprivation challenges the vigorous cellular plasticity of the young brain. A comprehensive understanding of the physics of the intracranial compartment, as well as in-depth knowledge of the vascular physiology of the brain and developmental peculiarities of the nervous system underscores the care of the critically ill child susceptible to neurological injury.

Embryology of the developing brain and spinal cord, changes from fetus to neonate to child

Embryogenesis of the brain

CNS development begins from a relatively simple single layer of cells and progresses to a very complex, multilayered central structure that eventually connects with every part of the body. The processes of CNS embryogenesis follow three steps: (1) neurulation, (2) canalization, and (3) retrogressive differentiation (Table 8.1).

Within 2 weeks of conception, a groove is formed in a plate of embryonic ectoderm, and contains the cells that will become the brain and spinal cord. By 1 month, *neurulation* concludes and the lateral edges of this groove are fused to form the neural tube (Fig. 8.1).

At this time, neural crest cells are excluded from the tube closure and subsequently migrate and differentiate to populate diverse neuronal structures such as the sympathetic chain ganglia, the enteric neuronal plexuses, the dorsal root ganglia, and adrenal medulla, as well as becoming melanocytes in the skin.

Rostrally, the neural tube undergoes differential growth, expansion, and folding to form the three primary brain vesicles: the prosencephalon, mesencephalon, and rhombencephalon. Caudally, the neural tube and surrounding mesoderm retain segmental characteristics and form the portion of spinal cord from the medulla to the midlumbar segments. Secondary brain vesicles are formed as the primary vesicles subdivide. The prosencephalon divides into the telencephalon (cerebral cortex and basal nuclei) and the diencephalon (thalamus, hypothalamus, and retinae). The mesencephalon (midbrain) does not subdivide. The rhombencephalon divides into the metencephalon (pons and cerebellum) and the myelencephalon (medulla) (Fig. 8.2).

Embryogenesis of the spinal cord

The spinal cord from the medulla to the midlumbar segments is derived from the caudal portion of the neural tube. The posterior neuropore closes within a month of gestation,

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

Table 8.1 Central nervous system embryogenesis

Phase	Gestational age (days)	Outcome
Neurulation	16–28	Brain, spinal cord through L2–L4
Canalization	30–52	Sacrococcygeal segments of the spinal cord
Retrogressive differentiation	46–birth	Filum terminale

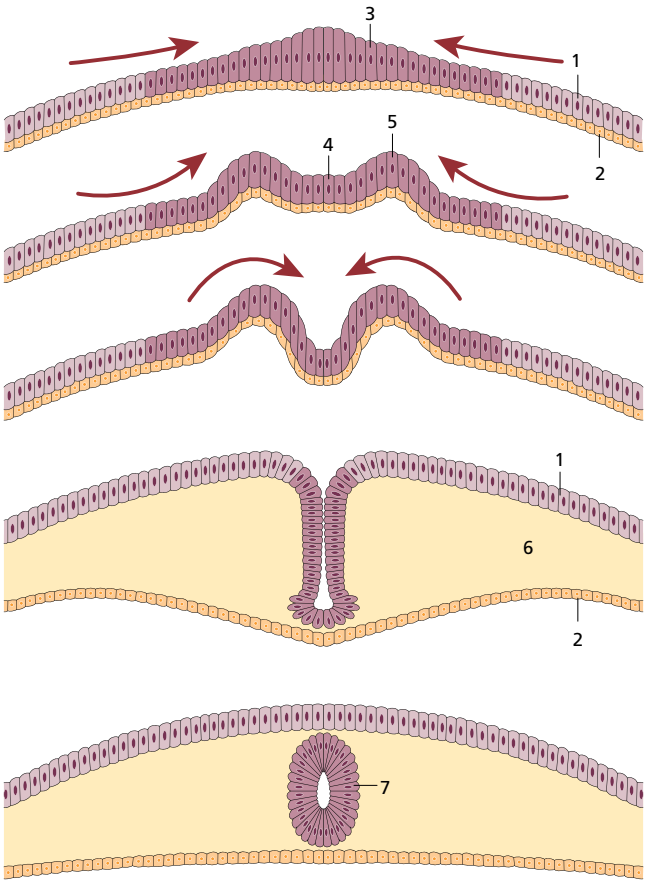


Figure 8.1 Neurulation (see text for details). The arrows indicate the direction of the cell movement. (1) Embryonic ectoderm; (2) embryonic endoderm; (3) neural ectoderm; (4) neural plate with neural groove; (5) neural fold; (6) mesoderm; (7) neural tube. *Source:* Modified from Karfunkel [169] with permission of Elsevier.

and subsequently elongates to form the distal spinal cord and conus medullaris. *Canalization* involves the fusion of the notochord and neural epithelium into a caudal cell mass to form sacral and coccygeal segments between 1 and 2 months of gestation. Microcysts develop and coalesce within this mass. *Retrogressive differentiation* denotes the necrosis of excess cells formed by canalization in the caudal neural tube leaving the filum terminale and cauda equina, a process that continues into the early postnatal period. Vertebral column growth exceeds spinal column growth, resulting in ascension of the conus medullaris from the L3 vertebral segment at birth to the L1 vertebral segment at adulthood (Fig. 8.3).

Neural tube defects

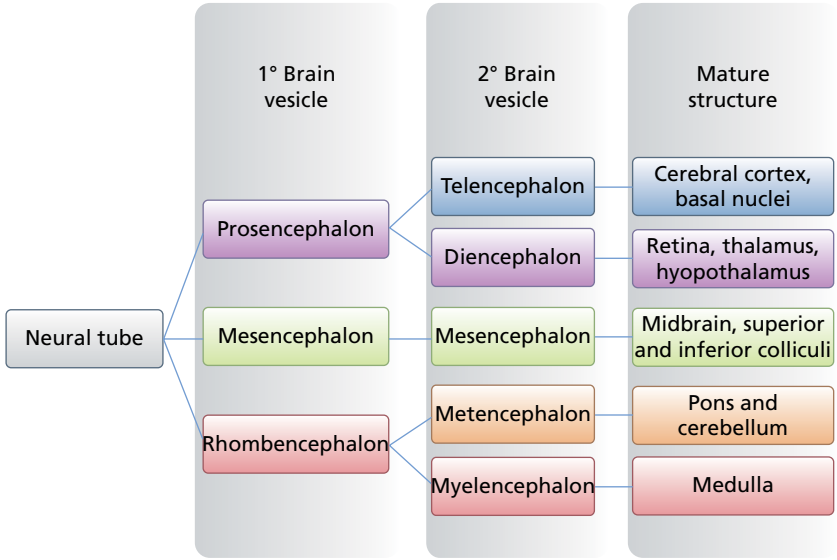
A neural tube defect refers to any defect that occurs during the development of the CNS. We can classify defects occurring during neurulation into: (1) those involving the brain and spinal cord; (2) those involving the brain only; and (3) those involving the spinal cord only. For example, when neurulation fails in early development, a condition of total dysraphism occurs within both the brain and spinal column. If only the brain fails to close, the condition is termed anencephaly. Later in development, many malformations of the brain can occur that have clinical relevance for the pediatric anesthesiologist, including congenital hydrocephalus. Abnormal neuronal migration results in cortical malformations that may be appreciated on gross surface anatomy [1]. Schizencephaly (clefts in the cerebral wall), pachygyri (sparse, broad gyri), and polymicrogyria are examples of anomalies strongly associated with migrational abnormalities. Lissencephaly (smooth brain) is a severe anomaly that may occur after either migrational anomalies or earlier disruptions in neurogenesis. Partial or complete agenesis of the corpus callosum may be associated with any of the above anomalies but it is believed to be a migrational abnormality in and of itself. Failure of canalization results in a myelocele if the lesion is flat, or myelomeningocele if there is an additional dorsal outpouching of the meninges/neural tissue.

Proliferation and migration

Exponential cellular proliferation follows closure of the neural tube, marks the second month of brain development, and continues into the second trimester. Within the second trimester, therefore, the CNS proves particularly susceptible to global insult from teratogen exposure. Radial migration, a well-characterized and robust element of cortical development, denotes a process whereby cells originating from the rapidly dividing periventricular cell layer, and destined to populate the neocortex as both glial and neuronal varieties, migrate along a glial network. They populate the six-layered cortex by migrating past the last-formed layer, such that the youngest cells are found at the outermost layers. At term, cellular proliferation in the cortex is largely completed. However, in premature infants, particularly those at the limits of viability near the beginning of the third trimester, the caudothalamic groove adjacent to the lateral ventricles contains residual germinal matrix. A transient network of fragile vascular overgrowth, which accompanies this ongoing germinal activity, predisposes this site to hemorrhage in the premature neonate [2,3].

Synaptogenesis and myelination

During the third trimester of neuronal development, a period of neuronal growth, synaptic proliferation, axonal growth, and myelination begins. The interplay between genetically determined anatomic directives and environmentally determined plasticity produces a myriad of interneuronal connections that form an incomprehensible network of logical units in the human brain. The basic strategy of network formation calls for the excessive population and interconnection of neuronal networks followed by thinning of these cell populations



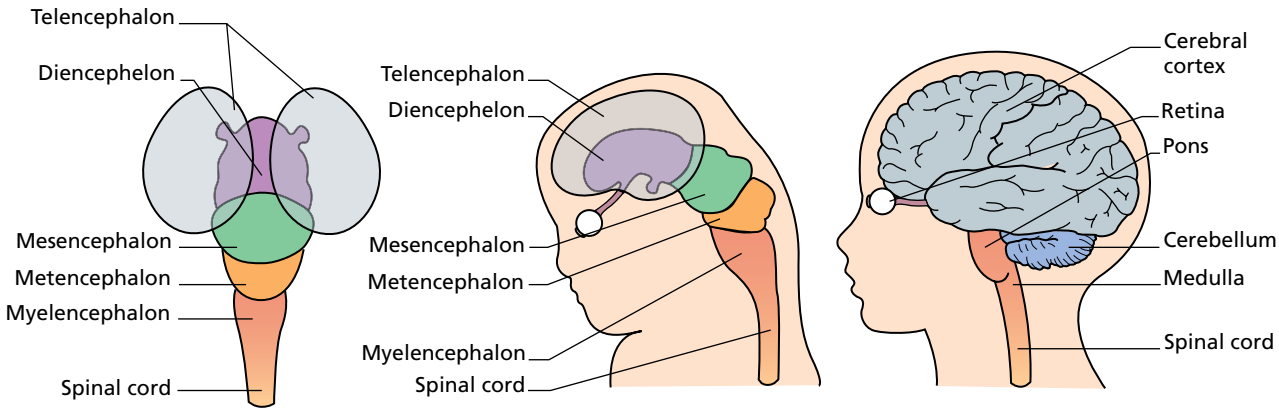


Figure 8.2 Brain development from the neural tube. The neural tube gives rise to three primary brain vesicles, which in turn form five secondary brain vesicles before completing development into the mature brain.

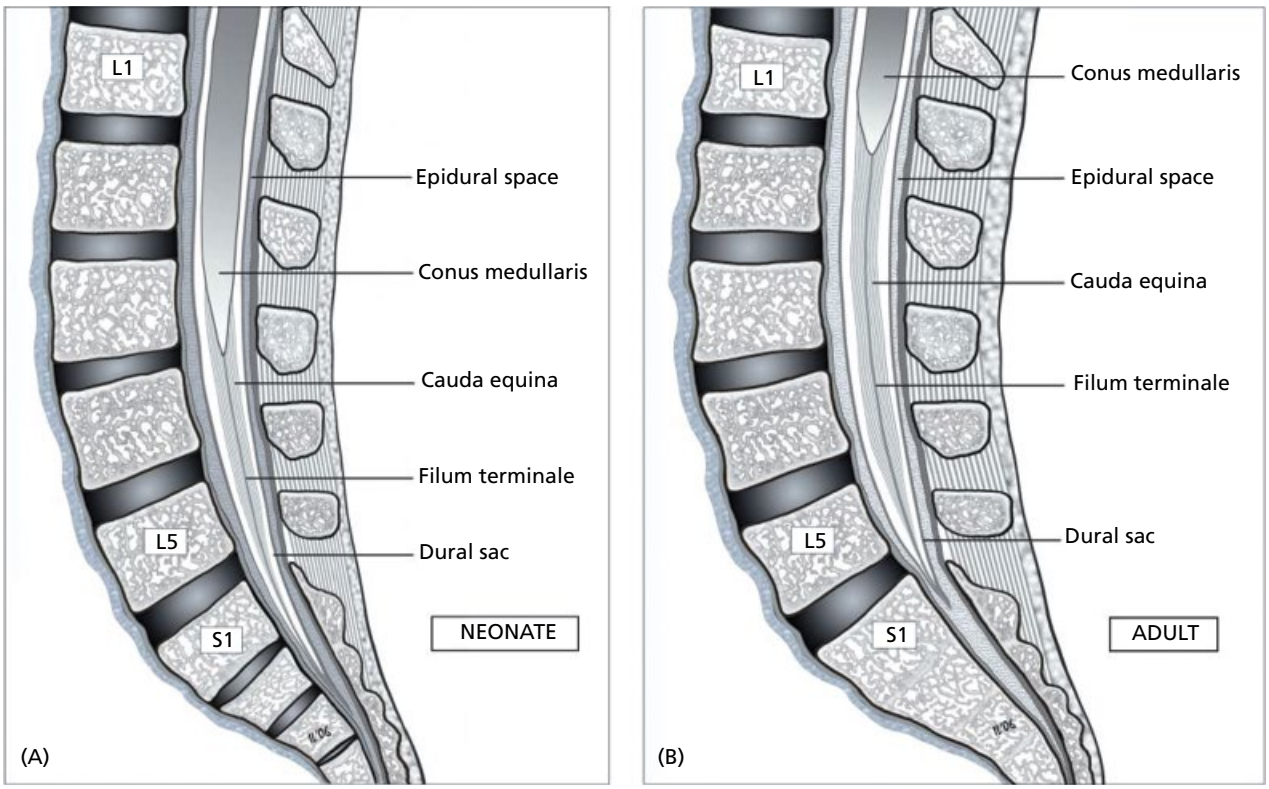


Figure 8.3 Asymmetrical growth of the spine and its vertebral canal causes a change in the position of the conus medullaris with respect to the vertebral column with growth from neonate (A) to adult (B).

by apoptotic mechanisms, pruning of inactive synapse formations, and reinforcement of functional and active connections. Thus, synaptic activity patterns determine the viability of neurons and synaptic connections. The resultant functionality of the network, therefore, depends on sensory and environmental inputs, some of which are known to be time sensitive.

Amblyopia represents the most striking example of synaptogenesis gone awry for lack of appropriate sensory input during a critical stage of development. Normal development of the occipital cortex requires spatially organized and synchronized neuronal activity along the visual pathway. Activity-dependent synapse reinforcement of the occipital cortex begins in darkness, *in utero*, as waves of electrical activity spontaneously pass across the retina, reinforcing spatially-coordinated synaptic connections throughout the visual pathway [4]. After birth, further synaptic reinforcement relies on light-mediated excitation in the retinae. If the retinae receive inadequate or disconjugate light stimulus through the critical development period up to 2 years of age, permanent blindness of the affected eye results from irreversible pruning of synaptic formations in the corresponding cortical network [5–7].

While critical periods for other neurodevelopmental processes are less well defined, we know that the perinatal surge in synapse formation continues through early childhood to the preteen years. The existence of a critical period distinguishes developmental, primary synaptogenesis from other forms of neural plasticity that continue throughout life. The relative permanence of synaptogenic modulation during infancy and childhood is even postulated to create a critical period for development of intellect, behavior, and affect. Environments rich in stimulation, interaction, and socialization promote increased synapse retention, where neglectful, stimulus-poor developmental environments yield synapse-depleted cortical networks, and may lead to permanent cognitive deficits [8–11]. The dendritic arborization of cortical pyramidal neurons has been shown to be environment dependent even in the mature mammalian brain (Fig. 8.4). Further, the introduction of a consistently noxious environment during critical developmental stages may yield undesirable affective changes.

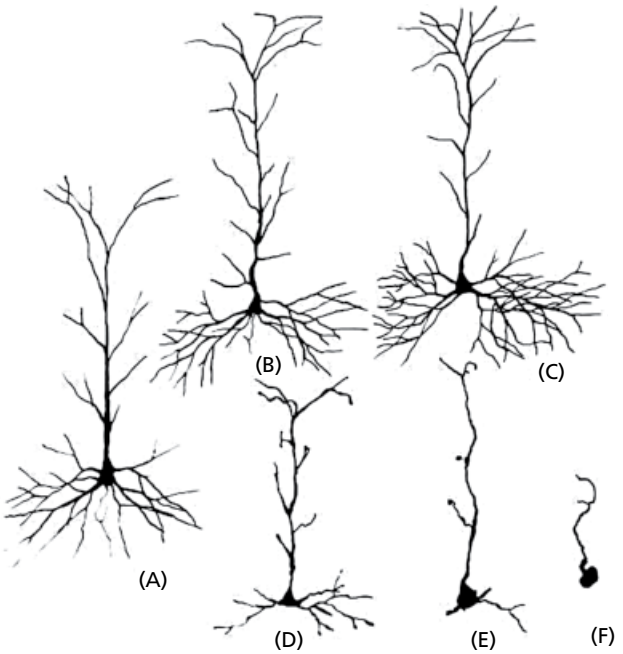


Figure 8.4 Age-related patterns of dendritic arborization of cortical pyramidal neurons. Mature pyramidal neurons (A) can undergo a stimulus-dependent process of stabilization and even increase in synaptic interconnection and dendritic branching (B and C). Alternatively, absent stimulus input, the mature neuron can undergo synaptic pruning and regressive loss of dendritic arborization (D–F). *Source:* Reproduced from Williams and Ramamoorthy [167] with permission of SAGE.

Myelination

Myelination and axonal maturation start in the third trimester, with a peak density of immature oligodendrocytes in the cortical white matter between 23 and 32 weeks of gestation, a time of white matter vulnerability in the premature infant [12]. Myelination continues through childhood and into the teen years, mirroring brain growth. The process of myelination and increased cell size, rather than cellular proliferation, accounts for brain growth from 450 g at birth, to 1000 g at 1 year, and 1400 g at 18 years.

Developmental milestones also follow patterns of myelination. For instance, myelination of the corticospinal tract, which progresses from short to long fibers, and occurs between 36 weeks of gestation and around 2 years of life, correlates anatomically with the head-to-toe disappearance of hyperreflexia and the increased tone seen during the same developmental period. Additionally, axonal maturation of the speech-dominant frontotemporal pathway continues through late childhood and adolescence, correlating with the development of increasingly sophisticated language competency [13]. As with synaptogenic processes, myelination patterns are activity dependent [14].

Magnetic resonance imaging (MRI) of term infants with congenital heart disease demonstrates immature patterns of myelination. Also, pre-cardiopulmonary bypass MRIs reveal lesions in an estimated one-quarter of infants with congenital heart disease, with brain immaturity a risk factor for new MRI lesions after cardiopulmonary bypass. Many of these lesions represent diffuse white matter injury, similar in nature to periventricular leukomalacia seen in preterm infants [15].

Development of pain pathways and responses

The understanding of nociception and the effects of "pain" on the developing infant and child represents, arguably, the greatest contribution of the relatively new pediatric anesthesia specialty. The nociceptive systems develop during the second and third trimesters of gestation, with further maturational changes occurring during the first 2 years of life. Historically, physicians undertreated the pain of neonates and infants due to a belief that the pain system was underdeveloped during these times [16]. However, despite the lack of a "verbal" response to pain, physicians recognized the "physiological" responses to pain that prompted careful exploration of the physiological basis of nociception.

Nociception begins with detection of a stimulus at the level of the peripheral nervous system [17]. Unlike the adult-specific sensations of touch, pressure, heat, or cold, no specific pain sensors exist in the developing fetus. Rather, free

non-specific nerve endings detect the "pain" stimulus. During fetal life, rapidly adapting pressure receptors appear first, followed by the development of slowly adapting pressure receptors, and then rapidly-adapting mechanoreceptors. The depolarization responses of these receptors to mechanical injury, chemical irritants, and inflammatory mediators compare to those of adult receptors [18]. Cutaneous sensory receptors appear in the perioral area at 7 weeks' postconceptual age (PCA), spread to the hands and feet by 11 weeks' PCA, and pervade all cutaneous and mucous surfaces by 20 weeks' PCA [19,20]. Synaptogenesis between afferent fibers and sensory neurons in the dorsal horn of the spinal cord precedes the development of these sensory reflexes.

Free nerve endings of A and C fibers mediate the sensation of pain. These fibers do not demonstrate fatigue; rather, repeated or continuous stimulation *increases* the ease of transmission of the impulse. Histological studies show that the density of nociceptive nerve endings in the newborn skin is similar to that of adult skin [21]. More importantly, the neurophysiological properties of the earliest nociceptors approximate those of adults. Myelinated fibers are the first to grow into the developing spinal cord and form connections with deeper layers of the dorsal horn, as well as generate collaterals to neurons in the substantia gelatinosa. With the ingrowth of unmyelinated C-fibers and their synaptogenesis with superficial dorsal horn neurons, these collaterals undergo developmental degeneration. Myelinated A-fibers transmit nociceptive stimuli in fetal life, and in the extremely premature neonate, until the maturation of C-fiber connections [22].

The first-order neuron, whose cell body lies in the paravertebral ganglion, carries the nociceptive input into the dorsal horn of the spinal cord. The first-order neuron synapses with a second-order neuron in the dorsal horn of the spinal cord. The second-order neuron then crosses the midline and ascends in various pathways including the spinothalamic tract, synapsing in the thalamus with a third-order neuron that projects to the sensory cortex [23]. In the dorsal horn of the spinal cord, nociceptive input is modified (amplified and inhibited) by descending fibers from the CNS and interneurons within the dorsal horn. This modulation is mediated via various chemical compounds (substance P, adrenergic agents, serotonin, and endogenous opioids), which bind to the first- or second-order neuron via specific receptor systems (Fig. 8.5).

In the first trimester of pregnancy, development of the spinal cord and CNS begins with the closure of the neural canal. At this time, the dorsal horn begins to appear. Electron microscopic and immunochemical studies demonstrate that the development of the various neuronal cell types in the dorsal horn with their laminar arrangement, interneuronal connections, and the expression of their specific neurotransmitters and receptors, begins before 13 weeks of gestation and is completed by 30–32 weeks' PCA. Initially, dorsal horn neurons possess a very large receptive field and an extensive overlap with the receptive fields of adjacent neurons. As maturation occurs, the receptive fields of individual dorsal horn cells progressively decrease and can be more precisely defined [24]. On a cellular level, the release of the excitatory neurotransmitters, such as substance P, glutamate, calcitonin gene-related peptide (CGRP), vasoactive intestinal polypeptide (VIP), neuropeptide Y, and somatostatin, mediates and modulates the transmission of nociceptive impulses through the dorsal horn of the spinal cord (Fig. 8.6). Modulation of this nociceptive transmission occurs by the release of met-enkephalin from

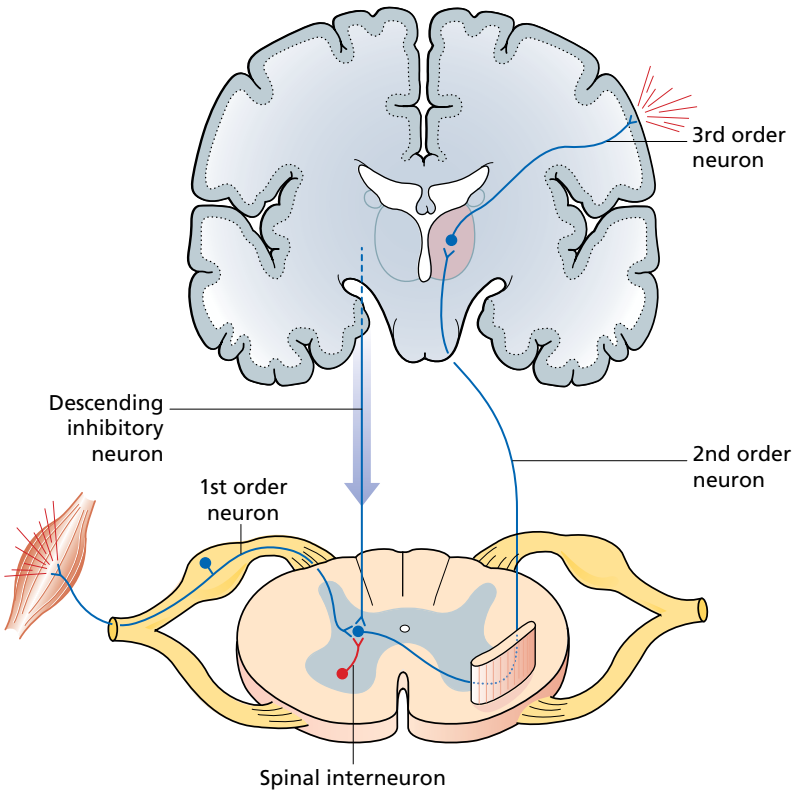


Figure 8.5 Descending inhibitory pathways and spinal interneurons modulate pain transmission at the level of the spinal cord.

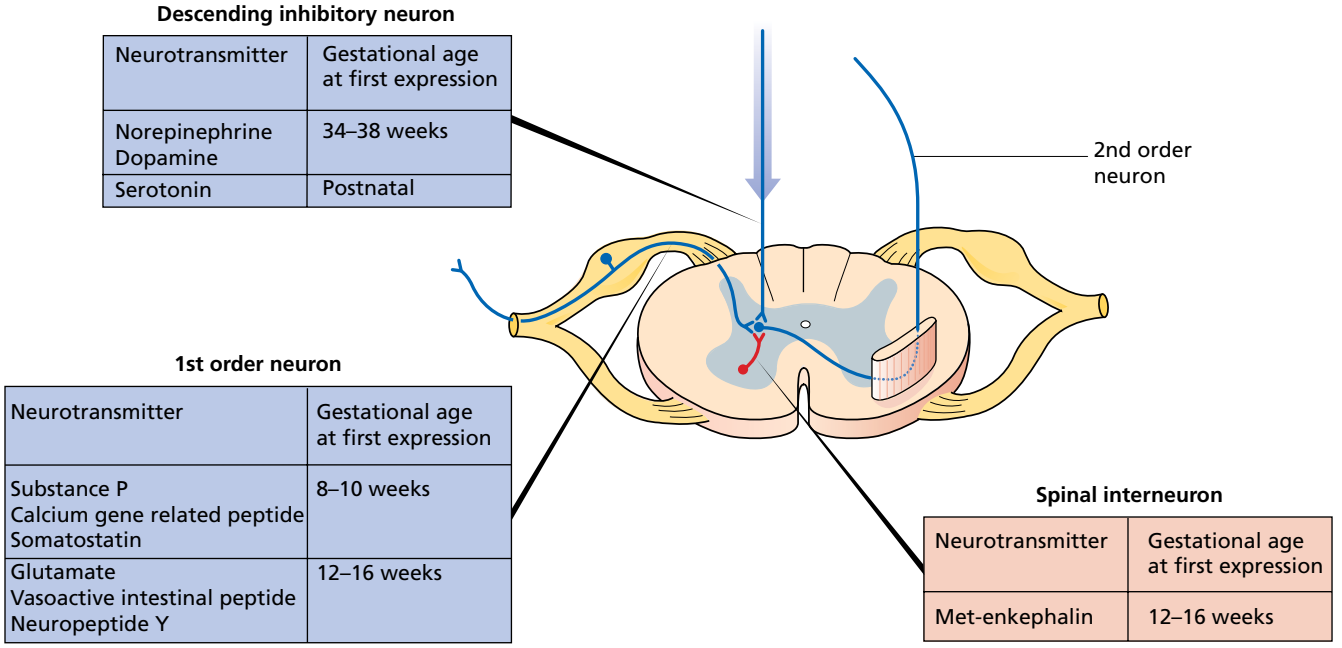


Figure 8.6 Neurotransmitters found in the spinal cord modulating activity of the pain pathway are shown with the gestational age at which they are first expressed.

local interneurons and norepinephrine, dopamine, and serotonin from descending inhibitory axons.

These descending inhibitory axons originate in supraspinal centers and terminate at all levels of the spinal cord and brainstem. During the first and second trimesters up until the latter half of the third trimester, nociceptive mechanisms are unbalanced, favoring amplification, rather than inhibition, of nociceptive input. By 8–10 weeks' PCA, the dorsal horn expresses the nociceptive neurotransmitters substance P, CGRP, and somatostatin. Glutamate, VIP, and neuropeptide Y appear at 12–16 weeks' PCA. Modulation of incoming noxious stimuli in extremely premature infants may occur through the local release of met-enkephalin, which is first expressed at 12–16 weeks' PCA. However, this mechanism likely cannot effectively diminish the transmission of intensive painful stimuli. In the latter half of the third trimester, with the maturation of the descending inhibitory pathways from supraspinal centers, inhibition of incoming sensory stimuli can occur with the release of dopamine and norepinephrine in the dorsal horn of the spinal cord. Inhibitory neurons first express these neurotransmitters at 34–38 weeks' PCA, followed by serotonin during the postneonatal period [25,26].

Conduction of nociceptive impulses to the supraspinal centers occurs via the spinothalamic, spinoreticular, and spinomesencephalic tracts located primarily in the anterolateral and lateral white matter tracts of the spinal cord. Scientists previously proposed the lack of, or decreased, myelination in these tracts as an index of immaturity of the neonatal CNS, and used this to support the argument that neonates cannot feel pain or do not react to it in the same manner as adults. This argument garnered wide support despite the common knowledge that incomplete myelination does not indicate lack of function, but a slower conduction velocity in the central nerve tracts of neonates. Additionally, the shorter interneuronal distances traveled by an impulse in an infant compared to the much larger (and longer) adult completely offset any slowing in the central conduction velocity [27].

Timing of the thalamocortical connection is also of crucial importance for cortical perception of pain since the majority of sensory pathways to the neocortex have synapses in the thalamus. The nociceptive tracts to the brainstem and thalamus are completely myelinated by 30 weeks of human gestation and the thalamocortical pain fibers are fully myelinated by 37 weeks. In the primate fetus, thalamic neurons produce axons that arrive in the cerebrum before midgestation. These fibers remain just below the neocortex until migration and dendritic arborization of cortical neurons are complete and finally establish synaptic connections at 20–24 weeks' PCA [27].

The presence of fetal and neonatal electroencephalographic (EEG) patterns, and the behavioral development of neonates, suggest the functional maturity of the cerebral cortex. Intermittent EEG bursts in both cerebral hemispheres appear at 20 weeks' PCA, become sustained at 22 weeks, and have bilaterally synchrony at 26–27 weeks' PCA. By 30 weeks, we can distinguish between wakefulness and sleep of a fetus using EEG patterns [28,29]. Investigators have recorded cortical components of somatosensory, auditory, and visually evoked potentials in preterm babies before 26 weeks' PCA [30]. Several forms of behavior also imply cortical function during fetal life. For instance, well-defined periods of quiet sleep, active sleep, and wakefulness occur *in utero*, beginning at 28 weeks' PCA. Furthermore, neonates display various cognitive, coordinative, and associative capabilities in response to visual and auditory stimuli in addition to specific behavioral responses to pain, attesting to the presence of cortical function and intact processing of nociceptive input [23].

Development of the response to pain stimulation

The human fetus moves spontaneously and demonstrates complex responses to stimuli early in gestation. Reflex movement in response to direct stimulation, initially localized to

the head and neck region, begins at 7.5 weeks' PCA [31]. Sensitivity develops in a craniocaudal direction with the lower limbs responding by 14 weeks' PCA. Data from the immature rat and other animals reveal inconsistent, non-specific, and poorly localized responses to stimulation initially [32]. However, if triggered, stimuli elicit extremely exaggerated and long-lasting responses [33]. These observations corroborate the neurophysiological animal data and clinical observations in preterm human infants. Single cell studies from the dorsal root ganglion of the rat show that cutaneous receptive fields appear in the hindlimb as soon as innervation to the skin takes place [34]. Initially stimulation of cutaneous afferents fails to produce suprathreshold excitation in dorsal horn cells, but by birth light touch alone initiates depolarization [32]. However, while the synaptic linkage remains weak at birth, suprathreshold stimulation provokes a long-lasting hyperexcitable state in the dorsal horn cells [34].

Polymodal nociceptors, which pass to the dorsal horn via C-fibers, display fully mature responses to pinch, heat, and chemical stimulation by birth [35]. However, despite their observed anatomical connections, these C-fiber afferents fail to evoke activity in the dorsal horn cells until a week after birth. Thus, while the C-fiber connections remain immature at birth and fail to directly transmit their nociceptive input, they may greatly increase the response to other noxious (A-fibers) and non-noxious inputs. Together with the large receptive fields observed in dorsal root ganglion cells, this may increase the likelihood of a central response from the relatively immature nervous system. The lack of functional descending inhibitory pathways from higher centers also contributes to the potentially excitable and poorly damped responses to afferent inputs.

Central integration of afferent inputs

In humans, complex central integration of afferent sensory and nociceptive input is present at 30 weeks' gestation. We can also detect visual and auditory evoked potentials, as well as a complex EEG reactive to external influences, at this time [28,29]. Klimach and Cooke demonstrated the presence of somatosensory evoked potentials (SSEPs) in the preterm neonate [30]. In fact, these authors measured SSEPs in infants as young as 28 weeks' gestation, and demonstrated that the velocity of both peripheral nerve conduction and central conduction increased with gestational age. However, they found considerable variability in peripheral velocity and central processing in the younger infants, suggesting that there are large individual differences in maturation rates. SSEPs continue to mature during infancy [36]. Subarachnoid injections of lidocaine in the ex-premature infant cause rapid loss of the SSEPs corresponding to the onset of motor and sensory blockade. The return of SSEPs and shortening of the latency back to the baseline indicates the offset of the block on monitoring of evoked potentials [37]. Positron emission tomography scans in infants demonstrate that glucose utilization is maximal in the sensory areas of the cerebral cortex, implying a high level of activity [38].

Recent evidence also suggests that cortical activation occurs after painful stimuli in preterm neonates [39]. Bartocci and colleagues, using near-infrared spectroscopy in preterm infants 28–36 weeks' PCA, demonstrated increased blood flow in the somatosensory cortex and not the occipital cortex after venipuncture [40]. In a similar study, Slater and colleagues recorded cortical activation after heel sticks in 18 infants between 25 and 45 weeks' PCA [41]. They noted no cortical response after tactile stimulation even when a reflex limb withdrawal was elicited by the heel stick. Taken together, these studies provide additional evidence that the conscious sensory perception of painful stimuli is present even in preterm newborns. Table 8.2 summarizes the behavioral and physiological nociceptive responses of the neonate.

Table 8.2 Main physiological responses to pain

Assessment	Effect of pain stimulation
Middle cerebral artery pulsatility index	Decrease
Intracranial pressure	Increase
Systemic blood pressure	Increase
Heart rate	Increase (inconstant in neonates)
Transcutaneous oxygen tension	Decrease
Vagal tone (amplitude of sinus arrhythmia)	Decrease
Palmar sweating	Increase
Near-infrared spectroscopy	Decrease

Molecular basis of pain perception

Studies of developmental cytochemistry in animal models focus largely on substance P, opioid peptides and receptors, N-methyl-D-aspartate (NMDA) receptors, and the expression of the C-*fos* gene. While we can detect transmitters early in gestation, they are usually present in very low concentrations and may not always be found at sites that suggest a functional role [42]. By contrast, we can detect receptors early in gestation at higher densities and with a more widespread distribution than in adult life, which may facilitate responses at a time when only low levels of transmitter are available [17]. The transient and puzzling appearance of receptor populations during gestation that cease to be expressed by birth exemplifies the large gap between the *in vitro* cytochemical findings and our current understanding of *in vivo* nociception [43]. Opioid receptors change both in numbers and in type during development. Pasternak et al demonstrated in newborn rats that in conjunction with a large increase in analgesic response to morphine, high-affinity binding sites for a tritiated encephalin ligand increased by up to three-fold in the first 2 weeks of life [44]. In contrast, the effects of morphine on ventilatory drive during this period (2–14 days after birth) remained constant. Other studies subsequently confirmed the increase in opioid receptor quantity and the changes in their binding affinities during *in utero* and postnatal development [45].

The ability to assess gene and protein expression on a cellular and tissue level has led to a more systems-based approach to the adaptation to nociceptive triggers, sparking new insights into the physiological responses to painful stimulus. Assessment of the earliest alterations in gene expression within peripheral nerves, the spinal cord, and brain in both acute and chronic pain response models allows us to evaluate the complex response to painful stimuli and nerve injury in rodent models [46]. Additionally, the development of proteomic and microarray techniques revealed previously unrecognized alterations in actual transcribed and activated

proteins from within a specific cell line and/or tissues [25,47]. The identification of genetic variations and altered expression within the opioid receptor illustrates the vital importance of these techniques. Following the studies of Pasternak and colleagues, these techniques have identified gene-splice variants and single nucleotide polymorphisms within animal and human populations that better explain the variable clinical response to opioid analgesics due to binding kinetics and molecular response [44,48]. Future directions in molecular pain research involve the development of molecular signatures of neuronal and receptor responses that correlate with our phenotypic definitions of acute and chronic nociception and will lead to more personalized pain treatments based on these molecular characterizations (pharmacogenomics) [49].

KEY POINTS: EMBRYOLOGY OF THE BRAIN AND SPINAL CORD

- The processes of CNS embryogenesis follow three steps: neurulation, canalization, and retrogressive differentiation, from the 16th day of gestation through birth
- Cellular proliferation and migration follows closure of the neural tube and continues into the second trimester. Synaptogenesis and myelination begin during the third trimester and continue into the first 2 years of life at a lower rate
- Pain perception pathways and responses start developing during the second and third trimesters, further maturing over the first 2 years of life

The intracranial compartment

The bony encasement of the mature brain both protects and threatens its integrity. The open sutures and fontanelles of the neonate and young infant provide some capability for intracranial contents to expand. The posterior fontanelle ossifies (closes) by about 2–3 months, and the anterior fontanelle by 9–18 months in the normal infant. The brain cannot tolerate acute mass effect because of the elastance of the skull and dura. The risks of herniation and stroke from elevated intracranial pressure have been described for nearly two centuries as the Monro–Kellie doctrine [50,51]. Elastance in the skull is not linear, given that movement of cerebrospinal fluid from the brain to the spinal canal functions as a reserve mechanism. When the increase in intracranial volume exhausts this reserve compliance, further increases cause blood to be pushed out of the skull. Herniation of brain matter occurs with terminal increases in intracranial volume.

Historically, intracranial elastance was estimated by injections of small volumes of artificial cerebrospinal fluid into patients with intracranial pressure (ICP) monitoring. Today, simple ICP monitoring when indicated satisfies most practitioners. More recently, the RAP index, derived from analysis of the pulse amplitude behavior of the intracranial pressure waveform, has been developed to delineate three clinical states of intracranial elastance. Specifically, the correlation coefficient (R) between the pulse frequency amplitude (A) and the mean pressure value (P) of the intracranial pressure wave across periods of slow change in mean intracranial pressure describes the RAP index [52,53]. In the normal state, RAP is near zero because the pulse amplitude of intracranial pressure is low and unchanging within a compliant skull. As compliance reserve is exhausted and the elastic properties of the skull and dura begin to dominate, the pulse frequency amplitude of the ICP becomes passive to slow changes in mean intracranial pressure and RAP trends toward 1. Finally, when ICP is terminal and herniation is imminent, further increases in ICP push blood out of the skull and diminish the pulse amplitude of the ICP, and the RAP becomes negative (Fig. 8.7). In patients with critical ICP, elastance, as represented by the RAP, improves when a surgeon performs a decompressive craniectomy [54].

Eight major bones separated by eight suture lines and six fontanelles form the intracranial compartment. Delayed ossification of these bones permits deforming *compression* of the skull by the birth canal during parturition. This observation leads to the erroneous corollary concept that fontanelles protect the brain against acute mass effect by allowing *expansion* of the cranial vault. In truth, slow growth and expansion of the sutures and fontanelles occurs in the setting of subacute mass effect, but the fibrous interosseous connections lack compliance, and do not accommodate mass added acutely to the intracranial compartment. Although the anterior fontanelle has no protective role in the setting of acute intracranial mass effect, physical examination of it serves as an important monitor of ICP. Tonometry has been applied to the anterior fontanelle to measure ICP non-invasively when ICP monitoring is desirable but not invasively accessible [55]. By 2 years of age, the fontanelles close and bones replace suture lines, but the fibrous sutures permit ongoing bone growth.

The tentorium, a dural separation between the brainstem and cerebellum posteriorly and cortex and diencephalic structures anteriorly, subdivides the intracranial compartment. This impacts the monitoring of ICP in children with posterior compartment neoplasms, given that ICP is monitored in the anterior compartment, and the tentorium divides the intracranial compartment into subdivisions with distinct pressure environments. Posterior compartment mass effect causes deformation of the brainstem, with signs of coma, bradycardia, and hypertension that can exist without bulging fontanelles or elevated anterior compartment pressures.

Cerebrospinal fluid

Derangements of cerebrospinal fluid (CSF) production, flow, and reabsorption account for significant morbidity in the pediatric population. Normal CSF physiology is well described in adults who have an average 150 mL of CSF, 30–40 mL of which is in the ventricles, and produce 20 mL/h of CSF at the choroid plexus. This causes a replacement of the entire CSF volume 3–4 times a day. The constant small pressure gradient between the spinal fluid space and the sagittal sinus drives the flow of CSF through the extracellular spaces of the brain, and its reabsorption through the arachnoid granulations. Age-dependent rates of CSF production have been described in children with external ventricular drains. However, the wide range of CSF production documented across studies likely represents variation that is due to the pathologies associated with the clinical need for drain placement. Nevertheless, Yasuda and colleagues found

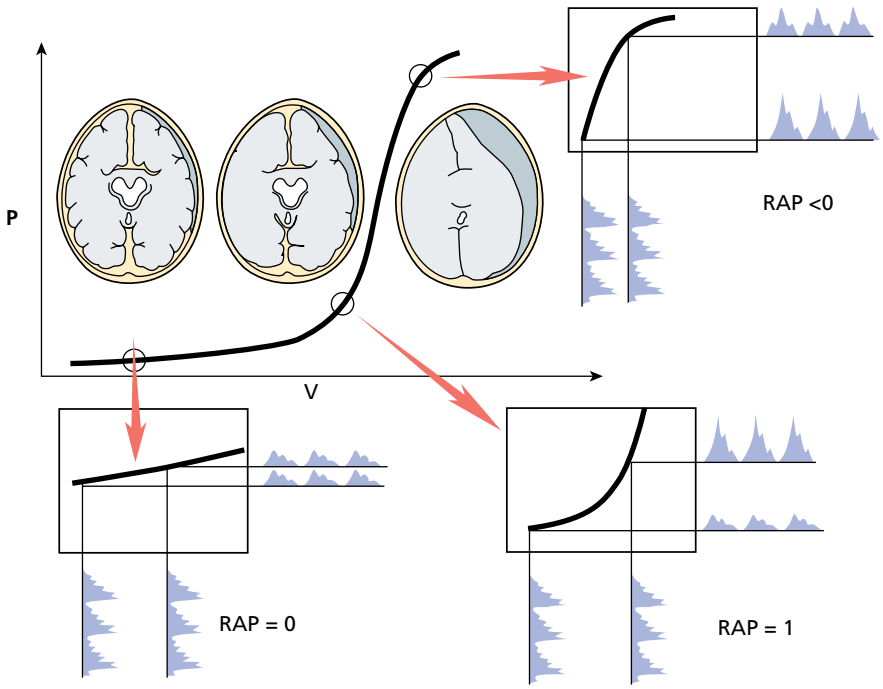


Figure 8.7 Intracranial pressure waves are schematized as a product of fixed cardiac stroke volume pulsations, occurring at different positions on the intracranial pressure–volume curve. Intracranial compliance reserve can be delineated with RAP: correlation (R) between intracranial pressure pulsation amplitude (A) and mean intracranial pressure (P). Three states of intracranial compliance reserve have been defined with this method. (1) RAP = 0: intracranial pressure pulse amplitude does not change with increases in mean intracranial pressure; volume changes are easily absorbed by intracranial compliance reserve. (2) RAP = 1: intracranial pressure pulse amplitude is correlated to changes in mean intracranial pressure; patients on the ascending portion of the intracranial pressure–volume curve have diminished compliance reserve. (3) RAP <0: intracranial pressure pulsations are inversely correlated to changes in mean intracranial pressure. When the RAP is negative, intracranial compliance reserve is exhausted and herniation is imminent.

that CSF production increases logarithmically during the first year of life and reaches 60% of adult production levels at 2 years of age [56].

KEY POINTS: THE INTRACRANIAL COMPARTMENT

- The posterior fontanelle closes by about 2–3 months, and the anterior fontanelle by 9–18 months in the normal infant
- The elastance of the mature skull is not linear; there is some reserve with movement of CSF from brain to spinal canal but when brain swelling or bleeding exhausts this reserve, brainstem herniation occurs
- Infratentorial posterior compartment mass effect causes deformation of the brainstem, with signs of coma, bradycardia, and hypertension that can exist without bulging fontanelles or elevated anterior compartment pressures
- CSF production increases logarithmically during the first year of life and reaches 60% of adult production levels at 2 years of age

Vascular anatomy of the central nervous system

Brain vascular anatomy

A healthy 3 kg infant with a normal 500 g brain has a cardiac output of 250 mL/kg/min, and a cerebral blood flow of 25 mL/100 g/min (= 42 mL/kg/min). The infant brain, therefore, consumes 17% of cardiac output, and also accounts for 17% of the body mass. For comparison, a healthy 50 kg teenager with a 1400 g brain and a cardiac output of 100 mL/kg/min has a normal cerebral blood flow of 22 mL/kg/min. The mature brain therefore comprises just over 2% of total body mass, but utilizes 25% of the cardiac output.

An extensive network of arteries originating from paired internal carotid and vertebrobasilar arteries supplies blood flow to the brain. These arteries branch into the anterior cerebral arteries and the posterior cerebral arteries, respectively, anastomose with each other on the ventral surface of the brainstem to comprise the anterior and posterior segments of the circulus arteriosus cerebri (circle of Willis), and complete the circuit by joining the anterior communicating artery and posterior communicating arteries. The circle of Willis provides collateral blood flow to the brain parenchyma; therefore, damage to any one vessel typically does not result in clinically significant ischemia. However, damage, obstruction, or incomplete formation of any one of the major cerebral vessels may result in a cerebrovascular accident (CVA). The vessels comprising the circle of Willis are prone to the formation of berry aneurysms, congenital birth defects related to defective arterial wall formation. Despite being congenital defects, these aneurysms rarely rupture until early to middle adulthood. Arteriovenous malformations (AVM), the most frequently occurring congenital cerebrovascular malformations, result in the shunting of blood from the arterial to the venous side secondary to anomalous dilated capillaries. Fifty percent of patients present with seizures or neurological deficits as a result of compression or a steal phenomenon, while the other 50% present with hemorrhage. The vast majority of AVMs

occur in the supratentorial compartment (typically in a lobar region), while only 10% occur in the infratentorial region.

The cerebral veins run in the pial layer, while the large collecting veins run in the subarachnoid layer. They eventually transverse the subdural space and open into the cranial venous sinuses. Venous sinuses located between the dura mater and the cranial periosteum primarily make up the venous drainage system of the brain. The walls of the venous sinuses lack both valves and muscle.

Other sinuses within the venous drainage system are of importance to the anesthesiologist, particularly the superior sagittal sinus. Its relatively superficial and midline location predisposes it to damage during surgical correction of craniosynostosis or during a morcellation craniectomy. The superior sagittal sinus ends by becoming continuous with the right transverse sinus 60% of the time, becoming continuous with the left transverse sinus in the remaining 40%. The transverse sinus courses laterally to the sigmoid sinus superior to the tentorium cerebelli. The S-shaped sigmoid sinus (hence its name) lies within the posterior cranial fossa and eventually enters the venous enlargements known as the internal jugular venous bulbs. Most of the venous drainage system empties into the sigmoid sinuses and subsequently into the internal jugular vein excluding the inferior petrosal sinuses, which enter the internal jugular veins directly. A thin plate of bone separates the sigmoid sinus anteriorly from the mastoid antrum and mastoid air cells. The occipital sinus, which lies along the foramen magnum, ends in the confluence of sinuses. The cavernous sinus, which surrounds the sella turcica, joins the superior petrosal sinuses draining into the transverse sinus.

Spinal cord vascular anatomy

The arterial supply of the spinal cord primarily arises from a single anterior spinal artery and two posterior spinal arteries, both originating from the vertebral artery. Radicular arteries originating from spinal branches of the ascending cervical, deep cervical, intercostal, lumbar, and sacral arteries also provide supplemental blood flow to the spinal cord. The anterior spinal artery supplies the ventromedial aspect of the spinal cord that includes the corticospinal tracts and motor neurons. The two posterior spinal arteries, forming a plexus-like network on the cord surface, supply the dorsal and lateral aspects of the spinal cord, which includes the sensory tracts responsible for such sensations as proprioception and light touch [57].

The anterior spinal artery courses ventrally on the spinal cord to supply the white matter tracts and penetrates the cord parenchyma, where it divides within the gray matter. Given the discontinuity of the anterior spinal artery one of the anterior radicular branches from the aorta, the arteria radicularis magna (great radicular artery of Adamkiewicz), supplies blood to as much as the lower two-thirds of the spinal cord from its usual, but variable, origin between T9 and L5 on the left. The ventral spinal cord largely depends on collateral flow through radicular arteries given the lack of collateral blood flow between the anterior and posterior circulations (Fig. 8.8). Only six to eight of the 62 radicular vessels present during intrauterine development persist into adulthood, with less than five present in up to 45% of the general population. Generally, most individuals possess one or two cervical, two to three thoracic, and one or two lumbar radicular arteries.

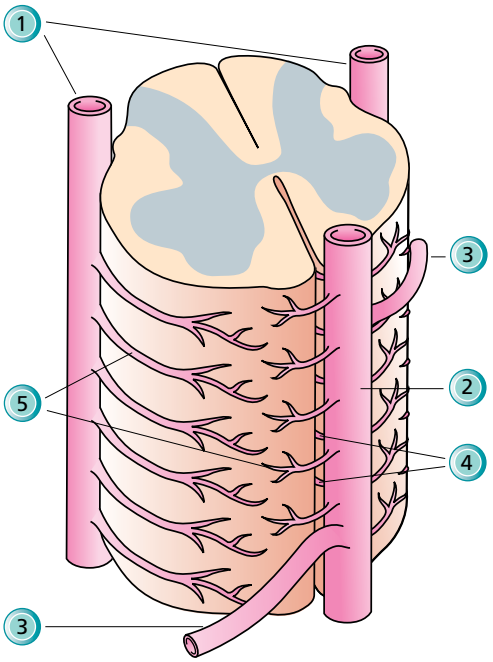


Figure 8.8 The spinal cord blood supply: (1) posterior spinal arteries; (2) anterior spinal artery; (3) anterior radicular artery; (4) sulcal branch arteries; (5) pial arterial plexus.

This leaves the spinal cord susceptible to ischemia at the upper thoracic and lumbar areas, especially during aortic or spinal surgery, or following trauma.

The venous return of the spinal cord consists of two median longitudinal veins, two anterolateral longitudinal veins, and two posterolateral longitudinal veins that drain into the vertebral venous plexus [58]. The venous drainage consists of an internal and external plexus that communicate with each other, as well as with the segmental systemic veins and the portal system. The internal plexus, consisting of thin-walled and valveless veins, connects to a vein from the spinal cord and basivertebral vein at each spinal segment, and communicates through the foramen magnum with the occipital and basilar sinuses. The internal plexus empties into the intervertebral veins that pass through the intervertebral and sacral foramina to the vertebral, intercostal, lumbar, and lateral sacral veins. Joined veins that exit from each vertebral body to form the anterior vertebral plexus form the external plexus. Veins that pass through the ligamentum flavum form the posterior vertebral plexus.

KEY POINTS: VASCULAR ANATOMY OF THE CENTRAL NERVOUS SYSTEM

- The circle of Willis provides collateral blood flow to the brain parenchyma; therefore, damage to any one vessel typically does not result in clinically significant ischemia
- The superior sagittal sinus is midline and relatively superficial, predisposing it to damage during craniosynostosis repair or craniectomy
- The arterial supply of the spinal cord arises from a single anterior spinal artery and two posterior spinal arteries, both originating from the vertebral artery

Cerebral vascular physiology

The data collected in the decades following the groundbreaking work by Kety and Schmidt led to the establishment of the normal adult cerebral blood flow values of 50–75 mL/100 g/min [59–62]. These values represent, in fact, an average of data with significant variability. The wide between-subject variability in these reports comes from the fact that cerebral blood flow itself varies and that substrate delivery is tightly matched to the cerebral metabolic rate of oxygen consumption, not from imprecise measurements. The adaptation of the technique for children age 3–10 years showed that preteen children have a cerebral blood flow nearly twice that of adults [63]. Subsequent measurements in healthy and preterm infants without respiratory distress syndrome revealed cerebral blood flow roughly one-third of adult values at birth, which also appeared to hover near the ischemic threshold of 20 mL/100 g/min in many infants [64–67]. Figure 8.9 depicts the normal developmental changes in cerebral blood flow across age.

The cerebral blood flow developmental pattern mirrors the trend of cellular growth, synaptogenesis, and myelination that occur in the first years of life. Global cerebral metabolism in infants begins at 30% below that of adults, only to increase between birth and 4 years of age to exceed adult rates by twofold [68,69] (Fig. 8.10).

Fully functional vascularity exists in the term brain, but infants born at the current limits of viability possess underdeveloped and anatomically incomplete cerebral vasculature. Neurovascular regulation as a generic principle requires complete vascularization and development of muscular arterioles capable of reactivity. As mentioned previously, a fragile periventricular vascular overgrowth accompanies the persistence of the germinal matrix in the premature infant that is prone to hemorrhage. Premature infants lack a complete system of penetrating arterial growth from the pial surface into deep white matter structures. Adult brains include a redundant arterial network in the white matter circulation whereas the premature infant brain contains a poorly anastomosed white matter circulation vulnerable to ischemic injury [70,71]. According to studies in fetal sheep, vasoreactivity to arterial pressure changes occurs at two-thirds gestation, which would correspond to the current limits of viability. However, the limits of reactivity are much closer to resting blood pressure than in the term animal [72]. Development of the muscularis layer

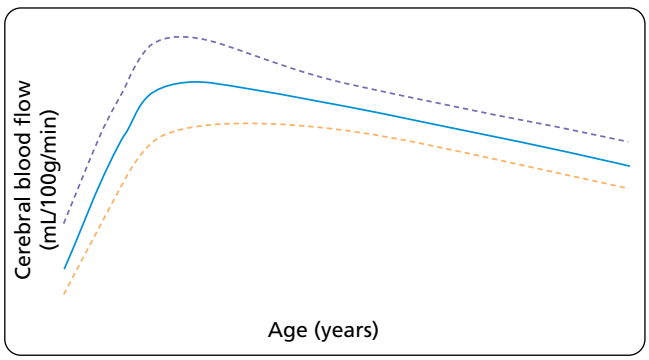


Figure 8.9 Developmental changes in cerebral blood flow. At birth, blood flow to the brain is low compared with adult levels of cerebral blood flow. During the first years of life, blood flow rates increase sharply to a peak at 4 years of age and then taper off during adolescence to adult values.

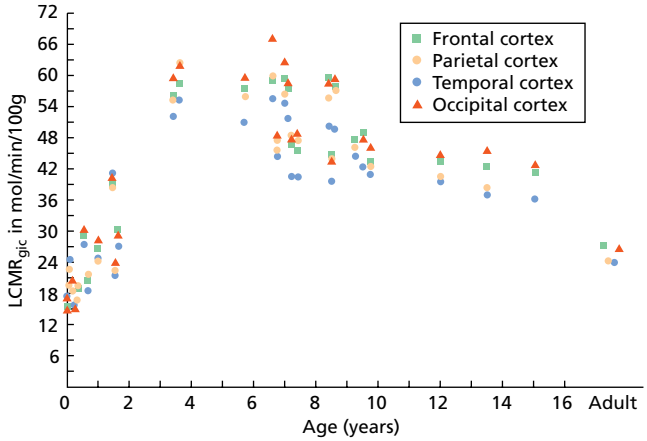


Figure 8.10 Cerebral metabolism, quantified by the local cerebral metabolic rate of glucose ($LCMR_{glc}$) utilization, is low at birth, increases in the first years of life and tapers during adolescence. This pattern recapitulates and explains the developmental pattern of cerebral blood flow changes.

involved in vasoreactivity of arteries and arterioles occurs during the third trimester, first in the larger pial vessels, and then in progressively smaller arterioles. This would predict coarse vasoreactivity in the extremely preterm infant and more fine-tuned vasoreactivity with increasing gestational age. Consistent with this, normal preterm infants appear to spend significant portions of time with pressure-passive circulation, a state seen in adults with shock or intracranial pathology [73]. The peculiarities of preterm circulation and pressure autoregulation pose a conundrum for the anesthesiologist making decisions about blood pressure management for critically ill preterm neonates. The special case of the preterm neonate is further discussed in the sections that follow.

Several layers of servomechanisms contribute to the critical homeostasis of cerebral metabolic demand and substrate delivery. These mechanisms operate at different frequencies, with distinct precision, and with varying regional specificity in the brain. This chapter presents four separate mechanisms of cerebral blood flow control. The first three are presented sequentially as increasingly precise mechanisms working in concert to fine-tune cerebral blood flow in a dynamic pressure-flow system: the systemic vasoconstrictive response, pressure autoregulation, and neurovascular coupling. Next, the cerebral vascular responses to homeostatic perturbations of arterial carbon dioxide, oxygen, and glucose concentration are discussed. The developmental considerations of these mechanisms are evaluated separately.

Systemic vasoconstrictive response

The systemic vasoconstrictive response, which renders cerebral blood flow independent of cardiac output, provides the crudest method for preserving cerebral blood flow. Decline in cardiac output results in increased sympathetic tone, activation of the renin–angiotensin–aldosterone axis, and increased vasopressin activity. All three of these axes exert a vasoconstrictive response on the systemic vasculature that is greater than on the cerebral vasculature. The net effect of the systemic vasoconstrictive response is to preserve cerebral perfusion at the expense of systemic perfusion [74–77]. For this reason,

renal failure and necrotizing enterocolitis may occur without neurological injury in normotensive shock. Thus, when systemic vasoconstrictive responses are functional, the brain takes a variable percentage of total cardiac output to maintain cerebral blood flow [78–80]. In severe low-output shock, as can occur with diarrhea, hemorrhage, or myocardial failure, this antagonistic relationship between cerebral and systemic perfusion can threaten systemic perfusion. Clinically, inadequate systemic perfusion manifests as progressive peripheral (digit loss), gut, or kidney ischemia, which can worsen after institution of pressor therapy titrated to maintain cerebral perfusion. Even during cardiopulmonary bypass, this mechanism preserves cerebral blood flow so long as perfusion pressure is adequate, and regardless of the flow rates [81].

This balance between systemic and cerebral perfusion presents a management dilemma in children with congenital heart disease. Afterload reduction is an essential therapy known to increase survival in the setting of congestive heart failure and shunted circulation post bypass. In this setting, clinicians must balance reduction of systemic vascular resistance against the need for adequate cerebral perfusion pressure (CPP). Even adult patients with heart failure, for whom more defined limits of CPP exist, suffer symptoms (syncope, presyncope) of cerebral hypoperfusion when aggressively treated with vasodilators. Pediatric patients, although less likely or able to report presyncopal symptoms, bear the same risk. Additionally, the strategy of maintaining infants undergoing cardiopulmonary bypass at a critically low CPP using vasodilator therapy improves renal and splanchnic perfusion, as well as overall survival, but decreases cerebral perfusion [82–84]. It should be noted that the impact of this strategy on the high incidence of neurological injury in children undergoing heart surgery has yet to be defined (Fig. 8.11).

The sympathetic nervous system develops early in gestation, and the parasympathetic nervous system develops and increases in tone near term [85]. This higher baseline sympathetic tone confers on the preterm vasculature a lower reserve for mounting a systemic vasoconstrictive response, compromising its ability to maintain perfusion pressure to the brain. The near maximal contractility and elevated heart rates also present at baseline limit the ability of the preterm heart to modulate cardiac output. Hence, preterm infants lack the first homeostatic cerebral blood flow mechanism, maintenance of perfusion pressure, which bestows vulnerability on the brain. The inability to maintain perfusion pressure manifests as hypotension, especially in the first hours and days of life when elimination of the low-resistance placental circulation (clamping of the umbilical arteries) increases the afterload against which the underdeveloped myocardium pumps [86].

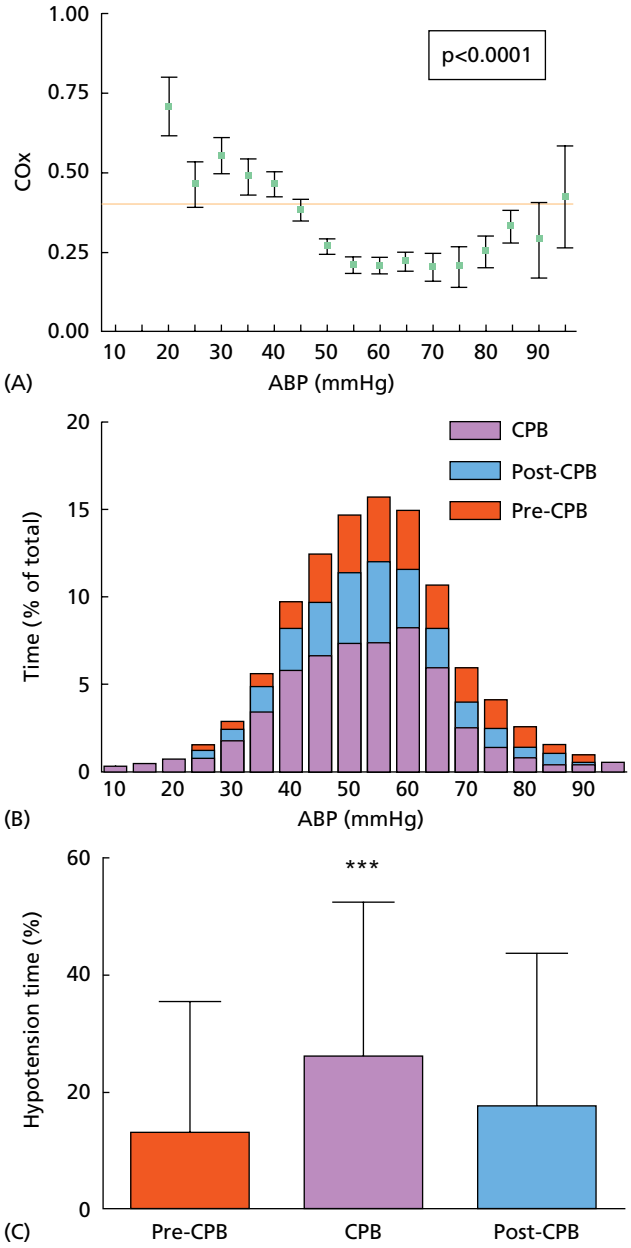


Figure 8.11 Cerebrovascular pressure autoregulation was quantified in children during cardiac surgery by correlation between arterial blood pressure (ABP) and cerebral oximetry (COx), which indicates pathological pressure passivity with increasingly positive values. (A) When normotensive, subjects showed intact pressure autoregulation that was increasingly disturbed with progressive hypotension. (B) The majority of time during the recordings was from normotensive periods with intact autoregulation. (C) Hypotensive recordings with impaired autoregulation occurred most frequently during cardiopulmonary bypass (CPB).

Pressure autoregulation

The next layer of cerebrovascular control, commonly referred to as pressure autoregulation, maintains a constant cerebral blood flow across a range of cerebral perfusion pressures. Impairment of pressure autoregulation is associated with death and poor neurological outcomes after traumatic brain injury in both adults and children [87–91]. However, newer methods for continuous monitoring of autoregulation suggest that the pressure autoregulation mechanism is robust and difficult to ablate entirely; rather, the loss of autoregulation is often due to hemodynamic management that exhausts vasodilatory mechanisms (blood pressure too low) or, less commonly, vasoconstrictive mechanisms (blood pressure too high). Deviation from "optimal blood pressure," specifically blood pressure that results in maximal pressure autoregulation, is associated with increased death and neurological disability after traumatic brain injury [92,93]. Morbidity and operative mortality in adults undergoing cardiopulmonary bypass are associated with greater magnitude and duration of time spent below the lower limit of autoregulation [94,95].

Pressure autoregulation, like the systemic vasoconstrictive response, allows the brain to steal and shunt blood flow to and from the systemic vasculature. In contrast to the systemic vasoconstrictive response, which reacts to changes both in arterial pressure and cardiac output, pressure reactivity is a response solely to changes in arterial blood pressure. Pressure autoregulation responds much faster than does the systemic vasculature, occurring within 4–10 s of a change in arterial blood pressure in one adult study, and within 2 s of a change in blood pressure in a study of neonates [96,97]. In animal models, direct measurement of the timing of the pressure autoregulation response showed that sustained blood pressure changes lasting 30–60 s fully engage the pressure autoregulation mechanism [98]. Pressure autoregulation allows for changes in cerebral blood flow at the pulse and respiratory frequencies, but acts as a high-pass filter that prevents fluctuations in cerebral blood flow that persist for longer than 30 s.

Physiological recordings of ICP, blood volume, blood flow, blood flow velocity, and oxygenation can reveal autoregulatory activity during slow changes of arterial blood pressure lasting between 20 and 300 s. In the normal autoregulating brain, blood volume and intracranial pressure are inversely related to blood pressure at these low frequencies. Dilatation and constriction of the resistance arterioles that mediate autoregulation cause this inverse relationship. The inverse relationship results in constant cerebral blood flow, flow velocity, and oxygenation during slow blood pressure changes. At blood pressures below the lower limit of autoregulation, the unresponsive cerebral vasculature dilates and constricts passively to changes in arterial blood pressure. In this setting, cerebral blood volume, ICP, cerebral blood flow, flow velocity, and oxygenation all positively correlate with slow changes in arterial blood pressure. These distinctions between intact and perturbed autoregulation form the basis of physiological monitoring of the state of autoregulation [99–102] (Fig. 8.12).

Additionally, the limits of pressure autoregulation, and its response times, vary and respond to changes in CO_2 tension. It is now understood that the lower limit of autoregulation, originally described at 50 mmHg in adults by Lassen, has a wide interpatient and contextual variability [62,103] (Fig. 8.13).

The lower limit of autoregulation in pediatric populations has yet to be defined, but infants on cardiopulmonary bypass have shown a lower limit between a mean arterial blood pressure of 30 and 40 mmHg [82,84]. Full-flow bypass is not protective against hypotension, as cerebral blood flow is reduced when arterial blood pressure is less than the lower limit of autoregulation regardless of the total systemic output (Fig. 8.14).

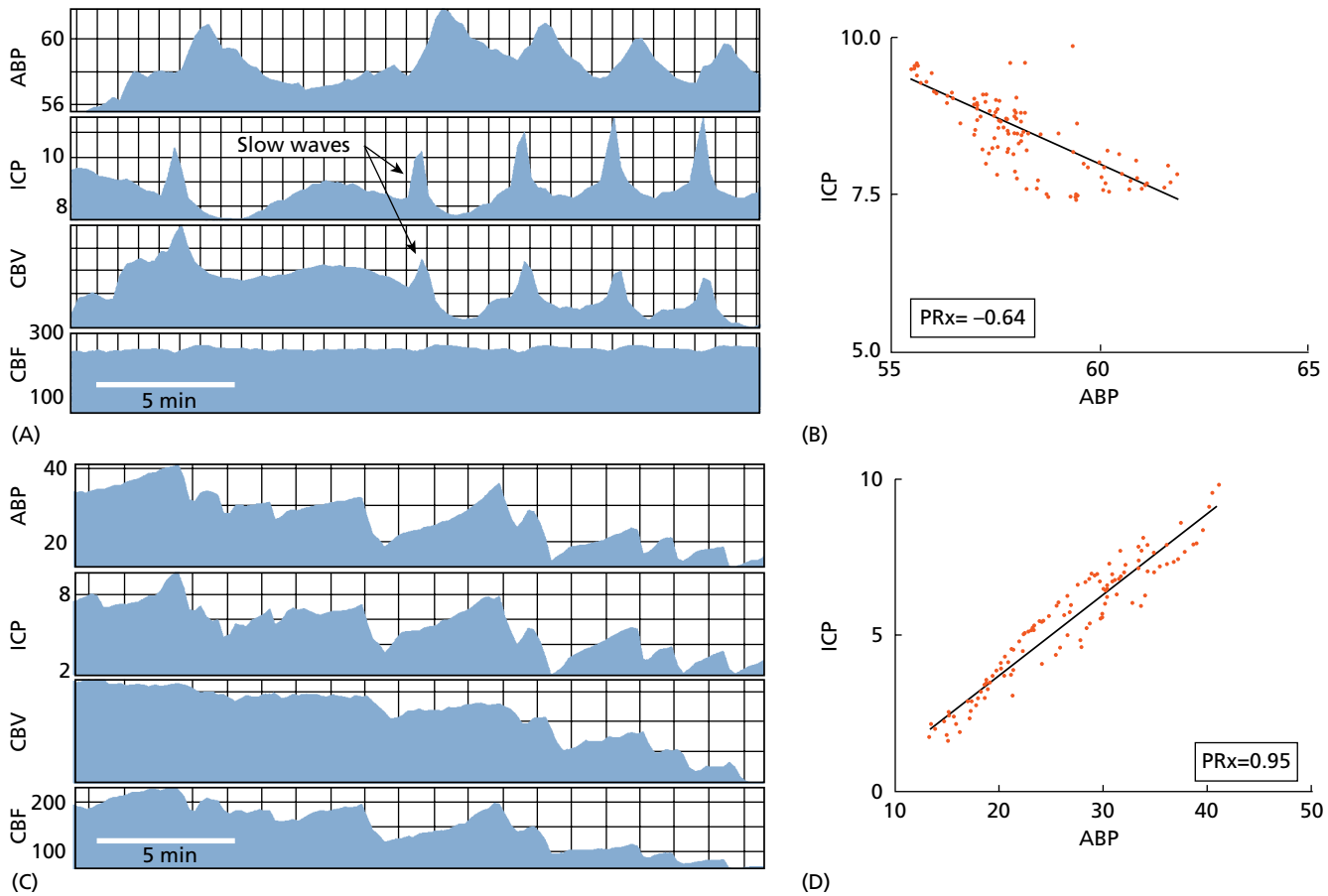


Figure 8.12 Pressure autoregulation and vascular reactivity can be quantified and monitored. Recordings from a normotensive piglet (A and B) of arterial blood pressure (ABP), intracranial pressure (ICP) cerebral blood volume (CBV) and cerebral blood flow (CBF) show intact autoregulation. Slow waves of ABP cause reactive dilatation and constriction of resistance arterioles, which is reflected in both CBV and ICP as slow waves that are inverted when compared with the ABP tracing. CBF is constant in this state of intact autoregulation. The pressure reactivity index (PRx) quantifies the inverted ICP–ABP relationship with a negative Pearson's coefficient of correlation, indicating healthy vascular reactivity. In a hypotensive piglet (C and D), ABP, ICP, and CBV are all in phase at the slow wave frequency, indicating pathological pressure passivity. CBF is fluctuant in this state of impaired autoregulation, and the PRx is positive.

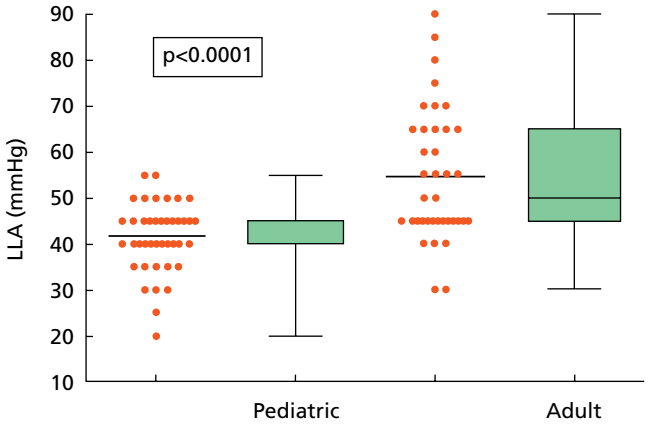


Figure 8.13 The lower limit of autoregulation (LLA) is not necessarily 50 mmHg. Individual determinations of the LLA were made for pediatric and adult populations during cardiac surgery. The blood pressure threshold associated with pressure-passive cerebral oximetry was determined for each subject in the study. Pediatric patients, in general, tolerated lower blood pressures than adult patients, and intersubject variability was high, suggesting that a single blood pressure threshold is not adequate for hemodynamic management guidelines. *Source:* Reproduced from Brady et al [84] with permission of Wolters Kluwer.

Pressure autoregulation and critical closing pressure in prematurity

Evidence of some pressure reactivity has been observed at surprisingly low pressures in preterm infants, but there is no consensus for a safe threshold of low blood pressure in the setting of prematurity [104,105]. Blood pressures in preterm infants are low during transition from fetal circulation. Causes for preterm transitional hypotension are variable but include a strained, immature myocardium adjusting to a sudden increase in afterload. The low blood pressure values seen after preterm deliveries are close to the critical closing pressure (the blood pressure at which flow to the brain is zero). Small variations in the critical closing pressure in these patients can therefore mean the difference between the presence and absence of cerebral blood flow. This precarious scenario is not seen in term infants without elevated ICP.

Rhee and colleagues studied middle cerebral artery blood flow velocity patterns, pressure autoregulation, and the critical closing pressure in a cohort of preterm neonates [106,107]. It was observed in many subjects in that study that cerebral blood flow was limited to the systolic phase of the cardiac cycle. When the diastolic blood pressure is less than

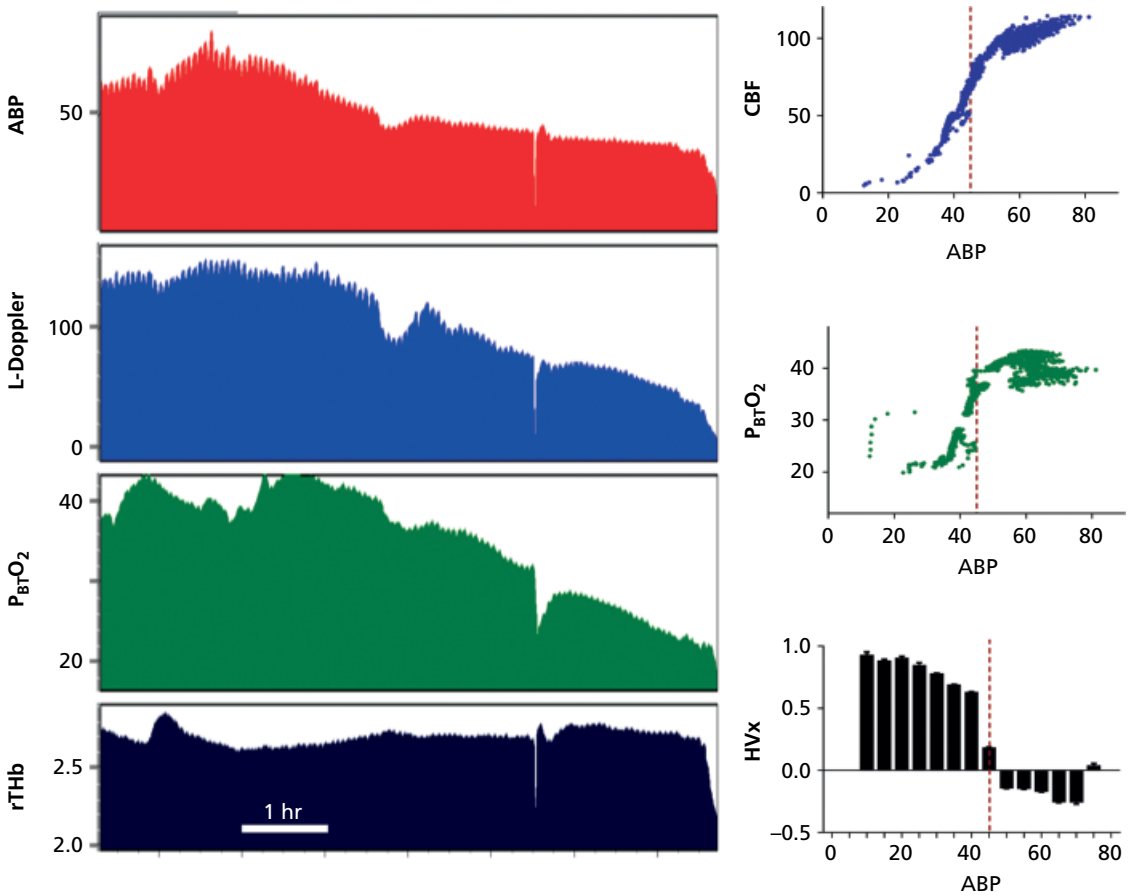


Figure 8.14 Full-flow bypass does not protect the brain from ischemia due to hypotension. A piglet on cardiopulmonary bypass at full flow (120 mL/kg/min) is made progressively hypotensive by the administration of enalaprilat. ABP, arterial blood pressure; L-Doppler, cerebral blood flow measured by invasive cortical laser Doppler flowmetry; $P_{BT}O_2$, oxygen tension in the white matter measured by Licox monitoring; rTHb, cerebral blood volume trended with near-infrared spectroscopy. Plots of cerebral blood flow (CBF), white matter oxygenation, and autoregulation (HVx, hemoglobin volume index derived from rTHb) all indicate a lower limit of autoregulation at an ABP of 45 mmHg. Despite full bypass flow rates, when ABP was below 45 mmHg in this animal, cerebral blood flow was decreased, white matter oxygen tension was reduced, and autoregulation was disturbed (positive HVx indicates a pressure-passive state).

the critical closing pressure, flow is absent during diastole, and cerebral blood flow becomes heart rate-dependent, a state which renders pressure autoregulation less relevant (Fig. 8.15).

To deal with the issue of the closing pressure in their cohort, Rhee and colleagues measured and analyzed systolic and diastolic values of cerebral blood flow and arterial blood pressure separately. They found that diastolic cerebral blood flow was either zero or passive to arterial blood pressure in nearly all subjects. However, in some subjects, systolic cerebral blood flow was constrained across arterial blood pressure changes even when diastolic blood flow was passive (Fig. 8.16). Thus, when they used systolic flow velocities to quantify pressure autoregulation in the preterm neonate, they found minimal evidence for pressure reactivity at 23–26 weeks of gestation, but progressively increasing reactivity across the second half of the third trimester [106–108].

Critical closing pressure is the sum of intracranial pressure (external vascular compression force) and vascular wall tension (intrinsic vascular compression force). As, by definition, the critical closing pressure is the pressure at which cerebral blood flow is zero, it follows that the closing pressure can be used to normalize arterial blood pressure to quantify cerebral perfusion pressure (cerebral perfusion pressure = arterial blood pressure – critical closing pressure) [109–111]. In the Rhee cohort of preterm infants, cerebral perfusion pressure was estimated in this way as the diastolic closing margin (diastolic ABP – critical closing pressure). Increases in diastolic closing margins were associated with intraventricular hemorrhages, when the uncorrected arterial blood pressure was not. This finding underscores the need for a normalization factor that accounts for variance in the critical closing pressure of preterm infants [112].

Until a clinically viable method is available to monitor the critical closing pressure and the state of autoregulation, absolute safe arterial blood pressure recommendations cannot be made. Furthermore, such recommendations might prove inapplicable to critically ill populations, as factors related to critical illness may impair autoregulatory function and shift the limits of intact pressure autoregulation. For instance, newborn piglets without intracranial pathology possess an average lower limit of autoregulation at a cerebral perfusion pressure of 30 mmHg, and piglets with hydrocephalus demonstrate an average lower limit of autoregulation at 50 mmHg [113]. Even monitoring ICP would fail to account for the shift in autoregulation function seen in that study. In the absence of information about the state of autoregulation, practitioners should still apply the crude concepts of blood pressure and cerebral perfusion pressure to the protection of the pediatric brain.

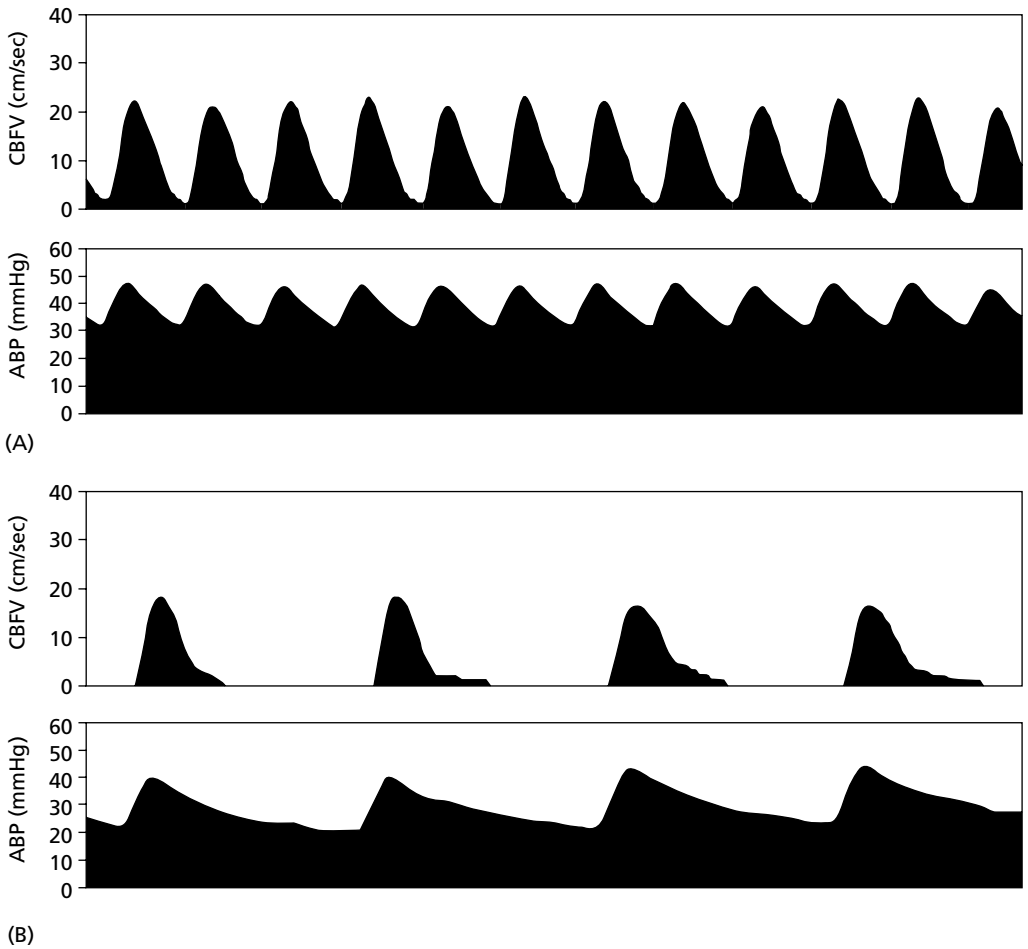


Figure 8.15 Middle cerebral artery flow velocity (CBFV) and arterial blood pressure (ABP) monitored in a preterm infant at baseline (A) and during bradycardia (B). Diastolic ABP in this infant is at or near the critical closing pressure, as evidenced by cerebral blood flow that is restricted to systolic events. Bradycardia dramatically reduces the overall cerebral blood flow in this state.

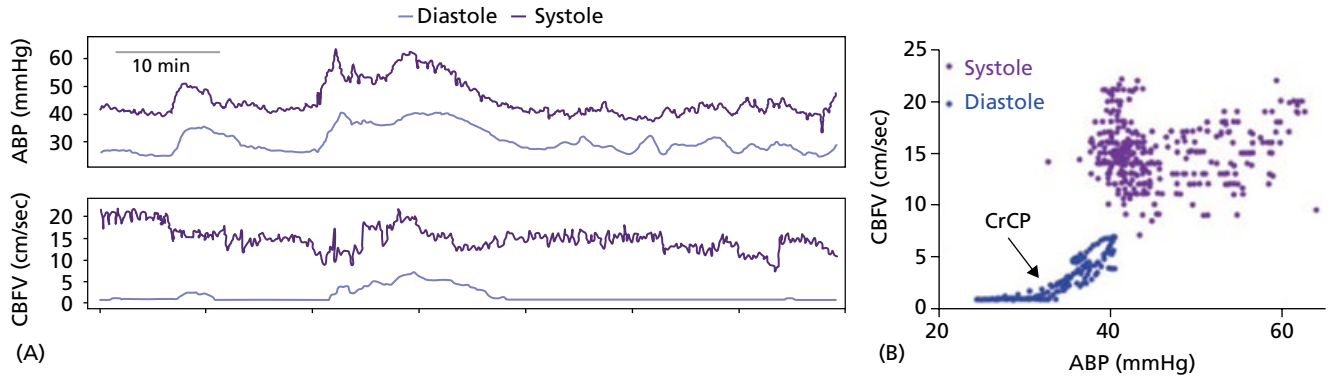


Figure 8.16 Arterial blood pressure (ABP) and middle cerebral artery flow velocity (CBFV) monitored in a preterm infant on the first day of life. (A) Time trends of systole and diastole are shown in purple and blue respectively for both ABP and CBFV. (B) When CBFV is plotted as a function of ABP, paired systolic values (purple) demonstrate autoregulation: a non-correlated relationship between CBFV and ABP. However, paired diastolic values (blue) from the same time interval show that diastolic cerebral blood flow is either zero or pressure-passive in this newborn. The diastolic ABP at which cerebral blood flow first occurs is demarcated with an arrow, and is the critical closing pressure (CrCP) for this infant.

Neurovascular coupling

In 1890, 54 years before the Kety–Schmidt technique was first applied to measure cerebral blood flow, Roy and Sherrington observed a relationship between neuronal activity and cerebral blood flow.

> We conclude then, that the chemical products of cerebral metabolism contained in the lymph which bathes the walls of the arterioles of the brain can cause variations of the caliber of the cerebral vessels: that in this re-action the brain possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity. Roy and Sherrington, 1890 [114].

Roy and Sherrington directly measured regional brain volume change in response to electrical stimulation of exposed sensory nerves in dogs to show activity–flow coupling in the brain. Since then, the advent of sensitive regional blood flow measurement techniques has renewed focus on investigating neurovascular interactions. Recently, Koehler et al explained activity-dependent flow using the emergent model of a neurovascular unit composed of an astrocyte that bridges a collection of synapses and penetrating arterioles [115]. From these studies it was learnt that neurovascular coupling affects flow only in the immediate region of neuronal activation (spatial specific), and initiates quickly, effecting vascular diameter change within 1 s of neuronal activation. Neurovascular coupling also produces a finer control of cerebral blood flow when compared to the relatively slow and global pressure autoregulation mechanism. Metabolic regulation of cerebral blood flow can cause large changes in cerebral blood volume, as seen with the induction of barbiturate coma for treatment of elevated ICP. With increasing doses of barbiturate, cerebral oxygen consumption and cerebral blood flow fall concomitantly. At doses sufficient to produce EEG silence, barbiturates reduce cerebral blood flow and volume to half-awake values, and higher doses fail to reduce cerebral blood flow further (Fig. 8.17) [116].

Propofol administration produces similar effects to burst suppression [117]. This technique aids in reducing the brain volume to improve the surgical field and to decrease ICP in patients with acute intracranial mass effect. When temperature is reduced to suppress brain metabolism, the plateau at EEG silence is not observed. Reductions in temperature

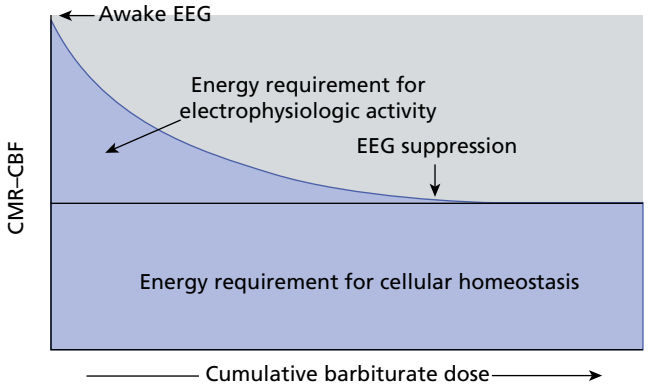


Figure 8.17 More than half of cerebral metabolism (CMR) is utilized for the maintenance of voltage gradients discharged during neuronal activity. EEG silence, induced with barbiturate administration, ablates this metabolic activity and results in a concomitant reduction of cerebral blood flow (CBF) as flow–metabolism coupling is maintained.

continue to reduce both cerebral blood flow and volume because of slowing of cellular metabolism not related to the discharge and maintenance of membrane voltage potentials. The moderately hypothermic brain maintains a cerebral blood flow that is half that of the normothermic brain, and deep hypothermia yields a cerebral blood flow that would be below the critical threshold for ischemia in a normothermic brain [118–120].

Both hypothermia and electrical suppression therapies maintain and utilize the coupling of metabolism and cerebral blood flow. Hypocarbia-induced cerebral blood flow decrements, however, reduce cerebral blood flow to below metabolic demand. This uncoupling of metabolism and cerebral blood flow creates an ischemic vulnerability, which may explain why patients with head trauma have worse outcomes when prophylactic hypocarbia is applied [121].

Flow response to homeostatic derangements

Non-physiological chemical derangements override the three flow and pressure control mechanisms of cerebral blood flow outlined previously. Well-characterized examples include

disturbances of arterial carbon dioxide, oxygen, and glucose. Logically, the brain would be expected to have fail-safe vascular compensations during states of inadequate substrate delivery, even in the context of otherwise adequate perfusion pressure.

Cerebrovascular response to carbon dioxide

Acute decreases in arterial carbon dioxide tension cause vasoconstriction of the cerebral vasculature, and acute increases in arterial carbon dioxide tension cause cerebral vasodilation. The carbon dioxide response of the cerebral vasculature largely occurs across the physiological range of carbon dioxide and correlates with changes in CSF pH. Low pH in the CSF adversely affects neuronal function. Although the blood–brain barrier is impermeable to hydrogen ions, carbon dioxide diffuses freely into the CSF to modulate its pH.

Two mechanisms working in concert control CSF pH. First, robust metabolic buffering occurs through rapid CSF turnover by ependymal cells of the choroid plexus that have a high carbonic anhydrase activity. Second, the coupling of cerebral blood flow to arterial carbon dioxide tension modulates the removal of carbon dioxide from the CSF. CSF buffering partially explains the time course of cerebral blood flow responses to changes in carbon dioxide. The vasoreactive response to a change in arterial carbon dioxide begins within seconds and reaches steady state within 10 min. A gradual return toward baseline cerebrovascular resistance follows over the next 3–6 h, consistent with the time course of pH regulation [122,123]. Persistent hypercapnia results in late hyperemia that is not explained by this model and that does not return to normal after normalization of serum carbon dioxide.

Pediatric anesthesiologists commonly use carbon dioxide as a drug to effect changes in cerebral blood flow. Decreasing cerebral blood volume using hyperventilation facilitates craniotomy in the presence of elevated ICP. But, as previously mentioned, using hyperventilation to manage intracranial volume also reduces cerebral blood flow and disrupts normal metabolic coupling to cerebral blood flow. Ischemic injury occurs in pediatric patients with traumatic brain injury when prophylactic hyperventilation is used to manage ICP. This led the Brain Trauma Foundation to declare prophylactic hyperventilation contraindicated except when used transiently during surgery or to prevent impending herniation.

Conversely, hypercarbia mitigates pulmonary overcirculation and enhances cerebral oxygen delivery in single-ventricle patients with a large left-to-right shunt. In this setting, serum hypercarbia and acidosis increase pulmonary vascular resistance, while hypercarbia and acidosis in the CSF cause decreased cerebral vascular resistance. When arterial carbon dioxide modulation is used as a therapy to change cerebral blood flow, the effect is mediated by changes in CSF pH. Because of rapid CSF turnover and a high range of responsiveness of carbonic anhydrase during CSF production, the magnitude of a pH change in the CSF is blunted after 3–6 h. Because the blood–brain barrier separates serum and CSF buffers, the brain pH returns to normal even if the serum pH remains abnormal. Thus, buffering of the CSF limits the duration of effectiveness of carbon dioxide-modulating therapies. Further, normalizing the serum pH of a patient after prolonged respiratory acidosis or alkalosis may cause injury. For instance, the presence of a low serum pH and a high serum carbon dioxide tension at the initiation of rescue cardiopulmonary bypass is associated with stroke and hemorrhage [124–126].

Cerebrovascular response to oxygen delivery

Arterial oxygen tensions between 60 and 300 mmHg do not appreciably change cerebrovascular tone. When arterial hypoxia or anemia impairs oxygen delivery, however, cerebral vascular resistance decreases and cerebral blood flow increases [127–129]. The response of the cerebral vasculature to extremes of arterial oxygen tension contrasts with the carbon dioxide response, which largely occurs within the normal physiological range of arterial carbon dioxide tension. Essentially, only when oxygen delivery hits a critical threshold does global hypoxic vasodilatation disrupt autoregulatory mechanisms.

Cerebrovascular response to glucose delivery

Despite having a metabolism 7.5 times that of the average tissue, the adult brain maintains only about 2 min worth of glycogen stores within neurons. The lack of a local glucose buffer means that the brain depends on a constant capillary supply. While most cells require insulin for glucose transport from the serum to the intracellular space, glucose diffuses readily into neurons, even in the absence of insulin. Glucose deprivation in the adult brain leads to vasodilation only after unconsciousness and EEG changes have occurred. In contrast, in the newborn brain the vasodilatory response possesses a higher threshold, with vasodilatory changes occurring at serum glucose levels of 30 mg/dL, without loss of consciousness or EEG changes [130–132].

Critical closing pressure

Traditionally, oxygen delivery to the brain is described as a function of cerebral perfusion pressure (CPP): the difference between arterial blood pressure (ABP) and intracranial pressure (ICP) (or jugular venous pressure (JVP) if JVP is higher than ICP). The CPP concept has oversimplifications that are evidenced by clinical scenarios such as vasospasm, in which the ABP, ICP, and JVP are apparently normal but cerebral blood flow (CBF) is reduced to the point of neurological deficit. An alternative view of perfusion pressure incorporates measurement of the critical closing pressure (CrCP) to understand impedance to CBF at the frequency of the cardiac cycle [111]. CrCP is the instantaneous sum of a theoretical collective vascular wall tension and ICP. When ABP is equal to CrCP, vascular patency fails and CBF ceases. Thus, only ABP greater than CrCP contributes to cerebral perfusion pressure (also referred to as the "closing margin"). In a progressively hypotensive child, the cessation of flow initially occurs only during diastole when diastolic blood pressure decreases below CrCP, represented as the diastolic closing margin [109]. Subsequently, further decrements of systolic blood pressure to below CrCP halt flow of blood to the brain altogether.

Measurement of CrCP has been proposed to better define optimal blood pressure goals for preterm infants. The lack of consensus on proper blood pressure goals for premature infants is due to conflicting pressure-associated outcome data in this population. Recently, Rhee and colleagues demonstrated that the ABP of preterm and low-birthweight infants is

close to CrCP, and sometimes below CrCP. They showed that intersubject variability in CrCP was as great as the variability in ABP, explaining why raw ABP is not a meaningful surrogate of CPP for preterm infants, even when ICP is low [106]. CrCP increases along with gestational age in premature infants through the third trimester, and increases with age after birth, tracking trends in ABP [106]. The same group subsequently found that a higher perfusion pressure (ABP normalized to the CrCP) was associated with intraventricular hemorrhage in preterm infants [112]. Currently, the only method available to monitor CrCP is estimation of the time constant between invasive ABP changes and middle cerebral artery flow velocity changes at the frequency of the cardiac cycle [111]. Although clinically impractical, this development may lead to a more effective management strategy for the preterm population as the technology advances.

KEY POINTS: CEREBRAL VASCULAR PHYSIOLOGY

- Cerebral blood flow in the infant is low compared with adult levels, increases dramatically until 4 years, then tapers during adolescence to adult values
- Pressure autoregulation develops during the third trimester, but from 23–26 weeks' gestation blood flow is pressure passive, and in many patients is limited to the systolic phase of the cardiac cycle
- Cerebral blood flow is acutely responsive to arterial CO_2 levels across the physiological range; excessive hyperventilation can lead to cerebral ischemia
- Cerebral vasodilation occurs only at critical levels of hypoxemia below 50–69 mmHg, and glucose below 30 mg/dL in the neonate

Electroencephalogram

When appropriately applied, electroencephalogram (EEG) monitoring provides a continuous recording of electrical activity between reference electrodes placed at specific positions on the scalp. Perioperatively, EEG may identify abnormalities and potential periods of cerebral injury or malfunction. The electrical activity is believed to originate from the postsynaptic potentials of the dendrites of cortical neurons, and EEG waveforms are classified according to frequency: delta (1–3/s), theta (4–7/s), alpha (8–12/s), and beta (13–20/s) (Fig. 8.18). Many factors such as age, state of awareness/alertness, tasks (e.g. eye opening), medications, and various disease states alter these waveforms. Sleep, in particular, can manifest unique alterations such as sharp waves (K complexes) and sleep spindles (regular 12–14/s) confined to the central electrodes. Various combinations and locations of spike and slow wave activity characterize seizure or epileptiform activity and may interfere with processed EEG validity. Therefore, adequate interpretation of continuous EEG tests requires good lead contact and continuous analysis by a trained technician/clinician. Brain maturation and environmental factors such as anesthetic agents, pain, cerebral metabolism, and temperature also affect EEG signals.

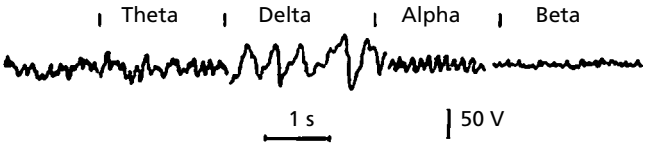


Figure 8.18 The electroencephalographic (EEG) waveforms are classically divided according to frequency as delta (1–3/s), theta (4–7/s), alpha (8–12/s), and beta (13–20/s). Notice that delta waves are also characterized by a higher amplitude (>75 μV), while beta waves have a very low amplitude (<10 μV). These waves are interpreted based on the clinical state of the patient (i.e. level of arousal or seizure activity). The propensity and distribution of these various waveforms change throughout life and during different mental activities. For example, adult subjects monitored with EEG who are sleeping have increased delta wave activity whereas those who are awake and thinking have more alpha and beta wave activity.

When used appropriately, EEG may confer diagnostic and management benefit. For instance, trained clinicians have used EEG during cardiopulmonary bypass to titrate cooling strategies, detect intraoperative events, and monitor for postoperative seizures. Both comprehensive (raw EEG waveforms from multiple leads) and processed (computer algorithm-driven simplified EEG display) EEG have been used in these studies [133]. Most patients demonstrate isoelectricity on the EEG during cardiopulmonary bypass [134]. With deep hypothermic circulatory arrest, waiting to achieve an isoelectric EEG during cooling before initiating circulatory arrest may confer neuroprotection [135]. Significant interpatient variability exists with regard to the degree of hypothermia required to induce electrocerebral silence. Temperatures at which electrocerebral silence on EEG occurs are lower than those when evoked potentials disappear, making EEG a more reliable method of neuromonitoring during cooling [136].

EEG activity resumes upon cerebral reperfusion and rewarming. The temperature at which continuous EEG activity returns predicts postoperative neurological dysfunction, as this appears to be related to intraoperative brain injury. In adult studies, the risk of postoperative confusion or stroke significantly increases with every degree higher at which continuous EEG activity resumes [137].

In addition, perioperative EEG monitoring detects seizures that clinically would be missed due to pharmacological neuromuscular blockade and sedation, including subclinical seizure activity [138]. Seizures may occur secondary to cerebral injury and worsen pre-existing or ongoing neuronal damage. Clancy et al performed EEG monitoring on 183 infants after cardiac surgery and identified that 11% of the patients had EEG-detected seizure activity postoperatively, though there were no clinically apparent seizures. Most recently, postoperative, diffuse EEG slowing has been reported in children during the first 48 h following cardiac surgery. However, EEG slowing was not associated with neurological deficits or MRI changes [139] (Fig. 8.19). Preoperative EEG monitoring has also been used in premature infants to detect seizure and ischemic events.

Despite the demonstrated potential for clinical benefit, the logistical and technical limitations, as well as the need for expert interpreters, limit the use of comprehensive and continuous EEG monitoring in the intensive care unit and operating room.

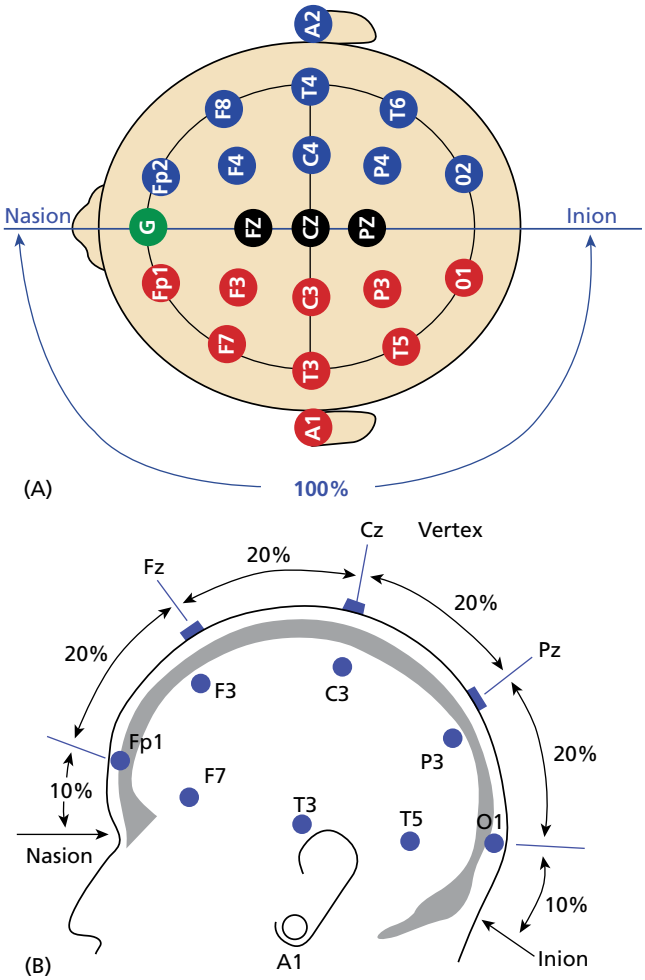


Figure 8.19 The standardized placement of scalp electrodes for a classical EEG recording has become common since the adoption of the 10/20 international system. (A) In the sagittal view, the "10/20" orientation of the electrodes can be related to the relative percentages of distance between the nasion-inion and other fixed points. These points are marked as the frontal pole (Fp), central (C), parietal (P), occipital (O), and temporal (T). The midline electrodes are marked with a z, which stands for zero. (B) In the coronal view, odd numbers are used to indicate positions over the left hemisphere, and even numbers over the right.

Processed EEG monitoring

Maynard and Prior pioneered the use of processed EEG monitoring in clinical anesthesia practice. Multiple studies described the use of comprehensive and processed EEG signals to help in the identification and management of patients at risk for adverse perioperative events. Prior and Maynard divided the clinical applications of such neurophysiological monitoring into three categories: (1) where it had been shown conclusively to reduce the risk of iatrogenic harm to an at-risk patient during elective procedures; (2) where it had provided additional useful information not obtainable by other means; and (3) where it could have been of potential value but its advantages in terms of reduced morbidity or mortality remained unproven [140,141]. Eliminating the need for a technologist/neurologist by using a processed EEG monitor is appealing to many perioperative clinicians. A review by Davidson provided an excellent review of this monitoring principle in children [142]. For the purposes of this text, we will focus on the available techniques/technologies in current clinical practice.

Amplitude-integrated EEG (aEEG) uses the P3–P4 positions and ground Fz to monitor the vulnerable watershed region in neonates. An amplified signal passes through an asymmetrical band-pass filter that strongly attenuates activity below 2 Hz and above 15 Hz in order to minimize artifacts from sources such as sweating, muscle activity, and electrical interference. Additional processing includes semi-logarithmic amplitude compression, rectification, and time compression. aEEG recordings with a cerebral function monitor, such as the "BraiNZ" monitor, obtained continuously from two biparietal electrodes, have also been shown to be useful in the early prediction of the severity of brain injury. Of 35 infants with a moderately abnormal or suppressed tracing and/or seizures, 27 died or survived with neurological abnormalities on follow-up at 18–24 months. Of 21 babies with normal amplitude, 19 were normal on follow-up [143]. Training bedside clinicians to recognize and interpret the background amplitudes of aEEG and to correlate the pattern with the clinical status of the patient poses a challenge [140]. With regard to anesthesia in particular, McKeever et al demonstrated poor prediction probability with aEEG in children younger than 2 years old [144].

Continuous comprehensive EEG can be technically difficult to use and interpret in the operating room. However, limited-channel EEG-based technologies with automated interpretation are easy to use and demonstrate correlation between electrical brainwave activity and depth of anesthesia or awareness in adults. The commercially available Bispectral Index (BIS) (ASPECT technologies, USA) and SEDline monitors (Masimo, USA) use algorithm-based analysis of multiple EEG characteristics and integrate these into a single dimensionless number. Unlike routine EEG, these monitors require placement of a single sensor containing multiple electrodes on the forehead and temple in an easily identified and reproducible location. The BIS utilizes a unilateral sensor array, while the SEDline uses a bilateral sensor. Glass et al demonstrated that BIS recorded using several different electrode arrangements (or montages) provided similar results across arrangements [145]. They used a frontal (Fp1 and Fp2) to CZ electrode montage, as well as an alternative placement (FPz–At) that approximates the BIS sensor electrode positions.

The SEDline uses a bilateral four-channel frontal array (FP1, FP2, F7, F8) to generate the Patient Safety Index or PSI. Although the US Food and Drug Administration (FDA) approved these monitors for assessment of anesthetic depth, authors have reported additional applications (i.e. burst suppression, sedation monitoring) [142,146,147]. The PSI and BIS indices both range from 0 (isoelectric EEG or electrocerebral silence) to 100 (awake), though studies have demonstrated differences in the actual interpretation of these scales in relation to depth of anesthesia. For instance, multiple studies correlate increased BIS values (>80) with awareness and decreased BIS values with increased depth of anesthesia, as well as hypothermia during bypass [148]. Similar studies demonstrate that PSI values from 25 to 50 provide protection from awareness and avoid issues of delayed emergence (seen with PSI <25) [149,150]. Limited studies evaluate the SEDline in children. However, several studies demonstrated good correlation of BIS values, when used to predict depth of anesthesia between the children younger than 2 years of age in these studies and previous adult studies, despite the BIS

algorithm being based on adult subjects [151]. Recent evidence suggests that BIS does have a better prediction probability in older children when compared to infants [152].

Other processed EEG monitors with similar functionality but differing lead array placement and signal analysis are available. The wireless and handheld Cerebral State Monitor (Danmeter A/S, Odense, Denmark) uses a proprietary algorithm and a 0–100 scale, with 40–60 indicating an adequate depth of hypnosis. The Cerebral State Index (CSI) derives from the time and frequency domain analysis that inputs into a fuzzy logic inference system to produce the index. A comparative study of the BIS and the CSI found a predictive probability statistic for depth of anesthesia of 0.87 for both monitors, which demonstrates good performance. The CSI performed better for deeper levels of anesthesia than the BIS, which performed better at lighter levels [152].

The Narcotrend monitor (MonitorTechnik, Bad Bramstedt, Germany) also processes raw EEG signals and uses either one-channel or two-channel recordings from different electrode positions. Early models graded the depth of hypnosis into six stages from A (awake) to F (very deep level of anesthesia). The latest Narcotrend software (version 4.0) calculates the Narcotrend Index, another dimensionless 0–100 scale similar to those calculated by the monitors described previously. The Narcotrend Index performed slightly better for depth of sedation when compared to the BIS (predictive probability statistic 0.88 versus 0.85) [153].

Additional approaches to brain monitoring in the intensive care unit and operating room include response entropy and state entropy [154]. The irregularity of the EEG signal can be quantified, using a publicly available algorithm, to reflect depth of sedation. This Entropy Monitor (GE Healthcare, Fairfield, CT, USA) utilizes the electromyographic (EMG) signal, which may provide information useful for assessing whether a patient is responding to an external stimulus, such as a painful stimulus. The combination of EEG and EMG is presented as the response entropy; the lower-frequency EEG signals alone are presented as the state entropy. The prediction probability values of the entropy indices for differentiating between consciousness and unconsciousness compare well with those for BIS [155]. Noxious stimulation does increase the difference between response entropy and state entropy, but an increase in the difference does not always indicate inadequate analgesia [156]. Additionally, Sciusco and colleagues recently demonstrated that for both response and state entropy, prediction probabilities increase with age, with indicators performing worse in infants and better in older children [152].

Evoked potential monitoring

A variety of evoked potential (EP) monitoring methods assess the integrity of both ascending and descending neural pathways. The stimulation of the CNS using a specific stimulus of the visual, auditory, sensory, or motor system produces an electrical response termed the EP. Perioperative evoked potential assessment tools and their application are summarized in Table 8.3.

Germaine to this chapter, the complex and sometimes dynamic interaction between patient-related factors and clinical management necessitates an understanding of the basic neurophysiology of these tests. As with the EEG, state of arousal, presence of various anesthetic agents, metabolic derangements, and temperature can dramatically impact these monitoring modalities. For ascending (dorsal/posterior) pathway monitoring, supracortical monitors detect changes in cortical electrical activity initiated by a peripherally applied stimulus. This allows for assessment of amplitude, latency, and decay. The experience of the team and the availability of resources necessary to perform continuous evoked potential monitoring limit its consistent utilization. Certainly, in spinal surgery, somatosensory evoked potentials (SSEPs) have become a widely accepted practice standard.

Table 8.3 Perioperative electrophysiological monitoring [157–167]

Monitor	Procedures	Current practice
EEG	AVM repair/clipping	Used in most centers
	Cardiopulmonary bypass	Used in some centers
	Level of consciousness	Used in some centers
BAEP	Acoustic neuroma	Monitoring recommended
	CN V decompression	Used in some centers
	CN VII decompression	Used in some centers
	Level of consciousness	Used in some centers
SSEP	Spine surgery	Monitoring recommended
	Aortic surgery	Used in some centers
MEP	Spine surgery	Used in most centers
	Aortic surgery	Used in some centers
VEP	ICU care of TBI	Used in some centers
	Optic surgery	Research

AVM, arteriovenous malformation; BAEP, *brainstem auditory evoked potential*; CN, cranial nerve; EEG, electroencephalography; ICU, intensive care unit; MEP, motor evoked potential; SSEP, somatosensory evoked potential; TBI, traumatic brain injury; VEP, visual evoked potential.

The assessment of the descending (anterior) pathways with motor evoked potentials (MEPs) involves the quantification of the peripheral motor response to stimulation of the cerebral cortex. The monitoring of intraoperative MEPs is an important practice in pediatric anesthesiology; however, as with other EP monitoring modalities, operative or anesthetic factors, as well as the neurodevelopmental status of the patient, can alter signals. A retrospective study of children age 2–12 undergoing surgery for idiopathic scoliosis revealed a strong correlation between MEP thresholds and age [161]. Although the exact mechanisms responsible for this finding remain debatable, these findings agree with the earlier observations of Parano and colleagues [168]. They hypothesized that delayed neuronal maturational changes with age led to significantly diminished delayed conduction and decreased EP amplitudes in the youngest children. Specifically, multifactorial issues of ongoing synaptogenesis, incomplete nerve integration, and decreased myelination represent this delayed neuronal maturation. This dynamic difference makes empirical numbers less useful, and often forces clinicians to use each patient as their own baseline. In addition, the impact of various anesthetic agents on these monitoring modalities varies greatly, and changes with both the age of the patient and agents used. Because of these issues, many centers favor intravenous anesthetic techniques to minimize or eliminate the use of inhalational agents [161,162]. MEPs can be monitored in conjunction with SSEPs to provide dual assessment of anterior and posterior spinal cord integrity. See Chapter 29 for further discussion of spinal cord monitoring.

KEY POINTS: ELECTROENCEPHALOGRAM AND EVOKED POTENTIAL MONITORING

- Perioperative EEG monitoring can detect an isoelectric state that may confer neuroprotection during deep hypothermic circulatory arrest, and clinically silent seizures that may be amenable to treatment
- Processed EEG monitoring algorithms are based on mature adult EEG patterns and have limited utility in infants and young children
- Somatosensory and motor evoked potentials have gained increasing use for spinal and aortic surgery and can prevent ischemic insults and permanent neurological damage

Conclusion

For the safe and effective perioperative care of infants and children at risk for neurological injury, pediatric anesthesiologists must command a working knowledge of the unique neurodevelopmental events and neurophysiological principles relevant to the pediatric patient. Our specialty continues to add to the growing body of knowledge that will reduce the toxicity of critical illness to the developing human brain. We can expect further refinement of anesthetic practices designed to protect normal neurodevelopmental processes. Neuromonitoring modalities will continue to adapt and provide an increasingly complex, real-time data set to the anesthesiologist caring for critically ill children. When combining this information with neurodevelopmental principles, the physics of the intracranial compartment, and neurovascular physiology, we improve the clinical decision making to yield improved outcomes for our patients.

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A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 9

Developmental Physiology of the Liver, Gastrointestinal Tract, and Renal System

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The liver

The embryological development of the liver, its subsequent transition at birth, and maturation in infancy constitute a hugely complicated subject. Hypoglycemia, jaundice, and impaired drug metabolism are common in the first weeks of life. Knowledge of the principles of hepatic development allows the anesthesiologist to understand the susceptibility of the liver to disease in infancy.

Embryology of the liver

The liver and gastrointestinal tracts arise from modifications of the primitive gut (see section "Basic gastrointestinal tract embryology") [1,2]. The liver develops from a thickening of the endoderm on the ventral surface of the foregut. These endodermal cells proliferate to form the hepatic diverticulum, which gives rise to cords of hepatoblasts within the mesenchyme of the transverse septum. The hepatoblasts are undifferentiated cells which can become hepatocytes, bile canaliculi, or hepatic ducts under the influence of Notch signaling; abnormalities of this process are associated with Alagille syndrome, described towards the end of this section. The hepatocytes divide rapidly and arrange themselves around vitelline veins to form hepatic sinusoids.

The transverse septum is an important area and develops at a junctional site in the embryo – internally between foregut and midgut, and externally where the endoderm of the yolk sac meets the ectoderm of the amnion. The mesenchyme of the transverse septum also gives rise to the stromal cells which provide the serous and fibrous tissues of the liver, such as the liver capsule and the falciform ligament. The various connective tissues and smooth muscle of the biliary tracts also form from this mesenchymal tissue.

The gallbladder and cystic duct originate from a thickened portion of the ventral duodenum just below the hepatic diverticulum at around 4 weeks; this is known as the cystic diverticulum. As the connection between the hepatic diverticulum and foregut (duodenum) narrows, the hepatic ducts form. The cystic duct and hepatic ducts form the common bile duct which enters the duodenum, initially anteriorly, later from the left (see section "Basic gastrointestinal tract embryology"). The growth of the liver and biliary tracts is rapid and by the 9th week the liver accounts for about 10% of the weight of the fetus (Fig. 9.1).

Fetal hematopoiesis

Hematopoietic stem cells capable of producing erythrocytes, megakaryocytes, and macrophages migrate from the yolk sac to the liver, where hematopoiesis begins [3]. There is a second influx of hematopoietic stem cells originating from mesoderm surrounding the dorsal aorta. These cells are later programmed to migrate to the bone marrow and other lymphatic tissue. The immature fetal erythrocytes are bigger than mature red cells and, like white cells and platelets, they increase in number throughout gestation.

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

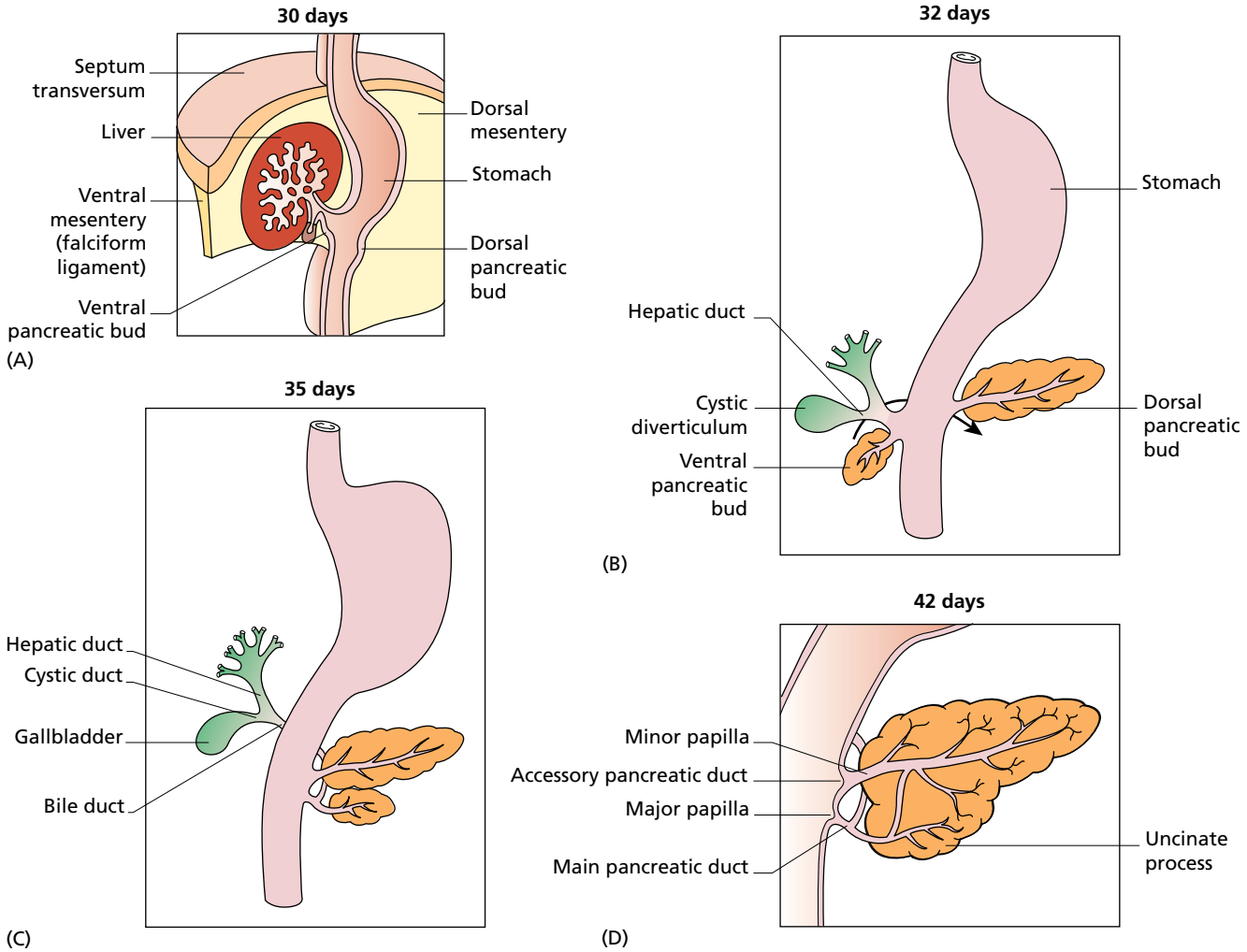

Figure 9.1 Development of the liver, gallbladder, and pancreas and their duct systems from endodermal diverticula of the duodenum. (A) The liver bud sprouts during the 4th week and expands in the ventral (anterior) mesentery. (B) The cystic diverticulum and ventral pancreatic bud also grow into the ventral mesentery, whereas the dorsal pancreatic bud grows into the dorsal mesentery. (C) During the 5th week, the ventral pancreatic bud migrates around the posterior side (former right side) of the duodenum to fuse with the dorsal bud. (D) The main duct of the ventral bud ultimately becomes the major pancreatic duct, which drains the entire pancreas. *Source:* Reproduced from Schoenwolf et al [1] with permission of Elsevier.

Development of the circulation in the fetal liver

The circulation in the fetal liver is complex, and the reader is advised to refer to Chapter 5.

The arterial supply to the liver, like the rest of the foregut, originates from the vitelline arteries arising from the yolk sac [4]. A plexus of arteries between the vitelline vessels and the dorsal aorta coalesces to form three distinct arteries, supplying the whole of the gut from the aorta as the yolk sac shrinks. The celiac artery supplies the foregut, the superior mesenteric artery supplies the midgut, and the inferior mesenteric artery supplies the hindgut. The arterial supply to the liver and gallbladder is the common hepatic artery, which originates from the celiac artery.

Venous blood is received into the two horns of the sinus venosus from three bilaterally symmetrical venous systems: the vitelline veins return blood from the developing gut, the umbilical veins return oxygenated blood from the placenta, and the cardinal veins return blood from the embryo.

The vitelline veins originate as a network of vessels in the yolk sac, which in time form the venous drainage of the primitive gut. A plexus of vessels arises between the paired vitelline veins in the septum transversum, and as the hepatic diverticulum expands in the transverse septum, hepatic cords arrange themselves around this venous plexus to form primitive hepatic sinusoids. Caudal to the liver, the vitelline veins form numerous anastomoses; the left vitelline vein receives blood from the splenic and superior mesenteric veins, and the distal right vitelline vein regresses. The anastomosis between the left and right vitelline veins becomes the distal part of the portal vein. The proximal part of the portal vein is formed from the proximal right vitelline vein. The proximal left vitelline vein disappears at the time when the left sinus horn regresses to form the coronary sinus, and a series of transverse anastomoses carry blood to the right vitelline vein. Cephalad to the liver, an enlarged right vitelline vein returns all of the blood to the heart, and in time will become the inferior vena cava.

The two umbilical veins receive blood from the chorionic villi of the placenta and thus deliver oxygenated blood, rich in nutrients, to the developing fetus. In the second month of development the right umbilical vein regresses; possibly

abnormalities in this process can cause abdominal wall defects (see Chapter 31 for clinical management of abdominal wall defects). The remaining left umbilical vein carries oxygenated blood to the fetus, entering the ductus venosus and then, via the inferior vena cava, the right atrium. Early in the neonatal period, the umbilical vein atrophies because blood is no longer flowing through it, forming the ligamentum teres. The atrophic ductus venosus forms the ligamentum venosum. In the presence of portal hypertension these ligamentous remnants can recanalize.

KEY POINTS: EMBRYOLOGY OF THE LIVER

- Major development of the liver and adjacent structures occurs at 30–42 days' gestation
- The fetal liver is incompletely developed
- The liver is a major source of hemoglobin production *in utero*
- Abnormalities of development are causes of later hepatic malfunction

Functional development

The liver constitutes 10% of the weight of the fetus at 9 weeks' gestation, decreasing to 4% of the neonate and around 2% of adult bodyweight. The fetal hepatocytes are smaller than the mature cells, lack many enzyme systems, and are deficient in glycogen.

Carbohydrate metabolism

Neonatal hypoglycemia is a common problem and highlights the crucial role that the liver plays in glucose metabolism. The fetus receives all its glucose from the mother, via the placenta; following birth, the newborn rapidly acquires the ability to maintain independent glucose homeostasis [5]. By the 9th week of gestation the fetal hepatocytes are able to synthesize glycogen. At term, stores of glycogen are high (40–60 mg/g of liver), providing some reserve for the neonate until milk production and digestion start. A healthy term baby can withstand a fast of 12 h by the liver generating and releasing glucose by glycogenolysis [6]. Glycogenolysis is catalyzed by glycogen phosphorylase, the activity of which is promoted by glucagon and epinephrine. Following delivery, there is a rise in glucagon and a fall in insulin levels. Premature neonates lack the ability to effectively store and break down glycogen and so are at greater risk of hypoglycemia.

Following birth and before the establishment of effective feeding, glucose is in short supply and ketogenesis has yet to commence. The neonate depends on gluconeogenesis from lactate and pyruvate, which is thought to be stimulated by the high circulating levels of glucagon and catecholamines following delivery.

Gluconeogenesis is insignificant in the fetal liver [7], probably due to high insulin levels and low levels of the rate-limiting enzyme phosphoenolpyruvate carboxykinase, the activity of which rises rapidly following birth. Similarly, levels of hepatic galactokinase, the enzyme responsible for phosphorylation of galactose, increase near term. This allows the newborn to metabolize galactose in its diet. Interestingly, the utilization of glucose by the fetal liver is low, using amino acids and lactate for energy instead. Following birth, there is little glucose utilization by the liver of the neonate; instead, galactose is preferred for carbohydrate synthesis, and glucose is utilized preferentially by peripheral tissues. Glucose-6-phosphatase activity, needed to convert glucose-6-phosphate into glucose, is low in the fetal liver. Thus glucose production is low, promoting the storage of glycogen to the required high level. Levels of this enzyme also increase near term.

The transition of glucose metabolism from the fetus to the newborn is highly complex and the controls of the enzyme systems responsible for glucose metabolism are still a matter of research. Delivery and suckling also have a role in the initiation of glucocorticoid pathways and the decrease in insulin levels.

Amino acid metabolism

The majority of protein catabolism occurs in the liver, producing amino acids which may be used for protein synthesis. Amino acids may also be deaminated by aminotransferases and used to produce glucose, ketones, or fatty acids. Ammonia is produced as a product of deamination and is converted into urea.

Animal studies suggest that amino acids provide about 40% of the energy requirements of the fetus, with even essential amino acids utilized as fuel. *In utero*, the fetal liver has a high uptake of amino acids, which declines following delivery. The urea cycle enzymes are well established in the second trimester, and the fetal liver accounts for the majority of ammonia clearance. Accumulation of ammonia is toxic and contributes to the raised intracranial pressure and encephalopathy seen in acute liver failure.

Nearly all amino acids cross the placenta from mother to fetus by active transport, the exceptions being glutamate, serine, and aspartate, which are produced by the fetal liver. The enzyme systems necessary for the regulation of amino acids are expressed at birth, but the appearance of p-hydroxyphenyl pyruvate oxidase may be delayed. This enzyme is responsible for the breakdown of tyrosine, and may account for a transient tyrosinemia following delivery.

Lipid metabolism

The oxidation of fatty acids provides a major source of energy for the developing fetus [8]. Fatty acids may be synthesized by the fetus; non-esterified fatty acids may diffuse from the placenta or, in the case of some long chain fatty acids, undergo active transport across the placenta to the fetus. Free fatty acids are stored in the liver and adipose tissue, but are not used by peripheral tissues.

Animal models suggest relatively low levels of acetyl coenzyme A carboxylase (responsible for fatty acid synthesis) in the fetal liver, as compared to adults. Ketones and glucose from the mother may act as precursors for fatty acid synthesis in the fetus.

Following birth, the accumulated fat in the fetal liver is mobilized for oxidation to produce energy as adenosine triphosphate (ATP), and for ketone body formation, which may be used peripherally in tissues. This ability to oxidize fatty acids matures rapidly in the first few days of life, in response to falling insulin and rising glucagon levels. The liver is the most

important source of ketone bodies (acetoacetate, 3-hydroxybutyrate, and acetone). Fat stores are particularly important for preterm infants, due to immature glucose metabolism.

Following birth, the newborn suckles and takes milk, which is relatively high in fat but low in carbohydrate compared to solid foods (see section "Breast milk, the suckling period, and bacterial colonization"). Long and medium chain fatty acids in the diet stimulate gluconeogenesis by increasing the supply of gluconeogenic substrate for the liver. Weaning increases the amount of carbohydrate in the infant's diet, and the ability of the liver to produce fat is again increased.

Drug metabolism

The liver's central role in the metabolism of substances absorbed by the gut means that it has many of the enzyme systems necessary to alter alien substances (xenobiotics), such as drugs. Liver immaturity may alter the ability to clear drugs, as well as rendering it susceptible to damage from them and their breakdown products. Infant drug metabolism is complex as it depends on liver mass (usually relatively greater than in adults), protein binding, and blood flow, as well as enzymatic metabolism and clearance processes.

The metabolism of most drugs involves chemical processes to modify their structure, followed by conjugation to make them more polar (water soluble), so allowing excretion. These are termed phase 1 and phase 2 reactions. Phase 1 reactions are the result of electron transfers carried out by the cytochrome P450 enzymes – nicotinamide adenine dinucleotide phosphate (NADPH) and NADPH-cytochrome c reductase. They cause oxidation by electron removal or sometimes reduction by electron addition. Phase 1 reactions also include hydrolysis of esters and amides, sulfation, dehalogenation, N-dealkylation, and O-demethylation.

Cytochrome P450 (CYP) is a group of iron-containing membrane-bound enzymes found in endoplasmic reticulum and mitochondria. There are at least 57 human CYP genes producing enzymes which are classified according to the degree of amino acid homogeneity shown [9]. There are at least 18 families of CYP enzymes; they are named "CYP" plus the family number, followed by a letter, then a final number.

Phase 2 reactions involve conjugation with a substrate to form a more polar and water-soluble conjugate, for example a glucuronide, sulfate, or acetylated derivative. Glucuronidation involves the addition of an activated form of glucose (uridine diphosphate glucuronic acid, UDPGA) by the enzyme glucuronyl transferase. The glucuronide compounds so formed are readily excreted in urine or, in the case of larger compounds, in bile. Bilirubin is excreted in this way; however, glucuronyl transferase activity is low in the newborn, so a significant amount of hemolysis will overload the conjugating capacity of the enzyme and result in an unconjugated hyperbilirubinemia. Phenobarbital may be used to induce the enzyme.

The expression of CYP enzymes is an important factor in the development of drug metabolism in the fetus and newborn. CYP enzymes are active in the human liver early in intrauterine development; indeed, many systems are available for xenobiotic metabolism before 8 weeks' development. There is a gradual increase in activity throughout fetal development, and a major increase following birth.

To analyze the development of all the CYP enzymes is beyond the scope of this chapter, so we will attempt to highlight some examples of the CYP enzyme groups. The CYP 3A family serves as a good example of development; it is the most abundant of the CYP enzymes and is involved in the metabolism of many common drugs [10]. CYP 3A7 is the most abundant CYP enzyme in the fetus, is present during organogenesis, and plays a role in steroid metabolism. Expression of this enzyme ceases at delivery. Conversely, CYP 3A4 is the most abundant member of the CYP 3A family following birth and is involved in 50% of CYP-dependent drug metabolism; its expression is low in the fetus but increases to 50% of adult levels by 1 year of life; there are more than 20 human CYP 3A4 alleles and hence a lot of variability in drug handling [11]. CYP 2E1 is involved in the metabolism of alcohol and is responsible for the conversion of acetaminophen to the hepatotoxic metabolite N-acetyl-P-benzoquinone-imine. CYP 2E1 expression is low in the fetus, increasing to around 40% of adult levels at 1 year of age, and is not fully expressed until 10 years.

The development of the phase 2 enzymes is less well understood; however, there are significant differences in gene expression between infancy and adulthood, as well as genetic polymorphism. The uridine glucuronyl transferase enzymes catalyze the glucuronidation of bilirubin, as well as agents such as morphine and acetaminophen. In the midterm fetus the glucuronidation of morphine is only 10–20% of adult levels. Following birth, morphine glucuronidation reaches mature levels at around 2–6 months, but this may be delayed until 2 years of age. Similar polymorphism has been identified for other glucuronyl transferase enzymes. Abnormalities of uridine glucuronyl transferase 1A (UGT1A) are responsible for Crigler–Najjar syndrome and Gilbert syndrome, which are described later in this chapter.

KEY POINTS: FUNCTIONAL DEVELOPMENT

- The liver is necessary for optimal nutrition during development
- Metabolism of carbohydrates, lipids, and proteins is often different than in older children
- Enzymes for drug metabolism are reduced *in utero* and tend to reach adult levels during the first year of neonatal life

Development of bile formation and secretion

The liver is responsible for the excretion of bilirubin, bile acids, and xenobiotics with bile into the small intestine, for ultimate elimination in the feces. It plays an important role in nutrition, as excretion of bile acids into the intestinal lumen is involved in the absorption of long chain fatty acids and fat-soluble vitamins as well as a number of drugs and hormones. This is of particular importance in the nutrition and thus growth of infants with cholestasis.

The immaturity of bile synthesis and secretion is clinically apparent in the susceptibility of the sick neonate to develop cholestasis in response to sepsis or administration of parenteral

nutrition (PN), as well as the phenomena of physiological jaundice and breast-milk jaundice in the healthy baby.

Bile secretion starts at 4 months' gestation and thereafter the biliary system always contains bile, which is secreted into the gut and gives meconium its distinctive color [12]. During fetal life, the placenta carries out bile acid metabolism and detoxification. Throughout the third trimester, the predominant bile acids present in the gallbladder change from taurine-conjugated dihydroxy bile acids (mainly tauro-chenodoxycholic acid) to taurocholic acid and glycocholic acid. The transition to glycine conjugate bile acids, as seen in adults, occurs approximately 2–7 months postnatally. Secondary bile acids are formed via cleavage by colonic bacteria, and hence are not formed in the fetus. Placental transporters of bile acids facilitate bile acid transfer between the maternal and fetal circulations. The fetal enterohepatic circulation is poorly developed due to poor bile acid reabsorption in the small intestine. This, combined with the clearance of bile acids into the maternal circulation, means that the fetus and neonate have a small bile pool. Due to the reliance on the placenta and maternal liver function, bile salt elimination from the fetus can be disturbed in the event of maternal hepatic dysfunction [13].

Bile secretion increases throughout infancy. The ability of the gallbladder to empty in response to a test feed occurs soon after birth, but is reduced in preterm neonates of 27–32 weeks' gestation.

Bile flow is driven by the secretion and enterohepatic circulation of bile acids. Bile acids absorbed from the small intestine are taken up from portal blood by bile acid importer proteins. Over 75% of conjugated bile salts are transported into the hepatocyte by Na-dependent secondary active transport, via the Na-taurocholate co-transporting polypeptide (NTCP). In contrast, unconjugated bile acids are transported by a non-Na-dependent mechanism, the organic anion transporting polypeptide family (OATP). The unconjugated bile acids then undergo N-acyl amidation within the hepatocyte. Following this, the bile acids are rapidly transported across the hepatocyte cytoplasm and secreted into the bile canaliculi. The ATP-dependent bile salt export pump (BSEP) is the transporter responsible for the secretion of the major bile acids. It performs this function against a steep concentration gradient [14].

Mutation of the gene responsible for BSEP is responsible for progressive familial intrahepatic cholestasis 2 (PFIC2); this and related conditions are described in the section concerned with metabolic causes of conjugated hyperbilirubinemia.

Conjugated bilirubin is secreted into bile by means of a separate transporter protein, MRP2, mutation of which leads to Dubin–Johnson syndrome. This autosomal recessive condition results in a mild conjugated hyperbilirubinemia with normal liver function tests. Dubin–Johnson syndrome is asymptomatic, and affected individuals have a normal lifespan (Fig. 9.2).

Cholestasis

Cholestasis is classically regarded as due to an anatomical blockage or obstruction of part of the biliary tree. However, the various constituents of bile are secreted by different transporter proteins and thus deficiencies, or abnormalities, of these may cause cholestasis. The hepatocyte is the main cell responsible for the manufacture and secretion of bile acids and bile; thus the liver is the organ most likely to be damaged by bile acid retention when bile flow is reduced. The intracellular accumulation of bile acids appears to be the most significant pathological consequence of cholestasis.

Obstruction of the biliary tree, as in biliary atresia, or impaired secretion by the hepatocyte (e.g. PFIC2) can lead to a high concentration of bile acids in the hepatocyte cytoplasm. Bile acids exert their deleterious effects by a number of mechanisms; they may act as detergents which alter membrane

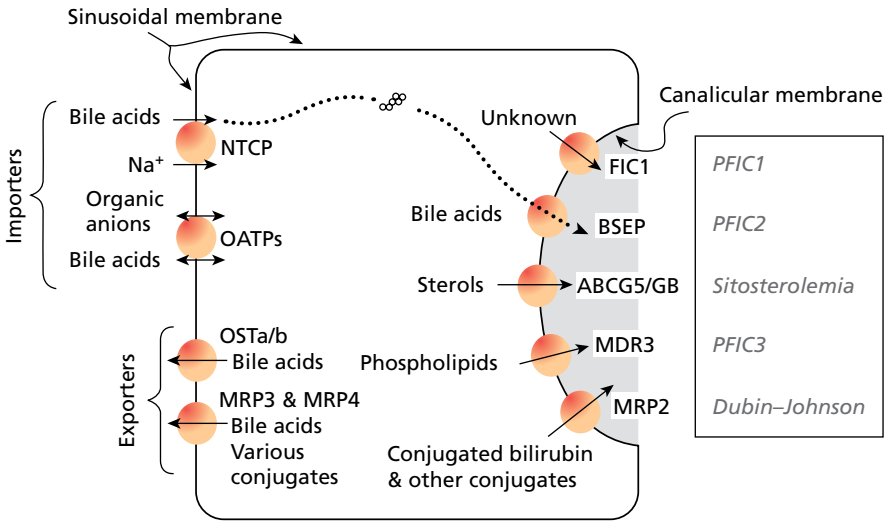

Figure 9.2 Roles for critical hepatic transporters in the formation of bile and adaptation to cholestasis. On the left is a representation of the sinusoidal surface, and on the right a canalicular surface. Diseases associated with defects in specific canalicular transporter genes are noted in italics. Note that bile acids have several means of transport across the sinusoidal membrane, both import and export, whereas there is one canalicular bile acid transporter, BSEP. These transporters allow for fine-tuning of intracellular bile acid concentrations as a way of adapting to a variety of cholestatic conditions. The principal means for bile acid flux across the hepatocyte is shown by the dotted line. NTCP, Na^+/taurocholate co-transporting polypeptide; OATP, organic acid transporting polypeptide; OST, organic solute transporter; MRP, multidrug resistance-related protein; FIC1, familial intrahepatic cholestasis 1; BSEP, bile salt export pump; MDR, multidrug resistance protein; PFIC, progressive familial intrahepatic cholestasis. Official gene designations: *FIC1 (ATP8B1)*, *BSEP (ABCB11)*, *MDR3 (ABCB4)*, *and MRP2 (ABCC2)*. *Source:* Reproduced from Karpen [15] with permission of Cambridge University Press.

structure and function, or may alter cellular signaling pathways and gene expression. CYP 450 pathways are activated to detoxify the liver; Kupffer cells, stellate cells, and myofibroblasts are also activated, potentially leading to fibrosis [15].

Neonatal jaundice

The following section deals with jaundice in infancy; it is not intended to be an exhaustive list of differential diagnoses but rather an illustration of the pathophysiological mechanisms described previously. Some of the conditions are rare, and a few only become manifest later in childhood; however, the jaundiced baby is a problem commonly encountered by the pediatric anesthesiologist. Neonatal jaundice has a variety of causes which may require investigation, and of crucial importance is the diagnosis of treatable conditions, such as biliary atresia. The causes of neonatal jaundice described here are divided into unconjugated and conjugated hyperbilirubinemia.

Unconjugated hyperbilirubinemia

The excretion of bilirubin, a breakdown product of heme, is one of the principal roles of the liver. Bilirubin is a toxic molecule, and diffusion of its free form into neural tissue, particularly the basal ganglia, can cause kernicterus in the premature neonate. As bilirubin is bound tightly to albumin, the usually low free levels may be increased by hypoalbuminemia or by drugs that displace bilirubin from its binding sites, e.g. sulfonamides and furosemide.

Physiological jaundice

Transient neonatal jaundice occurs in around 50% of babies in the first week of life [16,17]. It is due to immaturity of glucuronyltransferase, leading to an unconjugated hyperbilirubinemia. Occasionally the jaundice may be significant, with a serum bilirubin over 12 mg/dL, which may be associated with prematurity, bruising, and breast feeding. Physiological jaundice peaks at day 3 of life and declines thereafter, but the hyperbilirubinemia may persist for as long as 14 days. Treatment is usually unnecessary as the jaundice is self-limiting; however, if it is slow to clear, phototherapy can be used and is an effective treatment.

Breast milk jaundice

Unconjugated hyperbilirubinemia associated with breast feeding is common. Jaundice tends to occur after day 4 of life, may overlap with physiological jaundice, and can sometimes be protracted. The etiology is still to be elucidated but hypotheses include enhanced enterohepatic recirculation of bilirubin due to free fatty acids in breast milk, and the action of β-glucuronidase causing deconjugation of bilirubin. The diagnosis is clinical and no treatment is usually required other than reassurance and exclusion of more sinister causes of liver disease.

Crigler–Najjar syndrome

Crigler–Najjar syndrome is an autosomal recessive condition resulting from deficiency of the enzyme bilirubin uridine diphosphate glucuronyltransferase (UDPGT). The syndrome is divided into two types: type 1 has no UDPGT present, and in type 2 levels of the enzyme are reduced. Consequently, type 1 is the more severe condition and presents in the newborn with rising unconjugated bilirubin levels, with the risk of kernicterus.

Management of type 1 Crigler–Najjar syndrome often involves phototherapy. Acute exacerbations may be precipitated by sepsis and require plasmapheresis or exchange transfusion. Liver transplantation is a long-term option to avoid neurological deterioration. Type 2 Crigler–Najjar syndrome follows a more benign course.

Gilbert syndrome

Gilbert syndrome is a condition leading to mild unconjugated hyperbilirubinemia and results from a defect of the UDPGT gene. The affected individual, usually male, has mild jaundice worsened by intercurrent illness. Presentation is typically in teenage years, but heterozygotes for the genetic defect may present in the neonatal period. Treatment is unnecessary.

Conjugated hyperbilirubinemia

The identification of conjugated hyperbilirubinemia essentially allows the clinician to distinguish jaundice that is due to liver disease from the more common but generally more benign causes, which present with unconjugated hyperbilirubinemia.

The liver synthesizes all of the clotting factors except for the von Willebrand fraction of factor VIII, which is derived from vascular endothelium. Factors II, VII, IX, and X require vitamin K for their synthesis, so their levels are liable to fall if there is any biliary obstruction, because the fat-soluble vitamin K is poorly absorbed from the gut unless dietary fat is emulsified by bile salts. Vitamin K deficiency bleeding occurs in 1:10,000 babies. It classically occurs on the first day or in the first week of life, but in around half of cases it may occur after the first week, and is usually associated with breast feeding or liver disease. The risk of intracranial hemorrhage is high in this group. Vitamin K supplementation at birth is routine in Europe and North America.

Acquired cholestasis

Cholestasis associated with sepsis

Sepsis originating outside the liver is the most common cause of cholestasis in infants. It appears to be primarily an impairment of hepatocyte function causing reduced bile flow and intrahepatic cholestasis. This may explain the particular susceptibility of the immature liver to various insults. In animal models the administration of endotoxin lipopolysaccharide invariably leads to a sustained reduction in bile flow at the canalicular level. The mechanism responsible is a combination of inhibition of bile transporter activity and downregulation of bile salt transporter gene expression. Within an hour of endotoxin exposure, both BSEP and MRP2 proteins are reduced significantly. Cytokines also contribute via inhibiting cyclic adenosine monophosphate (cAMP)-dependent functions of transporters. There are also endotoxin receptors on the membranes of hepatocytes, and there is alteration in hepatocellular cytoskeletal structure, implying a direct action of endotoxin.

Hemolysis during sepsis can also contribute to jaundice. Excess bilirubin from red cell breakdown can exceed the capacity of the sepsis-challenged liver [18,19].

The liver also plays a central role in the acute-phase response to infection and injury. This is mediated by endotoxin, and results in expression of genes coding for a host of proteins and enzymes necessary to fight infection and repair tissue.

Cholestasis secondary to parenteral nutrition

Cholestasis associated with PN administration is particularly common in the neonatal population. The clinical scenario is familiar to the pediatric anesthesiologist – a premature neonate, who has undergone extensive bowel resection, is in trouble with sepsis and requires PN administration.

The mechanisms of PN cholestasis are multifactorial and complex; prematurity, infection, short gut, and toxic or missing components in the PN regimen all probably play a role. The inherently immature ability of the neonatal liver to produce bile and handle drugs suggests that neonatal livers are particularly susceptible to cholestatic insults. It is interesting that PN-associated cholestasis is rare in older children and adults. Recurrent central venous catheter infections will often provoke acute rises in serum conjugated bilirubin. A lack of oral intake interrupts the enterohepatic circulation of bile acids and may contribute to cholestasis, possibly secondary to abnormal gut hormone secretion. Bacterial overgrowth in the small intestine may lead to bacterial translocation and endotoxin production; metronidazole may sometimes be helpful. The absence or presence of certain constituents within PN remains an attractive explanation; excessive amounts of lipid (>1 g/kg/day) may overwhelm the liver's ability to handle it, and high levels of glucose infusion may cause increased insulin secretion which enhances the rate of fatty acid synthesis and impairs breakdown, and hence the accumulation of fatty acid within hepatocytes. It is therefore important not to overfeed with PN; introducing fasting breaks by avoiding continuous infusion is probably beneficial, if it can be tolerated.

The striking feature of PN-associated cholestasis is the association with prematurity, intestinal failure, and sepsis [20]. This provides the clinician with a therapeutic rationale to support the infant nutritionally, allowing growth and development while avoiding the progression of cholestasis to liver cirrhosis. Attention to strict aseptic technique is crucial to avoid central venous catheter infections. Innovative intestinal surgical techniques may lessen the chance of bacterial translocation and reduce the risk of sepsis. If possible, an increase in enteral feeding is encouraged, to reduce the volume of PN administered, stimulate gut hormone secretion, and support the enterohepatic circulation. The duration of PN administration should be limited as far as possible. The PN formulation should contain sufficient trace elements, amino acids, and essential fatty acids, although copper and manganese have been implicated as potential causative agents of cholestasis.

Structural abnormalities

Biliary atresia

Biliary atresia accounts for about a third of cases of neonatal cholestasis. It is an important condition, as delay in diagnosis and treatment can result in irreversible liver damage. It remains the most common indication for liver transplantation in children [21].

Biliary atresia is characterized by a progressive inflammation and destruction of the extrahepatic bile ducts, as well as damage to intrahepatic bile ducts; if left untreated, hepatic fibrosis and biliary cirrhosis develop. The most accepted classification system is based on the anatomical location of the damage (Fig. 9.3).

The condition has an incidence of around 1:10,000–15,000 in the United Kingdom and the United States. The etiology of biliary atresia remains obscure but the association with other anomalies makes an embryological hypothesis attractive (syndromic biliary atresia). Approximately 10% of infants with biliary atresia have associated anomalies including polysplenia, abnormal portal vein, interrupted inferior vena cava, and cardiac defects.

Infants with biliary atresia are typically healthy term babies who initially appear normal but soon develop persistent jaundice and pale stools. Lethargy, pruritus, and poor weight gain soon become apparent. Hepatomegaly is often noted and, as the condition progresses, signs of portal hypertension such as splenomegaly and ascites appear.

On confirmation of the diagnosis, the surgical treatment is the Kasai portoenterostomy, which involves excision of the atretic portion of the biliary tree, formation of a Roux-en-Y loop of jejunum and its anastomosis to the transected tissue at the porta hepatis, to allow bile drainage. As biliary atresia is a progressive inflammatory condition, many children proceed to liver cirrhosis despite achieving apparently adequate bile drainage. The success rate is much lower in those older than 8 weeks or with advanced hepatic fibrosis or established cirrhosis at the time of the operation. The Kasai procedure achieves some biliary drainage in 70% of infants, which may be adequate to ensure survival to 5 years in around 60% of cases; however, in around 30% of infants, hepatic dysfunction occurs later despite successful surgery [22,23], and by the age of 20 years nearly half of untransplanted cases have cirrhosis [24].

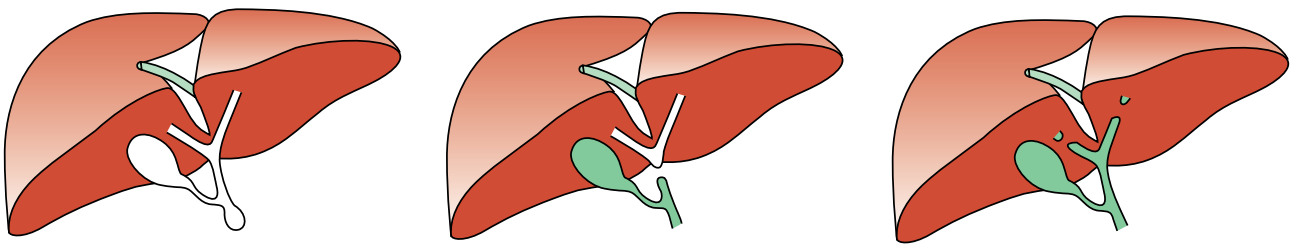

Figure 9.3 Classification of biliary atresia. Type 1: atresia affecting the common bile duct, often associated with proximal biliary cyst. Type 2: atresia affecting the common hepatic duct. Type 3: obliteration and atresia affecting the whole of the extrahepatic biliary tree. *Source:* Reproduced from Millar [21] with permission of John Wiley and Sons.

See Chapter 31 for additional discussion of the Kasai procedure. Liver transplantation offers excellent results for those who do not do well after Kasai portoenterostomy. See Chapter 30 for a discussion of the anesthetic management of liver transplantation.

Choledochal cyst

Choledochal cysts are congenital localized swellings of the bile ducts with an incidence of 1:100,000; they are more common in girls (female:male ratio 5:1). Interestingly, the condition is more prevalent in Japan. The position of the cysts is variable, leading to a number of classification systems; the cysts are most frequently found on the common bile duct, but may occur anywhere along the biliary tree (Fig. 9.4). The etiology of the cysts remains obscure.

Presentation may occur at any age and antenatal diagnosis on antenatal scanning sometimes occurs. Symptoms are classically pain and jaundice with a palpable abdominal mass. Diagnosis is confirmed by ultrasound scanning or magnetic resonance cholangiopancreatography. Secondary stone formation, cholangitis, pancreatitis, and spontaneous rupture may occur; the cysts also have a potential for malignant change in the long term. Portal hypertension may occur due to portal vein compression or as a result of cirrhosis. Treatment is by surgical excision of the cyst with biliary drainage via a Roux-en-Y anastomosis. The prognosis is generally very good and reversal of portal hypertension has been reported.

Alagille syndrome

Alagille syndrome is a rare autosomal dominant disorder affecting 1:100,000 deliveries and is characterized by the paucity of interlobular bile ducts. It is caused by a mutation of the *Jagged1* gene [25], which encodes for proteins involved in the Notch signaling pathway. The syndrome is characterized by triangular facies, butterfly hemivertebrae, and peripheral pulmonary stenosis often leading to pulmonary hypertension. The cardiac abnormalities are variable and may include hypoplastic pulmonary arteries, pulmonary valve stenosis, and ventricular septal defect. The affected infants are often developmentally delayed and short in stature. The severity of the liver disease is variable, with many children having mild disease, but pruritus is often severe.

Treatment is supportive with management of pruritus, nutritional support, and in some cases corrective cardiac

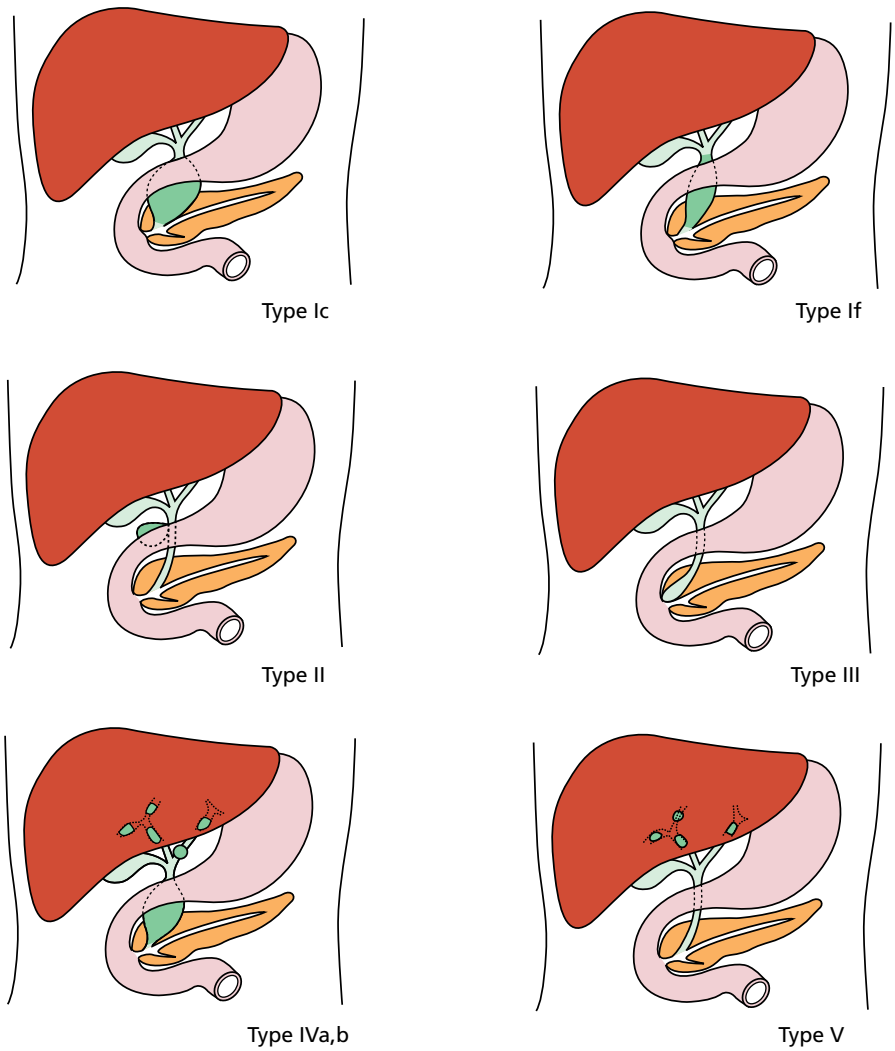

Figure 9.4 Classification of choledochal cysts. Type I dilations may be cystic (Ic) or fusiform (If) and typically associated with pancreaticobiliary malunion. Other types are II (diverticulum), III (choledochocele), IVa (multiple cystic dilations of the extrahepatic and intrahepatic ducts), IVb (multiple extrahepatic cysts), and V (single or multiple intrahepatic duct cysts). *Source:* Reproduced from Millar [21] with permission of John Wiley and Sons.

procedures. Liver transplantation is an option for those with decompensated liver disease or in whom pruritus is intolerable; however, the outcome following transplantation may be affected by the associated cardiac disease, and careful planning and assessment are necessary.

Metabolic conditions

α1-Antitrypsin deficiency

α1-Antitrypsin deficiency (α1-ATD) is the most common inherited disorder causing neonatal jaundice, with an incidence of 1 in 1600 livebirths. Only a few patients with the deficiency develop liver disease, but it is a common cause of emphysematous lung disease in adults [26]. α1-Antitrypsin is a protease inhibitor produced by the liver; it is an acute-phase reactant and responsible for inactivation of leukocyte elastase. Deficiency is due to mutation of its gene, which is found on chromosome 14. Over 70 phenotypes are described but the PiZZ phenotype (Pi stands for protease inhibitor, ZZ is the isoelectric focusing banding pattern of the abnormal α1-antitrypsin protein) is the most significant, with homozygous PiZZ individuals at risk of progressive liver disease. The pathogenesis of the condition remains obscure and is associated with a build-up of an abnormal α1-antitrypsin molecule in the hepatocyte. However, as not all individuals with the genetic defect develop liver disease, other pathophysiological processes are likely to be important.

The clinical presentation is similar to biliary atresia: a jaundiced baby with pale stools and hepatomegaly. Infants who are homozygotes have a low serum α1-antitrypsin level. Liver biopsy reveals histological findings of neonatal hepatitis and periodic acid–Schiff (PAS)-positive granules within the hepatocytes. Management consists of nutritional support, fat-soluble vitamin supplementation, and treatment of pruritus. The prognosis is variable; many individuals do well, but a proportion progress to cirrhosis and may deteriorate precipitately, requiring liver transplantation. The outcome following liver transplantation in α1-antitrypsin deficiency is good.

Progressive familial intrahepatic cholestasis

Progressive familial intrahepatic cholestasis (PFIC) is a group of autosomal recessive disorders associated with abnormalities of bile canalicular transport proteins [27]. PFIC-1 is caused by mutation of the *FIC* gene, which is expressed in the bile canaliculi; it is characterized by cholestasis, diarrhea, and pancreatitis presenting in the first months of life. Bile duct paucity is seen on liver biopsy. Treatment is generally supportive but external biliary diversion has been used in some cases. Liver cirrhosis occurs in early childhood and may progress to require liver transplantation. PFIC-2 is due to deficiency of the bile salt export pump and is similar to PFIC-1 except that pancreatitis is not seen. It has a worse prognosis and children often require liver transplantation in the first decade of life. PFIC-3 is due to a defect in the canalicular phospholipids transporter MDR3 and presents with intrahepatic cholestasis but with an elevated γ-glutamyltransferase, unlike PFIC-1 and PFIC-2. The condition is similar to PFIC-1, but presentation is often delayed into adult life and the prognosis is variable.

Cystic fibrosis

Cystic fibrosis affects around 1:3000 livebirths and is the most common life-threatening autosomal recessive condition. It affects the lungs, pancreas, sweat glands, and liver. There is great variation in the severity of liver disease; it affects one-third of individuals with cystic fibrosis but is the most important non-pulmonary cause of death. Liver disease usually presents in the teenage years but may rarely present in infancy with neonatal cholestasis, inspissated bile ducts, or meconium ileus [28]. Presentation with the last of these is particularly important, as it may be associated with sepsis and PN administration. The neonatal cholestasis usually resolves spontaneously, and appears not to predict future liver disease.

The reader should understand that although the causes of liver disease are varied, the pattern of progression to advanced liver disease may be similar. Therapeutic advances in hepatology and transplantation offer much hope to children with liver disease, but present an array of challenges to the pediatric anesthesiologist.

KEY POINTS: BILE FORMATION AND CHOLESTATIC CONDITIONS

- Cholestasis is a common finding in neonates due to physiological and anatomical lesions
- Common problems such as cystic fibrosis and α1-antitrypsin deficiency can affect multiple organs making anesthesia more challenging
- Biliary atresia with liver failure is a common reason for liver transplant

Developmental physiology of the gastrointestinal tract

Overview

Anesthesiologists tend not to take much notice of the gastrointestinal tract, except perhaps to wonder if the preoperative nil per os (NPO) period has been long enough. It probably merits more attention than this. The proper functioning of the gastrointestinal tract is fundamental to the well-being of the organism, in some ways as much as the cardiovascular, respiratory, and renal tracts, on which we concentrate so much, quite rightly. It is true that problems in the gastrointestinal tract may take longer to show their full impact, but we all know from experience of our own physiology how little we notice our gastrointestinal tract when it functions well and how ill we feel when it does not. Some of the sickest patients the anesthesiologist will ever encounter are in this desperate condition as a result of problems which have arisen in the gastrointestinal tract.

The great majority of animals, and all of those regarded as the more complex, conform to the same basic body plan: they are modified tubes and the inner surface is, or originates from, the gastrointestinal tract. The importance of this collection of structures and organs is indicated by the degree to which the developmental plan is conserved across classes of organisms which otherwise vary enormously. The genetic scientist can learn a great deal about the gastrointestinal tract of the human by studying that of the fruit fly or the nematode.

We are not so much interested in the details of the genetics of development, although the understanding of this topic has grown amazingly in the recent past, and our realization of its complexity similarly. This section will describe the embryology of the gastrointestinal tract in outline, and show how the anomalies which the anesthesiologist will encounter may have arisen. Relatively more attention will be given to those points which have a relevance to the diseases and conditions which may be seen by the practical pediatric anesthesiologist, but the management of these conditions will be covered in other chapters.

The development of the gastrointestinal tract is dictated by an unavoidable deadline. By the time a baby is born, the gastrointestinal tract must be ready to supply fully the baby's needs for fluid and electrolyte intake, to digest its food, initially completely milk, to provide sufficient energy and biochemical raw materials for extremely rapid growth and development, and to do so efficiently enough not to upset the immature homeostatic control mechanisms. At the same time, a sudden onslaught of pathogenic organisms and potential poisons has to be resisted. Within a few months of birth, the gastrointestinal tract has to be ready for weaning from its comforting milk diet to whatever the environment can be made to provide – one of the first crucial steps to independent existence. Thereafter, the demands made on the gastrointestinal tract do not alter so radically, and although there is a lot of growing to be done and full functional maturity will not be attained for some years, the processes remain more or less unchanged for the rest of the individual's life. This timescale means that the pace of development *in utero* is hectic, and after birth many of the remaining functional changes normally happen soon.

It will be obvious that physiological experiments on the developing gut are difficult to carry out, even in animal models, so there are gaps in scientific knowledge, sometimes glaring enough to be obvious to the non-specialist. Some (maybe even much) of what is known is extrapolated from data from other species, and although the homogeneity of gastrointestinal tract design means that this may often be accurate, some of it may not.

Basic gastrointestinal tract physiology

An abbreviated account of the physiology of the gastrointestinal tract follows. It is merely intended as an *aide-mémoire*. The interested reader is referred to standard physiology texts for a more complete account.

The gastrointestinal tract epithelium comprises four basic types of cell: enterocytes, goblet cells (secreting mucus), endocrine cells, and Paneth cells. The 'basic' gastrointestinal tract cell is the enterocyte, which has a brush border of microvilli facing into the gut lumen and tight junctions with its neighboring enterocytes. It sits on a basement membrane, beneath which capillaries and lacteals provide access to the circulation and lymphatic systems. Above the basement membrane, between adjacent cells, the basolateral surfaces border the fluid-filled paracellular space, which is crucial to the handling and transport of fluid and electrolytes. The enterocytes are arranged on villi, tiny finger-like mucosal projections into the gut lumen (Fig. 9.5).

The mass of crowded villi give the healthy gut luminal surface a velvety macroscopic appearance. Between villi, pits project down into the gut submucosa – these are known as crypts (of Lieberkühn). Enterocytes originate from stem cells in the crypts and there is a continuous procession of maturing cells from the crypts out and up on to the villi, gradually working their way to the tips of the villi, from where they are shed into the lumen.

The enterocyte has numerous digestive and absorptive functions. Substances can be taken into the cell by pinocytosis, passive diffusion, facilitated diffusion, and active transport. Enormously complex neural networks coordinate activity. This is explored in more detail in the section on the development of motility.

Basic gastrointestinal tract embryology

An understanding of basic embryology is necessary to make sense of the common structural anomalies.

By day 5 after fertilization, the late blastocyst consists of a hollow ball of cells. The outer cells will go on to form the trophoblast, and later the structures that will make the fetal component of the placenta. An inner cell mass forms a small mass lying against the side of the blastocyst. The inner cell mass soon develops into a bilayered structure: on one side, ectodermal cells border the amniotic cavity and on the other, the endoderm borders the yolk sac. The plate-like embryo starts to curl round and over, side to side and head to tail, so that the endoderm becomes more and more the lining of the inner side, and cells migrating inwards from the primitive streak on the ectodermal side become mesodermal cells, which surround the endoderm. The endoderm still communicates with the yolk sac, which lies outside the middle part of the embryo. By day 25, the caudal and cephalic ends of the endoderm have invaginated at the anterior and posterior intestinal portals to form the blind-ending tubes of the primitive gut. The gut has buds which grow out to form, in order from head to tail, the thyroid, the tracheobronchial bud, the liver, the pancreas, and the allantois, a hollow endodermal projection which still lies outside the embryo.

It is customary to describe the gut in four parts: the pharynx, which extends as far as the tracheobronchial bud; the foregut, from there as far as the liver bud; then the midgut, as far as the posterior intestinal portal, which is where the caudal blind-ending tube starts in the early embryo – in the adult, this point will be two-thirds of the way along the transverse colon. From here onwards is the hindgut.

The gut becomes an open tube at both ends; cephalad, a pit develops, which is closed by the buccopharyngeal membrane. This meets the pharynx and perforates to form the proximal opening. At the end of the hindgut a similar pit grows inwards to meet the hindgut and form the common opening of the gut and urogenital system, the cloaca. In the foregut, the tracheobronchial bud develops ventrally; normally the only communication between the two is where the larynx opens into the oropharynx. The esophagus elongates as the tracheobronchial bud grows downwards and the heart descends [29].

The most common congenital defect in this area is esophageal atresia with tracheo-esophageal fistula, which occurs about 1:4000 births [30]. The cause is unclear. In the most common form (over 80% of cases), the upper esophagus ends as a blind tube and the distal esophagus opens into the

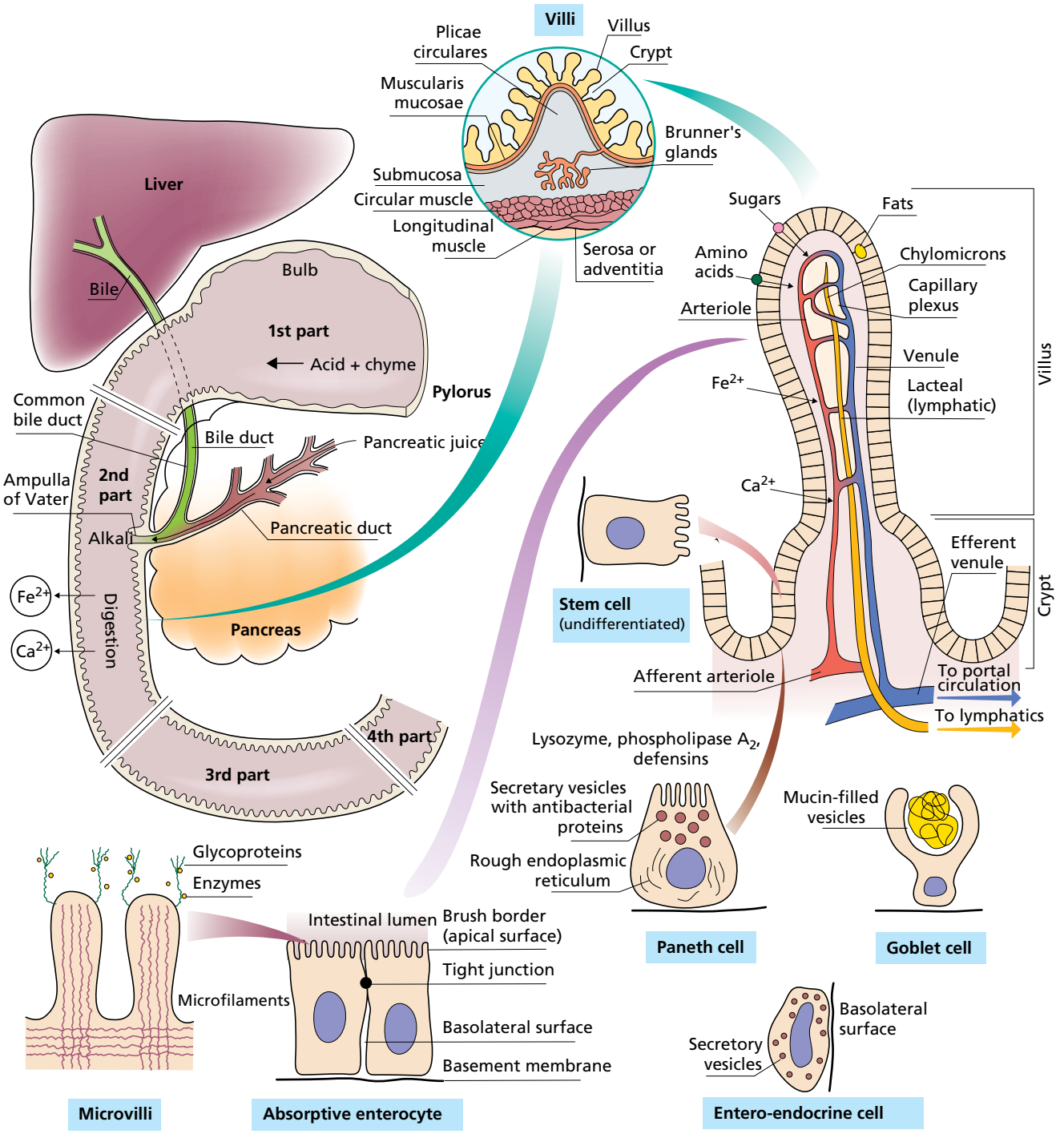

Figure 9.5 Basic structure and function of the gastrointestinal tract (duodenum). See text for further details. *Source:* Reproduced from Keshav and Bailey [161] with permission of Blackwell Publishing.

trachea posteriorly near the level of the carina. Other combinations are seen but esophageal atresia or stenosis without any fistula into the respiratory tract is unusual (Fig 9.6). Chromosomal abnormality (e.g. trisomy 21) is sometimes associated, and in more than half of cases there are associated anomalies, especially cardiac, renal agenesis, microcephaly, other gut atresias, limb reduction defects, and polycystic kidneys [31].

The stomach starts as a dilation in the foregut. It rotates round clockwise so that the left side becomes anterior and the right side becomes posterior; as this process occurs, its mesentery is dragged behind and forms a pocket of peritoneum behind the stomach – the lesser sac. The stomach is therefore surrounded by peritoneum, preventing its fixation and allowing for the necessary movement and expansion. The posterior wall (now left side) grows faster than the right, causing the distal part to be pushed out to the right. The liver bud develops from the ventral part of the duodenum; it grows up and forwards, so its upper surface lies in contact with the septum transversum and this structure, part of which gives rise to the diaphragm, is all that separates it from the base of the right lung and the heart. The duodenum also participates in

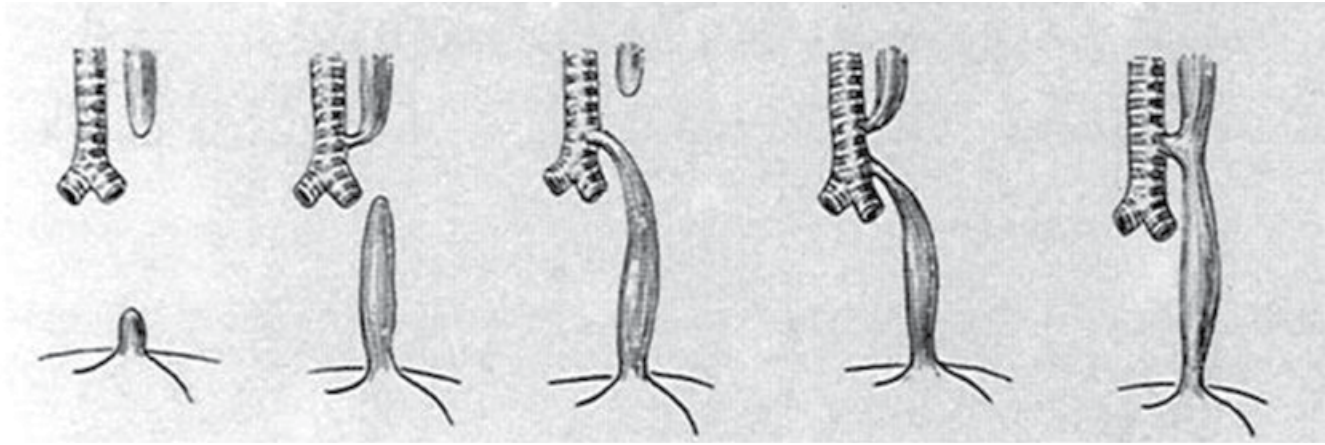

Figure 9.6 Anatomical classification of anomalies of the esophagus and trachea, with approximate incidences. Type A: esophageal atresia without tracheoesophageal fistula (TEF); Type B: esophageal atresia with proximal TEF; Type C: esophageal atresia with distal TEF; Type D: esophageal atresia with proximal and distal TEF; Type E: H-type TEF without esophageal atresia. *Source:* Reproduced from Gross [157] with permission of Elsevier.

this left-to-anterior rotation, so that the connection with the liver, which is drawn out into the thin common bile duct, is pulled behind the duodenum and ends up opening into the duodenum on the left side, at the papilla (see Fig. 9.1).

There are two pancreatic buds, ventral and dorsal. The ventral bud is also pulled round behind the duodenum and ends up touching and partially fusing with its dorsal counterpart. It is still recognizable in the adult as the uncinate process of the pancreas, which normally lies a little below the main body. The pancreatic ducts generally fuse to form a common pancreatic duct, which opens, with the common bile duct, into the duodenum at the papilla.

From here on, the midgut grows enormously, forming a long loop. Its blood supply, the superior mesenteric artery, is pulled out in the mesentery. The midgut undergoes rotation so the distal part is pulled upwards and to the right counterclockwise, so that the dilation that will form the cecum ends up in the right upper quadrant in front of the rest of the gut and the liver. As this part later elongates to form the ascending colon, it drops down towards the right lower quadrant, so the final rotation ends up approximating 270° (Fig. 9.7).

The small bowel loops repeatedly as it lengthens, whereas the colon does not. The growth of the midgut is so rapid that it cannot be accommodated in the abdominal cavity, so it herniates out. As the abdominal cavity becomes more spacious because of the growth of the whole fetus and the lifting up of the heart and liver, the midgut is gradually retracted back into the abdominal cavity by 11 weeks' gestation, the yolk sac obliterates, and the abdominal wall closes over it, leaving only the umbilical cord and its vessels passing out of the body cavity. At the point where the involuted yolk sac meets the midgut, a remnant may persist (Meckel's diverticulum) which may contain ectopic stomach epithelium, or there may be a fibrous cord, sometimes containing a vitelline cyst, tethering it to the anterior abdominal wall.

The hindgut is separated from the urogenital opening by the downward growth of the urogenital septum, which meets the cloacal membrane, dividing it into two: the anterior part, derived from the allantois, which will form the urinary bladder and genital tract, and the posterior part which forms the

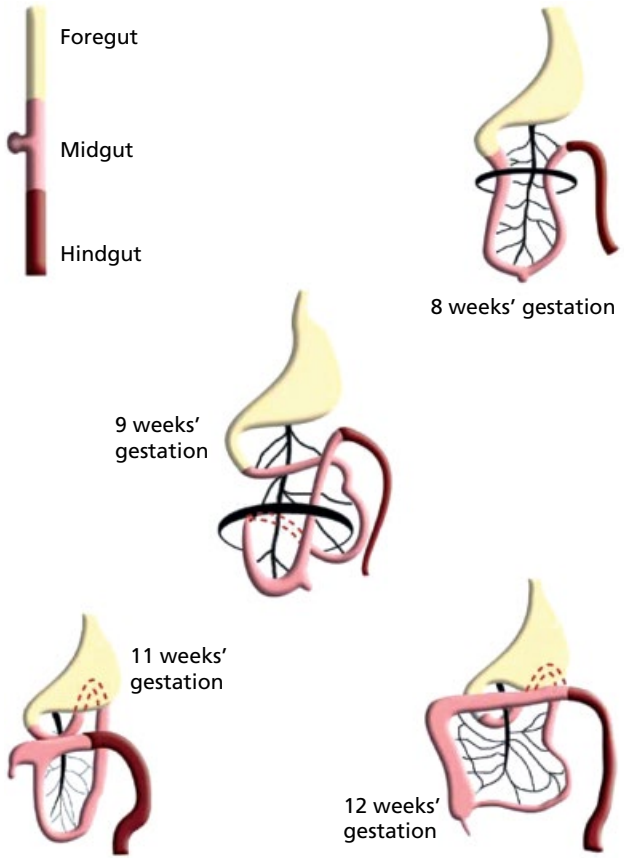

Figure 9.7 Rotation of embryonic gut. *Source:* Reproduced from reference [158] with permission of Health Education Assets Library.

rectum. By 9 weeks' gestation, the ectodermal anal pit perforates into the rectum, opening the distal end of the gut.

Imperforate anus occurs in around 1:5000 births and ranges from a thin membrane across the anus to complete failure of the formation of the anal canal and associated sphincters. There may be other defects in urogenital structures, and the anomaly may be associated with spinal defects, omphalocele, and aganglionosis [32].

Congenital abdominal wall defects: gastroschisis and omphalocele (exomphalos)

In gastroschisis, there is a defect in the abdominal wall, generally to the right of the umbilicus, and usually less than 5 cm across. The etiology is uncertain; there may be more than one causative factor [33], and explanations have been proposed for the rising incidence, including the effects of environmental pollutants [34]. It could be that a failure of mesenchymal cell migration means that the abdominal wall never completely closes over the defect left by the physiological herniation of the gut, which is normally retracted into the abdominal cavity around the 10th week of gestation, and so, as growth of the gut progresses, the gut reherniates. Possibly in some cases a weakness or ischemia of the abdominal wall causes it to rupture, having initially closed. The position to the right of the umbilicus may indicate defective involution of the right umbilical vein. Sometimes the liver is also herniated. The herniated gut is not covered and is exposed to amniotic fluid, and is necessarily exposed after birth. The blood supply to the herniated part can be compromised, and the ischemic gut can be reduced to fibrous bands or may contain segments of atresia. Even if this is not the case, the gut may not develop normally and its function may be impaired. Sometimes the gut is covered with a fibrinous "peel" which may form as a response to gut contents which have leaked into the amniotic fluid bathing the exposed gut; the presence of a peel predicts a worse outcome [35].

In omphalocele (also known as exomphalos), the gut herniates through the umbilical ring itself, which is wide open. The gut is covered by amnion, the membrane that surrounds the umbilical cord, which forms a sac, although this may rupture, especially if it is large. The size is variable; there may be anything from only a small amount of bowel in the sac to most of the small bowel, liver, and spleen.

The incidence of the two abdominal wall defects together is around 1:2000 births but the proportion of each varies by region and in many places is changing over time, the general trend in the developed world being that gastroschisis is becoming more common while omphalocele remains the same or is declining slightly, so that in many areas gastroschisis is seen slightly more frequently than omphalocele. Gastroschisis is related to young maternal age but is often the only abnormality, just 17% or so having other congenital abnormalities, whereas in omphalocele over 60% have anomalies elsewhere [36].

Congenital umbilical hernia resembles omphalocele, but in this case the abdominal wall originally closed normally, so when the hernia occurs it is covered by peritoneum as well as amnion.

Prune belly syndrome is an uncommon condition, occurring in less than 1:30,000 births, almost always in boys [37]. The muscles of the anterior abdominal wall are replaced by thickened collagenous bands, perhaps due to defective migration of mesenchymal elements which normally give rise to striated muscle. The abdomen therefore looks lax, the shapes of loops of bowel can be made out beneath the wrinkled skin, which gives the condition its name, and there may be visible peristalsis. The musculature of the bladder and renal tract is also affected and there may be a large thick-walled bladder, hydroureter, and renal dysplasia. The very rare megacystis–microcolon intestinal hypoperistalsis syndrome presents a similar appearance.

Malrotation

When the embryo's midgut is outside the abdominal cavity before the 10th week of gestation, the gut rotates through 270° so that the cecal bud, which would lie at 6 o'clock if there were no rotation, comes first to lie at 12 o'clock with the first 180° of rotation, and then finally round at 9 o'clock with a further 90°, which brings the cecal bud to lie in the right upper quadrant, next to the liver, and means that the colon lies over (anterior to) the duodenum. The gut loops on the left return first, so that as the cecal bud descends with the growth of the ascending colon, these structures lie on the right. Where the gut mesentery comes to lie on the peritoneum, it may fuse and so fix the gut at that point; normally the C-loop of the duodenum, ascending and descending colon, become fixed, and the small bowel loops and transverse colon retain a mesentery.

In malrotation, the gut rotation sometimes amounts to just 90°; if the left-sided structures return to the abdomen first, this will mean the distal parts will return first and the colon (all of it) will lie on the left and the small bowel loops will lie on the right.

If the malrotation is 90° clockwise instead of counterclockwise, then the duodenum will overlie the colon rather than the other way around.

The problems with malrotations are that the gut can be obstructed by the abnormal positioning or, lacking the normal fixation of parts of the gut to the retroperitoneum, the mesenteries can twist (volvulus), causing ischemic damage, or the abnormal peritoneal bands can themselves cause obstruction. This can commonly occur when the cecum lies to the left of the duodenum, so that the fibrous bands to the cecum lie over the duodenum (Ladd's bands) [38]. Sometimes the malrotated gut can function perfectly normally, and volvulus or obstruction occurs later in life, or it may cause no trouble and never be discovered, or only incidentally as a result of imaging or surgical exploration carried out for unrelated reasons. However, over 70% of cases present before the age of 1 year, and a similar proportion will have congenital abnormalities elsewhere. Malrotations are quite common, occurring in 1:500 births.

Intestinal atresias, stenoses, and webs

The duodenum is thought to pass through a solid phase in development, the lumen being re-established by the coalescing of vacuoles in week 8–10 of gestation (there is some doubt about this account [39]). If recanalization is incomplete then a stenosis, web, or atresia occurs, or if there is no connection to the lumen at all, a duplication cyst may result. Duodenal atresia is frequently (50%) associated with intrauterine growth retardation, polyhydramnios, prematurity, and congenital anomalies elsewhere which may be part of the VACTERL association (vertebral, anal, cardiac, tracheo-esophageal, renal, and limb anomalies [40]). Sometimes a duodenal stenosis can be surrounded by a ring of pancreatic tissue (annular pancreas), but it is not clear whether this is the cause of the stenosis or a result of it [41].

Jejunoileal atresias may be due to *in utero* interruptions in blood supply to a portion of the gut at a much later stage of development than duodenal atresias. They vary from stenosis, through cases where a small length of bowel is replaced by

a fibrous band, to multiple atresias with long sections of missing gut and defects in the mesentery. Sometimes the interrupted gut may be supplied by a marginal blood vessel, and therefore a length of progressively tapering hypoplastic gut winds around it in a spiral shape, giving rise to the "apple peel" or "Christmas tree" malformation (type IIIb) [42] (Fig. 9.8). They are not particularly associated with other abnormalities. Often the gut may be dilated proximal to the obstruction and collapsed or hypoplastic distal to it, although some stenoses may show distal dilation (wind-sock deformity).

Colonic atresias may occur by similar mechanisms but are more unusual – less than 15% of all intestinal atresias.

KEY POINTS: DEVELOPMENTAL ANOMALIES

- An understanding of the embryology of the gut is necessary for understanding many gut anomalies, e.g. tracheoesophageal fistula, malrotation of the gut, etc. (VACTERL syndrome)
- Omphalocele and gastroschisis occur commonly. The former is often associated with other congenital anomalies; the latter is not
- Malrotation of the gut leaves the child prone to midgut volvulus, a true neonatal emergency

Functional development of the gastrointestinal tract – vesicles, carbohydratase enzymes, transmembrane transporters

The epithelium of the gut changes from stratified to simple columnar between the 9th and 10th weeks of gestation [43]. Some absorptive processes are possible at the stratified stage, but significant functional capability does not become evident until the columnar stage. Maturation is not uniform, either between types of cell or between regions of the gut. In general, absorptive cells mature first, then goblet and endocrine cells, and Paneth cells last. Development also proceeds from proximal to distal. Villi appear first, proliferating to such a degree that the lumen may be obliterated. Crypts develop later. Epithelial cells differentiate from stem cells in the proliferative zone, which comes to lie in the crypts; Paneth cells migrate down into the crypts, all the others up towards the tips of the villi. There are therefore two axes of development: vertically on the crypt–villus axis and along the gut on the proximo-distal axis. The interaction between the endoderm-derived epithelium and the mesodermal elements that migrate into position beneath is crucial to the organized development of the gut [44]. The villi tend to be tallest in the jejunum and get shorter more distally. The mature colon does not have villi, only crypts, but there are villi in the immature colon.

A fundamental property of absorptive cells is that they can take up substances from the lumen in vesicles. Specialized

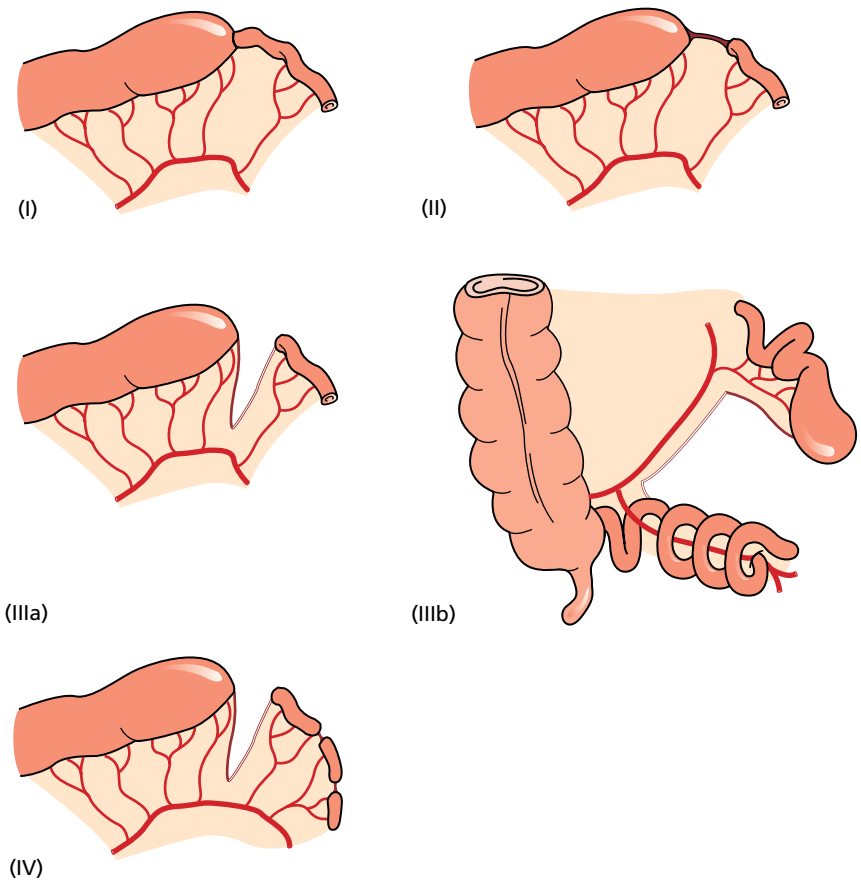

Figure 9.8 Classification of jejunoileal atresia describes the pathology as type I (mucosal web), type II (fibrous cord), type IIIa (mesenteric gap defect), type IIIb ("apple peel") or type IV (multiple atresias). *Source:* Reproduced from Welch et al [159] with permission of Elsevier.

proteins associated with vesicles (e.g. clathrins and caveolin) allow for selective absorption and onward intracellular distribution of substances from the gut lumen [45,46].

Developing enterocytes are structurally different from mature ones – at around 17 weeks' gestation, giant lysosomes can be seen in the ileum. There are more lysosomes in the adult gut than in the neonate, but no giant ones [47]. The developing gut needs to absorb more macromolecules undigested (growth factors, hormones, immunoglobulins) from amniotic fluid and milk, and is therefore more permeable to these, which may account for a greater susceptibility to pathogens and allergies at this stage.

Apical carbohydratase enzyme development has been studied in some depth, particularly lactase and the double complex sucrase/isomaltase [48]. Neither enzyme appears until the epithelium becomes columnar. Thereafter levels gradually increase. From 32 weeks' gestation there is a sudden large increase in lactase and sucrase activity. In most mammals (including humans), lactase activity declines sharply after weaning (later childhood in humans), typically to 10% or so of its peak, leaving most adult humans lactose intolerant [49]. Lactase is the only enzyme capable of cleaving the disaccharide lactose into its component glucose and galactose moieties. Lactose intolerance is by far the most common disaccharide intolerance. Other disaccharide intolerances are much rarer and are the result of transporter defects, not enzyme deficiency. In those of northern European ancestry, lactase activity usually persists into adulthood. These populations often have a tradition of consuming domesticated animal milk and milk products, and may at one time have been dependent on it or, at least, its availability conferred a survival advantage. Mutations reducing or eliminating the decline in lactase activity with age may have originated separately in several different human populations. The distribution of the enzymes also varies along both crypt–villus and proximo-distal axes; lactase is concentrated in more proximal regions of the small bowel, and towards the tips of the villi, where it is vulnerable to being sloughed off if there is any inflammatory process. Sucrase is evenly distributed up the villus and further along the small bowel, but neither enzyme is found in the adult colon [50].

Development of transporters

The principal carbohydrate transporters are: SGLT-1, which is a brush border (apical) sodium co-transporter for glucose and galactose; GLUT-5, which is a brush border facilitative transporter for fructose; and GLUT-2, which is a basolateral facilitator for all hexoses. Carbohydrate transporters start to be expressed during gestation, the number and density increasing and accelerating as term approaches. At birth, SGLT-1 is found along the whole length of the villus, whereas in adults it is found only on the third nearest the tip. Therefore the absorptive capacity per unit area of intestine tends to decrease with age but the total intestinal area of course increases, approximately proportional to the bodyweight after the neonatal period or slightly less [51]. The transporters are much more numerous proximally, where high carbohydrate concentrations would be expected. At the time of weaning, the transport capacity for sugars declines further and is at least in part genetically programmed, as it occurs even if a totally milk diet persists.

Amino acid transporters are more complicated; there are more types, absorbing different groups of amino acids, although their affinities may overlap with each other somewhat. Small peptides (mostly 2 and 3 amino acids) also have their own transporters.

There are specific transporters for bile salts which, unlike the other transporters, are much more numerous in the ileum. Curiously, they do not appear until weaning; presumably before that bile salts are absorbed passively all along the small bowel, as an enterohepatic circulation certainly exists during the suckling stage [52]. It may be that it is important for the development of colonic bacterial flora that bile salts enter the colon during suckling.

Carbohydrate malabsorption can be a dangerous problem. The consequences are that sugars reach the colon, where they cause an osmotic diarrhea. The sugars are fermented by colonic bacteria and hydrogen, methane, and carbon dioxide are produced. By far the most common cause is a loss of the brush border carbohydratase enzymes, the most common being lactase deficiency. Congenital lactase deficiency in infants was usually fatal before the advent of lactose-free milk substitutes. Genetic defects in the other carbohydratase enzymes are very rare, but acquired deficiency can be caused by a range of factors that may cause mucosal damage, including inflammatory, ischemic, or allergic processes.

Defects in nutrient transporters are rare. Glucose–galactose malabsorption is due to defective synthesis of SGLT-1.

The enteric nervous system

The enteric nervous system (ENS) is essential for the functioning of the gastrointestinal tract. All the nerves of the ENS are derived from neural crest cells and are broadly arranged into two plexuses: the inner submucosal plexus, situated as its name suggests; and the myenteric plexus, which lies between the inner circular smooth muscle layer and the outer longitudinal one. The ENS is much more than an extension of the parasympathetic branch of the autonomic nervous system. It contains a vast number of neurons (as many as the spinal cord) and many different cell types, and it is capable of functioning without any input at all from outside. Its neurons, which may be sensory, motor (both muscular and secretory), or interneurons, include types that resemble those found in the central nervous system (CNS): glial cells, astrocytes, and so on. One could go as far as to say that the complexity of the ENS, and its independence, allow it to be considered a "second brain." The largest share of the relatively tiny number of nerve connections to other systems comes from the vagus nerve, and 90% of those fibers are sensory – so perhaps in some respects the ENS controls the CNS more than the other way around.

Among the properties of the neural crest cells that find their way into the ENS are that they are highly migratory and highly pluripotent, and they originate from restricted areas – the vagal neural crest of the hindbrain supplies cells that populate the whole of the gut, starting proximally and eventually reaching the whole hindgut. Some neurons that derive from other parts (neural tube and sacral somites) also contribute to the ENS, and functioning ganglia cannot be generated anywhere without all the normal components in a favorable matrix. The factors that control this migration and differentiation are extremely complex.

Hirschsprung disease is a congenital defect in the development of the ENS in which ganglia are absent from a variable length of the gastrointestinal tract starting from the distal end (although occasionally, and disastrously, it may be complete). The presentation is of obstruction usually associated with megacolon. The fundamental defect is a failure of neuronal migration, and several different factors may be involved. The gene coding for a tyrosine kinase (c-RET) is clearly implicated, as are glial-derived growth factor and an endothelin receptor, ENDRB. Other genes that have a role in regulating development in neurons, *SOX-10* and *MASH-1*, can have mutations that mimic Hirschsprung disease in animals [53]. Many other genes are now known to be involved but still many cases of Hirschsprung disease (less than 50% in 2017) do not show mutations in any of these genes [54]. Clearly, the process of getting the right neuron in the right place is extraordinarily complex, and far from completely understood.

Motor function in the developing gut

The functionality of the immature gut is perhaps more limited by deficiencies in the motor function of the gut than by the lack of structural elements, cell types, or digestive enzymes and secretions. The development of motor function rather lags behind these other factors. It is at least 2 years before the system can be considered mature. The main movements that are required are swallowing, sucking, mixing and propulsion of gut contents, and evacuation. The esophagus, and those parts proximal to it, are striated muscle and under voluntary control. The muscle of the rest of the gastrointestinal tract, until the external anal sphincter, is smooth muscle; although neural projections and humoral influences from higher centers can modify its function, it is essentially autonomous and regulated by its own ENS and humoral factors.

Swallowing

Swallowing movements are evident in the fetus at 16 or 17 weeks' gestation, and there is a steady increase in the volume of amniotic fluid swallowed, from less than 20 mL daily at 20 weeks to around 450 mL daily at term [55]. There is much more to this than just "practice"; amniotic fluid contains nutrition and growth factors, and the development of the gut is promoted by it. An interruption of fetal swallowing can lead to polyhydramnios. In the premature infant, propulsive pressures in the esophagus are lower than at term; the movement may not be completely or properly coordinated, and complications due to reflux and aspiration are more likely. The function of the lower esophageal sphincter (LES) is particularly important in this. Although the lower LES pressure found in premature neonates would seem to make reflux more likely, reflux episodes appear to be more related to transient relaxations in the LES [56], the causes of which are not fully clear, than to inadequate resting LES pressure.

Sucking movements can be seen from 28 to 30 weeks' gestation but effective coordination with swallowing and breathing is generally not achieved until 37 weeks or so. Babies more premature than this may still be able to suckle by stopping breathing for short periods and then resting.

In both stomach and small bowel, the smooth muscle shows a typical pattern of slow-wave electrical activity, the periodicity of which is controlled by the pacemaker activity of the interstitial cells of Cajal. A muscle contraction is caused by a spike potential causing an additional depolarization on top of the slow wave and over the threshold for muscle contraction.

In the mature stomach and small bowel, in the fasting state the characteristic feature is the migrating motor complex (MMC), which is a wave of contraction passing from the stomach to the rectum. In the adult, these are seen every 90 min or so. Feeding abolishes them and for 3 or 4 h only segmentations and short peristaltic waves are seen, before the MMC re-establishes. A fully developed MMC is not seen until nearly full term [57,58] but this mature electromyographic pattern is not essential for successful enteral feeding. Gastric emptying can be seen up to 6 weeks before the appearance of the MMC, and contractile activity long before that, but in more premature infants nasojejunal feeding may be needed to overcome inadequate gastric emptying. It is clear that enteral feeding promotes the development of effective motor activity and so in conditions where full enteral feeding is impossible, at least some enteral feed is beneficial. Certainly, in some animals, bacterial colonization is also required for normal gut development.

The rate of gastric emptying is of course of great interest to the anesthesiologist wishing to provide safe anesthesia for his or her patient. Unfortunately, it is highly variable. Very dogmatic adherence to a protocol NPO period before anesthesia rather implies a lack of understanding of gastrointestinal physiology. The half-time for gastric emptying in premature infants is usually 20–40 min, rather slower than it is for term babies, and it will be slower for formula feed than for breast milk.

The colon also shows propagated waves of contraction when mature, and the passage of fecal material into the rectum may lead to reflex relaxation of the internal anal sphincter and defecation. The frequency of these contraction waves decreases with age from several times per hour in the term infant, especially just following a feed, to once or twice per day in the adult. Most babies pass their first stool within 2 days of birth, but it may be longer than that in the case of prematurity. There is normally no passage of meconium into the amniotic fluid *in utero*, and evidence of it is often considered a sign of fetal distress.

Many factors can interrupt the normal process of gastrointestinal tract motor maturation, including some that appear to be outside the gut; babies with hypoxic brain injury are much more likely to have problems with reflux and experience delays in establishing enteral feeding.

Meconium ileus is most commonly seen in infants with cystic fibrosis. Cystic fibrosis (CF) is caused by a defect in the gene coding for a protein that forms a cAMP-dependent chloride channel (cystic fibrosis transmembrane conductance regulator, CFTR). The disease is characterized by abnormally thick, viscid mucus, which typically causes blockage and infection in the respiratory tract or causes pancreatic insufficiency. There are other changes in CF goblet cell secretions and intestinal mucus apart from lack of chloride – for example, it contains more protein, specifically more albumin. The result is that the sticky meconium causes an intestinal obstruction. Rare cases that occur without CF may be due to motility disorders, for instance defective interstitial cells of Cajal.

KEY POINTS: FUNCTIONAL DEVELOPMENT

- Development of enzymes for uptake of material from the gut varies and usually increases with time
- Lactase is present in significant amounts in the infant but decreases in adults, possibly leading to lactose intolerance
- Hirschsprung disease is due to a lack of migration of the enteric nervous system of the gut, leading to macrocolon and occasionally bowel obstruction. The only effective treatment is excision of that portion of the gut

Immunity in the gastrointestinal tract

The very purpose of the gastrointestinal tract is to take substances in from the environment and transport them into the organism; it follows that this process is a major liability when that environment teems with potential pathogens. To protect the organism effectively from these myriad threats requires an extremely sophisticated multimodal defense system.

Innate immunity

The goblet cells secrete a mucus that forms a physical barrier, which also contains antimicrobial compounds, protecting the mucosa from pathogens. The number of goblet cells increases in inflammatory conditions and in response to some parasites. The enterocytes may contribute to immunity by an unusual mechanism [59]. The lifespan of enterocytes after birth is short, around 3–5 days. As these cells die and are shed into the lumen, they release histones, which are components of the cell nucleosome but which also seem to have significant antimicrobial activity (similar compounds are present in macrophages). So many enterocytes are shed into the lumen that this could be an effective protection, and it is not otherwise apparent why their lifespan needs to be so short; Paneth cells (originating from the same precursors) live much longer, as do fetal enterocytes in their sterile environment. Enterocytes therefore seem to have an immune function which is secondary to their main function. However, the primary function of Paneth cells is immunological. Paneth cells secrete a range of bactericidal compounds. They contain numerous granules (like neutrophils), and the granules seem remarkably similar, containing lysozyme, phospholipase A_2, and peptides known as α-defensins. All these components show antimicrobial activity. Most, and possibly all, of the Paneth cell granules are released into the lumen and so their antimicrobial activity occurs outside the cell, unlike neutrophils and macrophages; also unlike those cells of myeloid lineage, Paneth cells are fixed, in the epithelium of the crypts. Paneth cells can be detected in humans at about 13–14 weeks of gestation and produce low levels of defensins straight away. The levels increase markedly around the time of birth but defensin levels are still several times lower in neonates than in adults.

Acquired immunity

A detailed account of the mechanism of cellular and humoral immunity is outside the scope of this chapter, so we will assume some knowledge of these systems. The fundamental problem that the gastrointestinal tract poses to the immune system is that while the organism must be capable of defending itself against a vast array of pathogens that may attack by this route, it is unavoidable that the ingestion of food will also present an enormous range of foreign antigens and to respond to every one would be unfeasible, wasteful, detrimental, and potentially disastrous. Therefore there must be an accurate and subtle method for inducing tolerance to antigens that are harmless (and may be required), whilst maintaining immune vigilance against genuine threats. Perhaps needless to say, the precise and complete details of how this is achieved are not known and, anyway, the complexities of what is known need not trouble us too much for the purposes of this account.

Lymphocytes appear in the gastrointestinal tract in three broad areas: as intraepithelial lymphocytes, in Peyer's patches, and in the lamina propria.

Intraepithelial lymphocytes appear at around 11 weeks' gestation and increase continuously, so by 27 weeks about 70% of the infant level is reached [60]. In the lamina propria, B- and T-cells are present from 12 to 14 weeks' gestation, and similarly increase their number towards birth. The cell subsets present are distinctly different in these two areas and cell proliferation is seen throughout, whereas in the adult proliferation is confined to the Peyer's patches: these can be seen from around 18 weeks' gestation, mostly in the ileum, as in adults. There are typically around 100 at birth, increasing to 250 or so in teenagers, thereafter gradually declining. As soon as they appear, the epithelium overlying the patches changes from columnar to cuboidal, and the enterocyte-derived M-cells appear – their function is to transport antigens from the lumen and present them to lymphocytes [61]. Mature M-cells are surrounded by clusters of lymphocytes.

In utero, the sterile conditions do not test the immune system, but at birth there is a sudden influx of antigens. Premature infants are capable of mounting both humoral and delayed hypersensitivity-type reactions, but the response is less reliable than in term babies. After birth, the immune system continues to develop quickly, at least in part stimulated by luminal antigen (the process is less effective in parenterally fed infants), and normally after 1 year of age there are three times as many intraepithelial lymphocytes as in the neonate.

B-cells and the immunoglobulins they produce are crucial to the protection of the huge mucosal surface of the gastrointestinal tract. Peyer's patches are fundamental to the production of activated plasma cells. The clonal expansion of specific cell lines is carried out there, and the maturing cells disperse out into the circulation and so are distributed to the whole of the lamina propria. Immunoglobulin-secreting plasma cells produce predominantly IgA which is packaged with a secretory component and exported into the lumen by the enterocytes. In the neonate, significant amounts of IgA are supplied by the mother's breast milk, compensating to some extent for the immature humoral immune system.

Breast milk, the suckling period, and bacterial colonization

Breast milk is considered to provide many advantages over artificial alternatives [62]. The composition of human breast milk alters as the baby ages, is not uniform during a single

feed, and varies quite a bit between individuals. For the first few days postpartum, colostrum is produced; the volume is rather lower and its composition different from more mature milk.

Milk proteins

There are a very large number of milk proteins, which are classified into two groups according to whether they clot, forming a curd on exposure to acid (caseins), or not (whey). Caseins form micelles in the watery milk environment, containing ions, especially calcium and phosphorus. The principal caseins in human milk are β- and κ-casein. Of the whey proteins, those with the highest concentrations are α-lactalbumin, lactoferrin, secretory IgA (sIgA), and serum albumin.

Secretory IgA (90% of milk immunoglobulin) has an obvious immunological utility; the clonal varieties will be directed against antigens that the mother has encountered and are therefore tailored to the probable local environment. Immunosglobulins are resistant to degradation in the infant gut.

In addition, there are small amounts of important enzymes in milk, such as bile salt-activated lipase, which assists in the digestion of milk fat content. This enzyme, and the plasma membrane that encloses milk lipid droplets as they are secreted in the mammary gland, ensure that milk fat is particularly easily digestible.

Some growth factors, for example insulin-like growth factor, transforming growth factor, and epidermal growth factor, promote gastrointestinal tract cell proliferation, which can be extremely rapid after the first feed, intestinal mass as much as doubling within 3 days in piglets [63].

Hormones present in milk include insulin, thyroxine, and glucocorticoids, and these and other factors such as nucleotides may have important roles in gut maturation.

Cytoprotective substances such as prostaglandins and phospholipids are also present.

Non-protein components of milk

Mature human milk (produced at least 3 weeks postpartum) contains typically [64] 4% fat, almost all triglycerides of medium- or long-chain fatty acids, 7% carbohydrate, almost all lactose, and 1–1.5% protein (about 40% caseins, 60% whey).

Colostrum contains less fat and carbohydrate (about 75% of that in mature milk) and much more whey protein (about double) which includes up to 5–12 times as much sIgA, as well as high concentrations of trophic factors, especially in the first day or two [65,66]. By comparison, cow's milk is very different – it contains about half as much lactose, a little less fat, about three times as much caseins, and has a higher electrolyte concentration.

The infant stomach does not produce much acid (the pH in the neonate's stomach is 4–5), so pepsin activity and hence protein digestion are very limited. The stomach is much more important in the digestion of milk fat. Gastric lipase activity is very high in the neonate (even if premature) and it seems that this enzyme is required to start the breakdown of the membrane-coated milk fat globule, which otherwise resists the activity of bile salt-activated lipase (a milk constituent).

Initially there is significant transport of macromolecules unaltered across the gut mucosa. This certainly occurs *in utero*, and factors present in amniotic fluid appear in the fetal circulation. Later, the gut becomes much less permeable, a process known as closure. The precise timing of closure is difficult to determine; it happens rather earlier in humans than in some other mammals – in the rat, closure occurs long after birth. Certainly the human gut is more permeable in the neonatal period, and factors in breast milk may promote closure; this may be protective against infection.

Gut colonization and the development of the microbiome

It is now recognized that the human is in fact not a single organism but rather a colony of many different creatures living in association; if the DNA from every cell in or on a human were sequenced, up to 99% of the genes found would be discovered to be not human but from a variety of bacteria, fungi, viruses, Archaea, and others. Most of them are tiny, so of course by weight we are mostly human. The great majority of these organisms that make up the microbiome are beneficial or at least benign, but the characterization of these relationships is still at an early stage. The gastrointestinal tract harbors the largest population of these symbionts. Before birth, the gastrointestinal tract is sterile, so the appearance of the various species that later populate it is a matter of great interest. It is postulated that the species that inhabit the gut are significant for healthy development, and evidence is accumulating that this is true. Furthermore, the microbiome does not relate only to the health of the gastrointestinal tract itself but also to that of many other organ systems. A faulty or pathological microbiome has been implicated in the development of necrotizing enterocolitis, inflammatory bowel diseases of various sorts, atopy, allergy (especially pathological sensitization to food allergens), autoimmune diseases, neuropsychiatric disorders such as autism and attention deficit hyperactivity disorder, diabetes, obesity, and many others.

The origins of many early colonizers of the gastrointestinal tract are the mother's genital tract, and breast milk. It is clear that these colonizing organisms are different in infants who have been delivered vaginally and breast fed compared to those who have effectively bypassed the usual sources of colonizing organisms by being delivered by caesarean section and fed on formula milk. The breast-fed infant's gut is primarily colonized by bifidobacteria and lactobacilli, whereas those on formula feed have a smaller population of organisms in total but more *Bacteroides*, enterococci, *Atopobium*, clostridia, and anaerobic streptococci. As the infant ages and grows, the balance of species alters as the gut itself matures and the variety and type of foods taken changes; an 'adult'-type microbiome is generally established by the age of around 3 years. Some exposure to a range of microbes appears protective against the development of pathological allergies; these are less common in children living in close proximity to domesticated animals and exposed to water-borne microbes [67].

Antibiotic therapy and indeed just being in hospital can change the gut microbiome in a possibly harmful way. The study of these features has largely not reached the stage where cause and effect can be attributed to the presence or deficiency of particular communities of microorganisms and the appearance of a disease state in the human host. Still less can any attributions be made that a therapeutic effect can be achieved by the manipulation of the microbiome by the administration of probiotic substances, direct introduction of desirable species, or reduction of undesirable ones by antibiotic or phage

agents. There is a growing volume of research addressing these questions and undoubtedly this new knowledge will be translated into novel medical interventions. For now, most research is geared towards finding possible associations between diseases and the composition of the microbiome. Infants are much more susceptible to infection by *Salmonella*, *Campylobacter* and pathogenic *E. coli* strains than are adults.

KEY POINTS: DEVELOPMENT OF THE MICROBIOME

- *In utero*, the bowel is sterile. The microbiome develops rapidly after birth
- The microbiome differs between breast-fed and bottle-fed infants
- Alteration of the normal microbiome may affect development of postnatal complications, e.g. necrotizing enterocolitis

Necrotizing enterocolitis

Necrotizing enterocolitis (NEC) is the most common gastrointestinal disorder in the neonate. Despite its frequency, and a large volume of research, the causes remain obscure [68]. It is much more prevalent in premature babies, affecting about 10% of babies born weighing less than 1500 g, and the more prematurely the baby is born, the more likely it is to develop NEC. The condition is unusual in babies born later than 35 weeks' gestation. When it does occur in a term neonate, the onset is typically within a few days, but may be several weeks after birth in very premature babies.

It is attractive to ascribe an infective cause and it is true that in advanced severe cases, the clinical picture is of sepsis. Cases also sometimes cluster, suggesting an epidemic etiology. However, it is clear that no one particular organism is responsible. Many cases of NEC show heavy gut colonization with clostridia, but these bacteria are commonly found in healthy babies and this finding is not universal. In a breast-fed infant, bifidobacteria tend to predominate, and counts of these species are lower in NEC cases; possibly giving probiotics to enhance their growth may be protective [69]. Breast milk has a protective effect against NEC and contains anti-inflammatory substances, sometimes in higher concentrations in the milk of mothers of premature babies [70]. The gut of the preterm infant has an increased expression of Toll-like receptor 4 (TLR-4) which clearly plays a role in normal gut development. It may be that endotoxin from gram-negative bacteria binds to TLR-4 and produces an exaggerated inflammatory response via a number of different cytokine intermediaries, which culminates in gut ischemia, bacterial translocation, and systemic sepsis [71].

The clinical picture is often of a premature baby who may initially progress well on enteral feeds but then becomes feed intolerant and may have abdominal distension and vomiting. Apneas are common, and the baby may seem lethargic or appear to be uncomfortable. Radiographs may show dilated bowel loops and gas in the gut wall or, if the condition progresses to full-thickness ischemia and intestinal perforation, free gas in the peritoneum. Systemic signs may be hypothermia, acidosis, and other electrolyte disturbances, and eventually cardiovascular collapse and multiorgan failure.

Treatment consists of resting the gut (PN may be required), general supportive measures and antibiotic therapy, and celiotomy if the condition worsens. Sections of ischemic gut may have to be resected, and stoma formation may be necessary. Mortality remains high, up to 50% in babies weighing less than 1500 g at birth. Survivors may suffer later complications from short gut or malabsorption disorders.

KEY POINTS: NECROTIZING ENTEROCOLITIS

- NEC is a common cause of gastrointestinal illness in neonates, especially in those who are preterm
- Mortality increases with decreasing gestational age and may be as high as 50%
- Breast-fed infants may have some protection against NEC

Developmental physiology of the renal system

Developmental abnormalities of the kidney and urinary tract are the most common cause of childhood renal failure in the United States [72]. Defects occur in as many as 1:100 livebirths and range from benign, asymptomatic duplications to lethal conditions such as bilateral renal agenesis [73].

Embryology and development

Kidney and urinary tract

The definitive kidney has two embryonic precursors: the pronephroi and the mesonephroi. Although ultimately both degenerate, they are essential for normal renal development. The pronephroi arise from intermediate mesoderm early in the 4th week and are rudimentary, non-functional kidneys composed of simple tubules in the neck region [72]. The pronephroi drain into bilateral ducts, precursors of the Wolffian (nephrogenic) ducts, which elongate caudally to fuse with the cloaca. The mesonephroi develop caudally to the pronephroi at the end of the 4th week. They comprise well-developed nephrons and vascular glomeruli that drain into the Wolffian duct and function as interim kidneys for about 4 weeks. They regress at the end of the first trimester although they have several adult derivatives in the male [74].

Development of the permanent kidneys begins early in the 5th week. A diverticulum known as the ureteric bud arises from the caudal end of the mesonephric duct and is the precursor of the ureter and renal collecting system (Fig. 9.9). It penetrates a specialized area of intermediate mesoderm at the level of the hindlimb termed the metanephric mass, which is the precursor of the renal parenchyma. The ureteric bud elongates to form the ureter and branches to form calices and collecting tubules. The end of each collecting tubule induces cells of the metanephric mass to form vesicles that elongate to become definitive tubules (Fig. 9.10).

Nephron development commences around the 8th week. It occurs in a centrifugal pattern with cortical nephrons

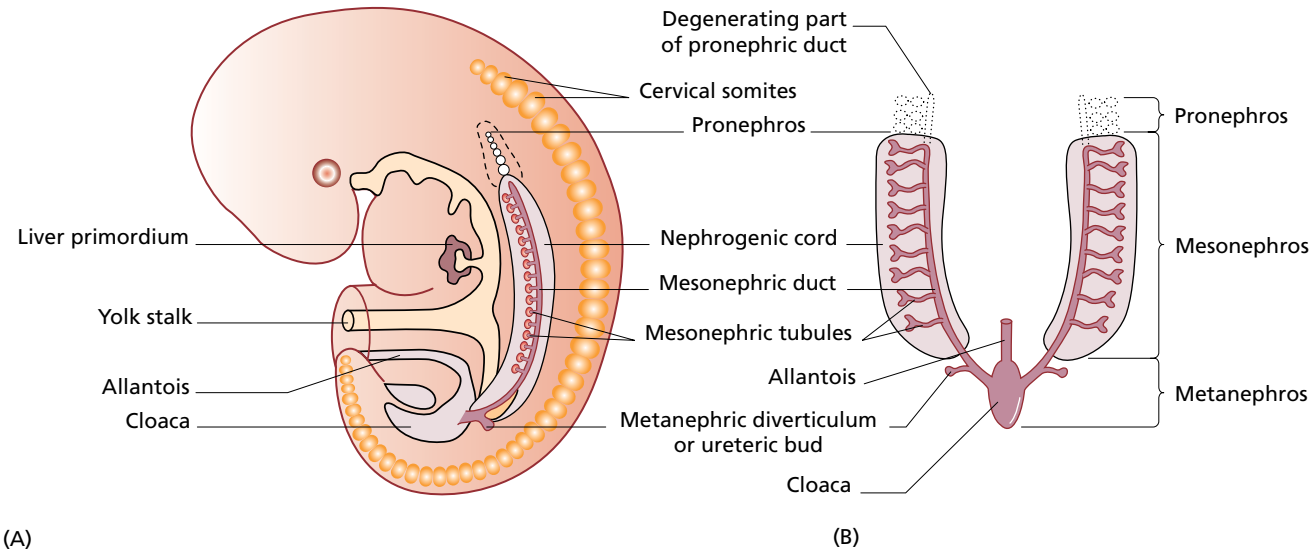

Figure 9.9 The three sets of excretory systems in an embryo during the 5th week. (A) Lateral view. (B) Ventral view. The mesonephric tubules have been pulled laterally; their normal position is shown in (A). *Source:* Reproduced from Moore and Persaud [74] with permission of Elsevier.

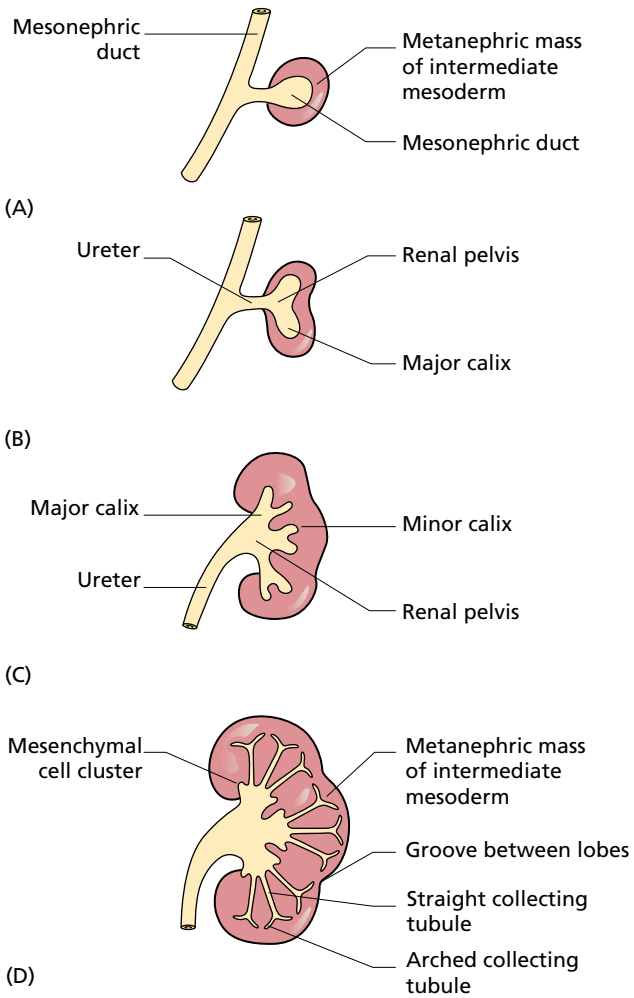

Figure 9.10 Development of the permanent kidney. (A–D) Successive stages in the development of the metanephric diverticulum or ureteric bud (weeks 5–8). Observe the development of the ureter, renal pelvis, calices, and collecting tubules. *Source:* Reproduced from Moore and Persaud [74] with permission of Elsevier.

formed after juxtamedullary ones. The rate of development increases rapidly after 18 weeks' gestation and is complete by 34–36 weeks, with each kidney possessing between 800,000 and 1,000,000 nephrons [75]. Renal growth after this is mainly due to elongation of the proximal convoluted tubule and an increase in interstitial tissue. Abnormalities in ureteric bud induction of nephrogenesis underlie many congenital defects; details of common ones are given in Table 9.1. Premature and low-birthweight infants have fewer nephrons, leading to high nephron filtration rates and glomerular hypertrophy [78]. Low nephron numbers are clearly associated with the development of hypertension, cardiovascular disease, and increased susceptibility to renal disease in later life [79,80].

Urinary bladder

The cloaca is partitioned by the urorectal septum into a ventral urogenital sinus and dorsal rectum. The bladder arises mainly from the vesical part of the urogenital sinus, with the trigone derived from the caudal ends of the mesonephric ducts. As the ducts are incorporated, so the ureters come to open into the bladder, their orifices moving superolaterally as a result of "traction" from the ascent of the kidneys. The bladder is initially contiguous superiorly with the allantois (a vestigial structure) which constricts to become the urachus, represented in adults by the median umbilical ligament. If fetal bladder emptying is obstructed, the urachus may remain patent, allowing urine to leak out around the umbilicus.

Renal migration and blood supply

The kidneys initially lie close to each other in the pelvis and attain their abdominal, retroperitoneal adult position by the 9th week. This apparent migration is due to embryonic growth caudal to the kidneys rather than movement of the kidneys themselves, and abnormalities in this process are common (see Table 9.1).

Table 9.1 Common abnormalities of the urinary tract and their embryological origins

Condition	Embryological etiology	Clinical effects
Renal agenesis	Failure of ureteric bud to contact metanephric mesoderm	Unilateral – 1:1000 livebirths. Usually detected incidentally, may be associated with higher risk of chronic kidney disease in later life
	Complete involution of a severely dysplastic kidney	Bilateral – 1:10–30,000 livebirths. Absence of fetal urine leads to oligohydramnios sequence (see text). Usually fatal
Urinary tract duplication	Ureteric bud division	Bifid ureter with either a divided kidney or a supernumerary kidney
	Duplication of ureteric bud	Two ureters each with their own kidney on the affected side
Renal ectopia	Arrested or aberrant migration ± fusion while kidneys lie in fetal pelvis	Pelvic kidney – unilateral failure to ascend. No symptoms but may be confused with tumors or damaged during surgery
		Crossed renal ectopia – one kidney migrates to contralateral side. May occur with fused kidneys
		Discoid or "pancake" kidney – complete fusion in pelvis. Kidney mass lies above bladder with short ureters
		Horseshoe kidney – 1:500 livebirths (7% of those with Turner syndrome). Fusion of kidney poles (usually inferior). U-shaped kidney lies in hypogastrium as normal ascent is prevented by root of inferior mesenteric artery. Usually no symptoms
Dysplastic or hypoplastic kidneys	Failure of induction of nephrogenesis by the ureteric bud	From small kidneys with low numbers of normal nephrons to normal-sized kidneys with a wide variety of tubular defects. Dysplastic kidneys may also be multicystic – these often involute spontaneously *in utero* or the first few years of life. Together, the most common cause of established renal failure worldwide. Molecular mechanisms are being elucidated [76]
Wilms tumor	Nephrogenic rests: abnormal structures arising from failure of mesenchyme differentiation	Kidney malignancy affecting 1:10,000 children. Nephrogenic rests are found much more frequently in children with Wilms tumors [77]

Renal arteries and veins start as branches of the common iliac vessels; as the kidneys ascend, they receive new branches from successively more superior points of the aorta and inferior vena cava. Inferior vessels usually degenerate but their persistence explains much of the variation seen in the renal vasculature. A single renal artery to each kidney is present in only 75% of adults, and 25% of kidneys have two to four accessory arteries [81]. These usually drain into the hilum but accessory arteries may be end-arteries, rendering portions of a kidney vulnerable to ischemia, and those to the lower pole may obstruct the ureter and cause hydronephrosis [82].

Fetal urine production and the oligohydramnios sequence

Urine production by the fetal kidney begins by week 10 and is responsible for 90% of amniotic fluid volume by week 20. Production increases from 0.1 mL/min at 20 weeks to 1 mL/min at 40 weeks' gestation, which is far in excess of urine production rates in the term neonate [83]. Fetal urine production may be measured by ultrasound and in cases of uteroplacental insufficiency low values predict adverse perinatal outcomes [84]. The absence of adequate amniotic fluid gives rise to the oligohydramnios sequence. Characteristic facial features, known as Potter's facies, include micrognathia, wide-set eyes, flattened nasal bridge, and large, low-set ears which lack cartilage [85]. Skeletal anomalies associated with oligohydramnios include club feet, hip dysplasia, scoliosis, torticollis, and contractures. Amniotic fluid is also essential for normal lung development; pulmonary hypoplasia is the main reason for the high mortality associated with significant oligohydramnios [86]. The fetus swallows significant volumes of amniotic fluid daily which is absorbed by the intestine. However, fetal waste products are transferred across the placenta for excretion by maternal kidneys. The kidneys do not assume their excretory role until after birth (see Table 9.1).

Developmental physiology

Glomerular filtration

Glomerular filtration is the process whereby water and solutes cross the glomerular membrane. Ultrafiltrate is virtually identical to plasma apart from containing very little protein. The rate of ultrafiltration is governed by four factors: the balance of Starling forces across the capillary wall; plasma flow rate; glomerular capillary wall permeability; and total surface area of the capillaries.

Quantifying glomerular filtration rate (GFR) is important for the rational prescribing of drugs and in monitoring chronic kidney disease. Comparing direct measurements from small infants to adults requires scaling to a standard of reference. Although kidney weight cannot be directly measured, both kidney weight and absolute GFR correlate well with body surface area (BSA). Adjusting GFR for BSA removes the variability caused by the variation in pediatric body size [87]. BSA in children and adolescents may be calculated from the formula [88]:

$$\mathrm{BSA}\left(\mathrm{m}^2\right) = 0.024265 \times \mathrm{Weight}^{0.5378} \times \mathrm{Height}^{0.3964}$$

The most common method of measuring GFR is based on the concept of clearance. The renal clearance of a substance x (C_x) is expressed by the formula:

$$C_x = U_x V / P_x$$

where U_x is the urine concentration, P_x the plasma concentration, and V the urine flow rate. If a substance is freely filtered and not metabolized, synthesized, or transported by the kidney then its clearance is equal to GFR.

Despite the importance of GFR, accurate measurement remains problematic. Renal clearance of inulin is still the gold standard in all age groups. However, its utility is compromised by availability, difficult assays, and the practical problems of collecting urine samples in children. Urine volumes

are inaccurate in the presence of vesicoureteric reflux and conditions that preclude complete voiding [89]. Creatinine is freely filtered and secreted by tubular cells but measurements are affected by diet and muscle mass. Furthermore, extrarenal clearance of creatinine is markedly increased in the presence of renal dysfunction so GFR tends to be overestimated [90]. Radiolabeled isotopes are accurate but not ideal agents in children, particularly for repeated assessments.

More recent approaches have used alternative markers. Iohexol is a non-ionic contrast agent already used at higher doses for radiological procedures even in the presence of renal dysfunction. Cystatin C is an endogenous cysteine protease inhibitor that is produced constantly and freely filtered, independent of inflammatory conditions, sex, muscle mass, and age above 1 year. Equations utilizing iohexol plasma clearance and serum cystatin C appear very accurate, but these assays are not widely available [91]. Iohexol may be accurately quantified from blood spots on filter paper, which may facilitate late sampling by patients at home and the use of iohexol as an epidemiological tool [92].

The Schwartz formula is commonly used to calculate GFR in children and has undergone several iterations to incorporate both newer biomarkers and more accurate laboratory assays [93]. The full Schwartz equation uses iohexol plasma clearance as its gold standard and now incorporates serum creatinine, blood urea nitrogen, cystatin C, height, and gender. A simpler bedside version, utilizing only height and creatinine, shows reasonable accuracy but the association with measured GFR is poorer and the rate of disease progression overestimated. For accurate GFR estimation utilizing endogenous markers, the complete Schwartz equation is to be recommended [94,95].

Glomerular filtration begins in the fetus during the 9th week. GFR reaches 12 mL/min/1.73 m^2 in the premature infant at 30 weeks and 20 mL/min/1.73 m^2 by term. Maturation continues rapidly in the postnatal period with a doubling of GFR by 2 weeks, a proportional rise that is seen in both premature and low-birthweight babies [96,97]. Adult values of GFR (corrected for BSA) are reached by 18–24 months of age [98]. Low GFR is primarily mediated by vasoconstriction through the renin–angiotensin system (see section "Control systems") and may represent a necessary adaptation to prevent excessive fluid and electrolyte loss secondary to tubular immaturity [99].

Tubular function

Sodium

Fractional excretion of sodium (FE_{Na}) falls from 12.8% at 30 weeks to 3.4% at 38 weeks and 1% in the normal adult [100]. Prematurity is associated with significant salt wasting and a risk of hyponatremia. Term neonates have a limited capacity both to conserve sodium necessary for growth and to excrete a sodium load. Excessive administration of sodium to term neonates may cause extracellular volume expansion, edema, and significant hypernatremia with serious short- and long-term consequences [101,102]. Sodium excretion usually exceeds oral intake (breast or formula milk) in the first few days of life, leading to negative sodium balance with associated weight loss. As FE_{Na} falls further and oral intake increases, birthweight is regained in 5–7 days. The ability to excrete a sodium load matures by around 1 year [103].

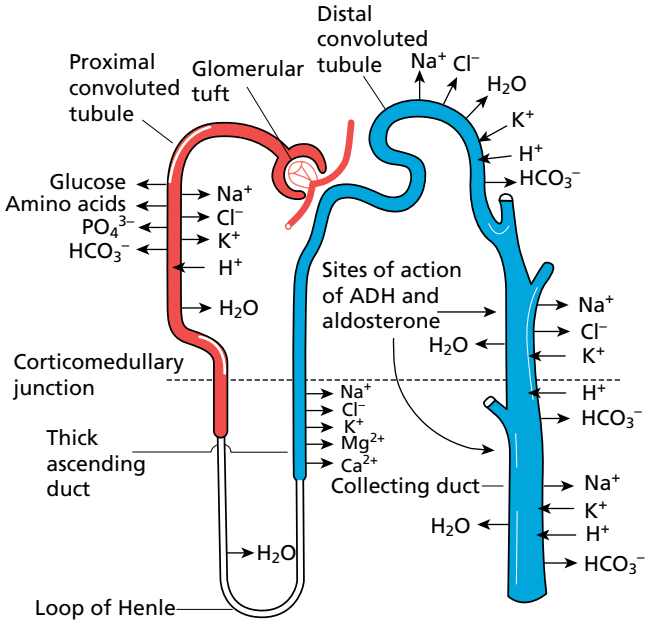

Figure 9.11 Excretion and reabsorption of water and electrolytes. Water is reabsorbed in the proximal tubule together with glucose, amino acids, phosphate, sodium, and bicarbonate, and from the distal nephron under the influence of antidiuretic hormone and the hypertonic medulla. In the distal tubule sodium is reabsorbed under the influence of aldosterone with associated excretion of potassium and hydrogen ions. *Source:* Reproduced from Cumming and Swainson [160] with permission of Elsevier.

Sodium is reabsorbed along the entire nephron length via different mechanisms. A key component is the Na-K-ATPase enzyme, located on the basolateral membrane of tubular cells, which actively transports sodium out of the cell into interstitial fluid and the peritubular capillaries, creating an electrochemical gradient for the movement of sodium out of the tubular lumen (Fig. 9.11). This movement often occurs via specific transporter proteins to which the transfer of many other electrolytes and compounds is coupled. In the neonate, reabsorptive mechanisms in both the proximal and distal convoluted tubule are immature and, despite reduced sensitivity to mineralocorticoids, aldosterone is essential for adequate sodium retention [104].

Water

Infant nutrition is entirely liquid, so a high urine flow rate is necessary to maintain fluid balance. This is achieved with a high fractional excretion of water (FE_{H2O}). Water reabsorption in the proximal convoluted tubule is isotonic. Neonates have reduced plasma protein, so the hydrostatic and osmotic forces acting from lumen to capillary are reduced, resulting in decreased proximal water reabsorption. Distally, water reabsorption is under the influence of antidiuretic hormone (ADH), to which even preterm babies are sensitive. Neonates are able to adjust water excretion appropriately from day 2 of life and can achieve FE_{H2O} of up to 13% (a similar value in adults would produce 20 L of urine per day) [105].

While minimum urine concentration equals adult levels of 50 mmol/kg at birth, maximum urine concentration is only 600–800 mmol/kg, which is about half that of older children. This reflects both shorter loops of Henle and reduced tonicity of the medullary interstitium (urea levels are low, reflecting

the anabolic state of the growing infant). Assuming a solute load of 10–15 mOsm/kg, the minimum urine flow rate required to prevent solute retention is 25 mL/kg/day [106]. This approximates to 1 mL/kg/h and is the basis for the use of this figure as an indication of renal failure.

Potassium

The immature kidney has a reduced capacity to excrete potassium; neonates excrete 9% of the filtered potassium load whereas children and adults excrete around 15%. The main site of potassium excretion is the distal convoluted tubule and cortical collecting ducts. Aldosterone acts on the principal cells of these regions to enhance the activity of the Na-K-ATPase pump on the basolateral membrane, which elevates intracellular potassium. It also increases the permeability of the luminal membrane to potassium, thus promoting its excretion. Aldosterone levels are high in infants but the cellular response is attenuated. In addition, lower tubular flow rates lead to higher potassium concentrations, reducing the gradient for diffusion. Normal values are achieved by around 3 months of age. The reduced ability of infants to excrete potassium is only likely to be of significance in cases of excess administration or pathological cellular release, where hyperkalemia may ensue more rapidly [107].

Glucose

Glucose is completely reabsorbed in the early portion of the proximal convoluted tubule by a stereo-specific transporter protein. The process involves secondary active transport and is saturable (see Fig. 9.11). Term infants have a threshold for glucose that is equal to older children and adults when corrected for GFR. However, premature infants demonstrate significant glucose wasting, which may be due to reduced nephron numbers, reduced basolateral Na-K-ATPase pump activity, or changes in the expression and density of the transporter proteins [108].

Phosphate

Rapid growth requires the normal infant to be in positive phosphate balance; plasma phosphate is high *in utero* and in infancy and decreases with age. Neonates demonstrate a reduced fractional excretion of phosphate that is not attributable to reduced load from a lower GFR. Rather, the immature kidney has an increased ability to reabsorb phosphate in both the proximal and distal convoluted tubules that is independent of parathyroid hormone activity and dietary phosphate. Growth hormone may have a regulatory effect, suggesting that this represents an appropriate physiological response to the need for phosphate, rather than an immature system [109].

Acid–base balance

Neonates have a reduced capacity to maintain acid–base status for several reasons including a reduced ability to reabsorb bicarbonate, secrete organic acid, and produce ammonia and a low level of titratable acid, specifically phosphate. However, the ability to acidify urine is acquired by 1 month, even in premature infants, suggesting that distal tubular hydrogen ion secretion is inducible independent of the gestational age of the kidney [110].

Bicarbonate is usually 85–90% reabsorbed in the proximal convoluted tubule, an energy-dependent process requiring the secretion of hydrogen ions in exchange for sodium. The renal threshold for bicarbonate (the level at which it appears in the urine) is 18 mEq/L in the premature infant, and approximately 21 mEq/L in the term neonate, rising to adult levels of 24–26 mEq/L by around 1 year [111]. Decreased bicarbonate reabsorption may be due to immature luminal Na-H antiporters or a reduced activity of the Na-K-ATPase pump which lowers the driving force for sodium. The main site of hydrogen ion secretion is the distal convoluted tubule, which in maturity can excrete hydrogen against a gradient of as much as 1000:1 (compared to gradients of 4–10:1 by secondary active transport in the proximal convoluted tubule) [112].

Amino acids

Infants demonstrate a transient physiological aminoaciduria in the first few weeks of life. This is unlikely to represent a generalized disorder as not all are wasted to a similar degree [113]. Amino acids are freely filtered at the glomerulus; adults reabsorb 98–99% in the proximal convoluted tubule, against a concentration gradient, using secondary active transport across the luminal membrane and facilitated diffusion across the basolateral membrane (see Fig. 9.11). These specific transport systems exist from birth but do not function at full capacity for reasons that remain unclear [114]. Neonates and infants are more susceptible to dietary protein inadequacies. For example, taurine is important for retinal development and has been shown to be low in plasma of low-birthweight infants receiving PN without supplementation [115].

Control systems

Plasma renin is high in the fetus and is approximately twice adult levels at term. Levels increase for the first few weeks of life and then start a gradual decline until adult levels are reached at around 6–9 years of age. As renin is the rate-limiting step in angiotensin II (AII) production, levels of the latter follow a similar pattern. AII has important trophic effects on the developing renal system. Maternal administration of angiotensin-converting enzyme inhibitors (ACEi) during the second and third trimesters results in renal dysplasia, renal failure, oligohydramnios, and pulmonary hypoplasia [116]. AII is a potent systemic vasoconstrictor in adults; it reduces renal blood flow but preserves GFR by constriction of efferent arterioles. This pressor response is present but reduced in neonates, possibly due to high occupancy of AII receptors by existing high levels of AII. Prostaglandins are the most important counterbalance to AII and mediate afferent arteriole dilatation.

Renal blood flow

The proportion of cardiac output distributed to the kidneys is 2.5–4% in the fetus, 6% by 24 h of life, 8–10% by 1 week, and 15–18% by 6 weeks. Effective renal plasma flow reaches adult levels (corrected for BSA) by 12–24 months [117]. The neonatal kidney can autoregulate its blood flow at appropriately lower systemic perfusion pressures although the response appears to be less efficient. Intrarenal blood flow is distributed differently, with a higher proportion of neonatal blood flow going to juxtamedullary nephrons, leaving cortical nephrons at higher risk of ischemia. The rise in renal blood flow with

maturation is probably due to alterations in cardiac output, perfusion pressure, and renovascular resistance. While AII seems important in maintaining a basal tone, other neurohumoral agents also play a role, including ADH, atrial natriuretic peptide, adenosine, and endothelin [118].

Pediatric renal disease

Acute kidney injury

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines define acute kidney injury (AKI) as an abrupt decrease in kidney function that occurs over a period of 7 days or fewer [119]. It is characterized by the inability of the kidney to fulfill its excretory functions and manage fluid and electrolyte balance appropriately. Causes of AKI may be divided into prerenal injury, intrinsic renal disease, and obstructive uropathies (Table 9.2). Etiology is age dependent: cortical necrosis and renal vein thrombosis are more common in neonates, whereas hemolytic uremic syndrome (HUS) is more common in young children, and rapidly progressive glomerulonephritis (RPGN) is generally found in older children and adolescents.

AKI in hospitalized children is likely to be multifactorial, with prerenal as well as hypoxic/ischemic and nephrotoxic insults being important; those at risk include children with sepsis, those receiving stem cell transplants, those undergoing cardiopulmonary bypass or extracorporeal membrane oxygenation (ECMO), and low birthweight/premature neonates [120].

Epidemiological study has mainly considered acutely ill children in single-center studies and has been limited by the lack of a standardized definition of AKI. Nonetheless, over the last two to three decades there appears to have been a shift in etiology from primary renal disease to systemic illness as the leading cause of AKI. The overall incidence is also increasing, reflecting increased use of invasive management and a higher illness severity of critically ill children [121]. The first attempt at a standard definition came from the Acute Dialysis Quality Initiative group with the RIFLE criteria [122]. These criteria have subsequently been modified three times: the paediatric version of the RIFLE criteria (pRIFLE), the Acute Kidney Injury Network (AKIN) classification, and lastly the KDIGO guidelines [119,123,124]. All use serum creatinine as their biomarker and the clinical measure of urine output. When applied to a paediatric ICU population all three performed well but produced differences in both incidence (between 37% and 51%) and staging [125]. Whilst all have their relative merits the need to adopt a single definition remains.

The use of creatinine as a biomarker is pragmatic but inadequate. Creatinine is a measure of kidney function, not damage, and serum levels do not rise until 48–72 h following injury when significant damage has already occurred. More sensitive biomarkers are required to allow earlier diagnosis and timely implementation of protective and preventive measures. Most promising are panels of investigations including plasma cystatin-C, neutrophil gelatinase-associated lipocalin, urinary interleukin-18, and kidney injury molecule-1 [126].

Prerenal injury

Prerenal injury occurs when blood flow to the kidneys is reduced. If prolonged, this may result in a hypoxic/ischemic acute tubular necrosis. However, this process is not sudden and the insult is reversible provided the kidney is intrinsically normal [127]. Compensatory mechanisms include the relaxation of afferent arterioles under the influence of intrarenal prostaglandins, a response that may be impaired by administration of cyclo-oxygenase inhibitors. The use of these agents to promote ductus arteriosus closure in premature newborns carries a risk of renal insufficiency, although this appears less with ibuprofen than indomethacin [128].

Urinary parameters may assist in distinguishing prerenal from intrinsic renal injury. In response to decreased perfusion, functioning tubules will appropriately conserve sodium and water, producing concentrated urine with osmolality 400–500 mOsm/L, urinary sodium 10–20 mEq/L, and fractional sodium excretion of less than 1%. The renal tubules of neonates are relatively immature so corresponding values for renal hypoperfusion are osmolality >350 mOsm/L, sodium <20–30 mEq/L, and fractional excretion <2.5%.

Tubules that have sustained injury are unable to conserve sodium in this manner, producing dilute urine with osmolality <350 mOsm/L, sodium 30–40 mEq/L, and fractional

Table 9.2 Etiology of acute kidney injury in neonates and children

Type	Etiology
Prerenal	Decreased intravascular volume – dehydration – salt-wasting renal or adrenal disease – hemorrhage – third space losses – sepsis, trauma Renal hypoperfusion (with normal intravascular volume) – cardiac failure/tamponade – hepatorenal syndrome
Intrinsic renal disease	Acute tubular necrosis – ischemic/hypoxic injury – drug induced, e.g. aminoglycosides, contrast agents – toxins – endogenous, e.g. hemoglobin, myoglobin – exogenous, e.g. methanol, ethylene glycol Interstitial nephritis – drug induced, e.g. penicillins, NSAIDs, sulfonamides – idiopathic Rapidly progressive glomerulonephritis Vascular lesions – renal artery or vein thrombosis – cortical necrosis – hemolytic uremic syndrome Uric acid nephropathy and tumor lysis syndrome Congenital abnormalities – hypoplasia/dysplasia with or without obstruction – idiopathic – maternal drugs, e.g. ACEi, NSAIDs – polycystic kidney disease
Obstructive uropathy	Congenital malformations – posterior urethral valves – ureteroceles – vesicoureteric reflux – prune belly syndrome Acquired obstruction – kidney stones – tumors, e.g. sacrococcygeal

ACEi, angiotensin converting enzyme inhibitor; NSAIDs, non-steroidal anti-inflammatory drugs.

sodium excretion of >2%. However, these values require that initial tubular function was normal, and urinary indices are difficult to interpret in those with pre-existing renal disease or those who have received diuretics [129].

Intrinsic renal disease

Hypoxic/ischemic AKI is characterized by early vasoconstriction followed by patchy tubular necrosis, although the mechanism of cellular injury is not yet clear. ATP depletion occurs early and leads to disruption of the cytoskeleton and loss of cellular polarity, with Na-K-ATPase found on the luminal as well as the basolateral membrane. The same mechanism has been shown to contribute to kidney dysfunction in transplanted kidneys [130]. Alteration of vascular tone regulation by nitric oxide and endothelin, as well as the generation of reactive oxygen and nitrogen molecules, may also play a role [131].

Nephrotoxic injury may be caused by a wide variety of agents. Aminoglycoside toxicity is common and thought to be related to lysosomal dysfunction of proximal tubules. The incidence is dose and duration dependent, but is reversible once therapy is discontinued. Hemoglobin or myoglobin in urine produces tubular injury via several mechanisms, including vasoconstriction, precipitation in the tubular lumen, and/or heme protein-induced oxidant stress [132].

Uric acid nephropathy and tumor lysis syndrome are most commonly seen in children with acute lymphocytic leukemia and B-cell lymphoma. The pathogenesis is complex, but an important mechanism relates to the precipitation of uric acid crystals in either tubules or the renal vasculature. The rapid breakdown of tumor cells can also cause severe hyperphosphatemia with subsequent precipitation of calcium phosphate crystals also contributing to AKI. There is growing interest in the role uric acid may play in AKI associated with both heat injury and other etiologies [133].

Prognosis

AKI is far from a benign diagnosis: its presence has been associated with marked mortality increases in paediatric ICU patients with a wide variety of diagnoses. It is also associated with increased length of stay both within and outside an ICU setting [120,125]. In survivors, although clinical recovery of renal function occurs in most cases, one study revealed that 34% of 176 children had reduced renal function or were dialysis dependent on discharge from a tertiary center after an episode of AKI [134]. It appears that histological repair is often incomplete and a progressive focal tubulointerstitial fibrosis can be demonstrated [121]. Children who have apparently recovered from an episode of AKI remain at risk of subsequent renal impairment and this is true for all ages and all conditions [135,136]. The term acute kidney disease has been proposed to define the clinical course following AKI in patients in whom the pathophysiological processes are still active [137].

Chronic kidney disease

Chronic kidney disease (CKD) is defined as abnormalities in kidney structure or function that persist for more than 90 days. The main cut-off value for GFR is less than 60 mL/min/1.73 m^2 although there is some suggestion that a value of <75 mL/min/1.73 m^2 would be more appropriate for children older than 2 years, adolescents, and young adults [138]. CKD is characterized by progressive decline in renal function associated with significant morbidity and mortality. It may present at any age from the antenatal period onwards; because of the renal role played by the placenta, even lethal malformations may not result in biochemical disturbance for several days. Causes of established renal failure (ERF) are given in Table 9.3 [139].

Table 9.3 Etiology and prevalence of established renal failure in children in the UK

Etiology	Percentage
Renal dysplasia with or without reflux	35
Obstructive uropathy	19
Glomerular disease	11
Congenital nephrosis	10
Tubulointerstitial disease	7
Renovascular disease	5
Polycystic kidney disease	4
Metabolic	4
Uncertain diagnosis	3
Malignancy and associated disease	2
Missing from registry	1

Source: Reproduced from Hamilton et al [139] with permission of Karger Publishers.

Cardiovascular disease is much more common in children with ERF than age-matched controls, and accounts for up to 30% of deaths in children undergoing dialysis [140]. Growth retardation is proportional to the decrement in GFR, and is more common in children undergoing dialysis than those being treated conservatively or with a transplant. Factors contributing to poor growth include metabolic acidosis, renal osteodystrophy, malnutrition, glucocorticoid therapy, and reduced responsiveness to growth hormone. Catch-up growth after transplant is poor with 60% of children with CKD having short stature in adulthood. Daily dialysis regimes and use of recombinant growth hormone (rGH) may ameliorate matters although clinical response to rGH is not always maintained and there are concerns about its post-transplant use precipitating rejection [141]. A variety of neurocognitive deficits have been identified, from severe developmental delay to more subtle verbal and attention deficits; improvements in dialysis, correction of malnutrition, and decreased aluminum exposure have improved outcomes [142].

Treatment of CKD in children is not easy; dialysis and the access it requires pose particular problems (see Chapter 30). Only one clinical trial that looked at strict blood pressure control has demonstrated any means of modifying disease progression [143]. Novel urinary and serum biomarkers to quantify and monitor CKD are being investigated and these may assist in developing new treatments [144].

Polycystic kidney disease

In children, polycystic kidney disease mainly consists of two hereditary diseases: autosomal dominant polycystic kidney disease (ADPKD), and autosomal recessive polycystic kidney disease (ARPKD). Worldwide, ADPKD is the most common hereditary renal disease, affecting 1:400–1000 livebirths, but only around 2% of cases present in childhood. By contrast, ARPKD affects 1:10,000–40,000 livebirths but is a disease of children, so the prevalence of each in pediatric practice is

approximately equal [145]. In ADPKD epithelial-lined cysts arise from about 5% of tubules and detach from the parent tubule (usually at about 2 cm). There is massive enlargement of the kidneys secondary to cyst growth and progressive renal impairment. Associated features include hepatic cysts and intracerebral aneurysms. In ARPKD renal cysts arise from the distal collecting duct and cause progressive renal impairment without renal enlargement. Congenital hepatic fibrosis is a universal feature, although renal symptoms are more common in early life and hepatic complications later. In older children, features of hepatic fibrosis and portal hypertension tend to dominate the clinical picture; combined renal and hepatic transplantation is used successfully [146].

ADPKD is caused mainly by two genes: *PKD1* on chromosome 16 encoding the transmembrane protein polycystin 1 (85% of cases), and *PKD2* on chromosome 4 encoding polycystin 2. ARPKD is caused by mutations of the *PKHD1* gene on chromosome 6 which encodes a protein polyductin. All three proteins have been found in primary cilia where they appear to interact and share intracellular signaling pathways that alter intracellular calcium and cAMP levels. Elucidation of these pathways has given rise to new therapeutic strategies. Tolvaptan is a vasopressin V2 receptor antagonist that lowers cAMP in cystic tissues. It is effective at reducing the progression of cystic kidney disease in adults and a trial is ongoing in children [147]. Manipulation of the renin–angiotensin system and the use of pravastatin are also being investigated in this population [148].

Renal cysts also occur in other disease states. Nephronophthisis (NPH) is a chronic tubulointerstitial nephritis. The infantile form is characterized by cortical microcysts and progression to ERF by 5 years of age, whereas cysts occur much later in the juvenile form [149]. Up to 20% of patients with tuberous sclerosis complex (TSC) will have multiple, bilateral renal cysts. The gene *TSC2*, which accounts for around 75% of sporadic cases of TSC, is found within 48 base pairs of *PKD1* on chromosome 16.

Prune belly syndrome

Prune belly syndrome (PBS) occurs in 1:29,000 to 1:40,000 livebirths [150]. It is 20 times more common in males, four times more common in twins, and infants of younger mothers appear to be at greater risk [151]. The syndrome comprises a triad of abnormal abdominal muscles, bilateral cryptorchidism, and dilated ureters. It takes its name from the characteristic wrinkled and prune-like appearance of the abdominal wall in which normal musculature fails to develop [152]. Urinary tract abnormalities include a dilated, thick-walled bladder, tortuous, dilated and thick-walled ureters, and kidneys that may be hydronephrotic or dysplastic.

The mechanism by which PBS occurs remains unclear. Some theories emphasize early urethral obstruction which leads to bladder distension, degeneration of the abdominal wall musculature, and prevention of testicular descent. However, a more convincing theory proposes abnormal mesenchymal development, termed mesodermal arrest, between weeks 6 and 10 as the underlying abnormality. This is supported by findings of abundant collagen, smooth muscle, fibrous and connective tissue throughout the renal tract; these features are difficult to explain with a purely obstructive lesion [153].

Attempts can be made to alleviate lower urinary tract obstruction *in utero* with vesicoamniotic shunting or fetal cystoscopy, and scoring systems have been developed to target treatment appropriately [154]. Renal failure occurs in around 30% of children due to renal dysplasia and scarring secondary to infections. Dialysis is required earlier than in children with other causes of renal failure, and mortality is higher than in those with other obstructive uropathies [155]. The abdominal wall abnormalities do not appear to increase the complication rate associated with peritoneal dialysis if it is required [156].

KEY POINTS: THE RENAL SYSTEM

- Differences in renal function may result in abnormal electrolyte function and make neonates more subject to excessive fluid and electrolyte administration
- Neonates have reduced ability to correct acid–base abnormalities due to immature ability to resorb bicarbonate and secrete acids
- Glucose wasting is increased in preterm neonates due to reduced numbers of nephrons and glucose transporters. This may result in an osmotic diuresis and hypovolemia

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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Further reading

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CHAPTER 10
Pharmacology

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Introduction

Children are not small adults. Their body hydric content, and the partition between central and peripheral blood, their metabolic rates, their pulmonary volumes, and cardiac and hemodynamic variables markedly differ from those of adults. However, *children are also small adults* in that they have the potential of their future in their genes. Some phenotypic expression may be absent in the early life, but most genetic traits are fully expressed at birth.

Development of uptake, distribution, protein binding, metabolism, and excretion systems for drugs in the fetus, newborn, infant, and child [1]

Uptake, disposition, and elimination

Volumes, flows, and rates

Body composition differs markedly among neonates, infants, and adults (see Chapter 11). This is particularly important for total body water, which decreases from 80–85% of bodyweight in 26 and 31 weeks' gestation infants to 75% at full term and to 60% in adolescents. The extracellular compartment, which is mainly regulated by the sodium intake after birth, decreases from 65% of bodyweight at 26 weeks' gestation to 40% at full term and 20% by 10 years [2,3]. Therefore, the volume of distribution of hydrophilic drugs, e.g. succinylcholine, is higher in newborns and infants than in older children. Membranes are also immature at birth. For example, drug efflux systems are not fully mature at birth, making cerebral bioavailability of numerous hydrophobic (the term hydrophobic will be used instead of lipophilic throughout the text) drugs higher in newborns than in children or adults [4,5]. Cardiac output is also different and is closely related to body surface area. The volume of the central compartment of volatile anesthetics is higher in neonates than in adults on a weight basis.

Scaling

Until recently, the only way of correcting for these differences was to use the rule of three, i.e. to divide by 70 kg or 1.73 m^2 and multiply by the weight or surface area of the subject. Different approaches are used today [6–8]. Allometric scaling considers that extensive parameters, such as metabolic rates or clearances, are related to the corresponding adult parameters raised to an empirical power:

$$CL_{Ped} = CL_{Adult}\left(\frac{BW_{Ped}}{BW_{Adult}}\right)^{x}$$

where CL_{Ped} and CL_{Adult} are the pediatric and adult parameters respectively (clearance in this example) and BW_{Ped} and BW_{Adult} are the pediatric and adult bodyweights respectively; x is the empirical scaling factor. This approach has excellent predictive powers when incorporated in pharmacokinetic (PK) or pharmacodynamic (PD) models (Fig. 10.1) [9]. Allometric scaling cannot account for all the changes observed during development. Therefore, other approaches, such as physiological models, may provide more accurate results [7,10].

Uptake and absorption

The gastric pH rapidly increases from 1–3 to 5–7 immediately after birth and remains basic during the first month of life [11]. Gastric emptying and intestinal transit are also slower in

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

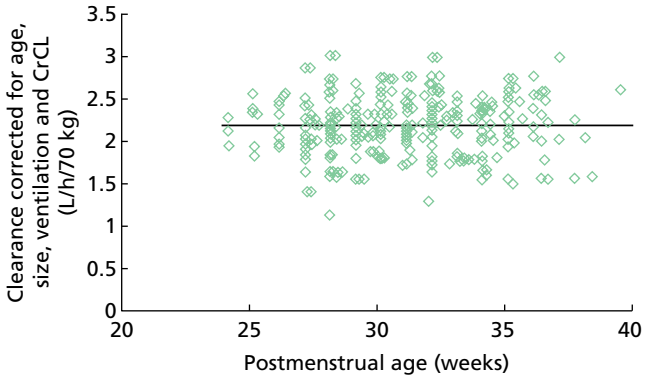

Figure 10.1 Predicted vancomycin clearances in individual premature babies. The data are standardized to a 70 kg person, using allometric scaling, and corrected for age and creatinine clearance (CrCL) (NONMEM). Simple covariates included in the model markedly decreased interindividual variability. *Source:* Reproduced from Anderson et al [9] with permission of John Wiley and Sons.

newborns than in infants and adults. The rate and extent of gastric and intestinal absorption are variable, due to immature membrane transport, pancreatic enzyme activity, and bile salt secretion. Oral medications may have erratic bioavailability and absorption rates in this age group. Also, the first-pass effect is often reduced in neonates due to immature liver metabolism. Consequently, drug potency may increase in some cases.

Absorption by other routes is often rapid in infants and children. For example, after topical anesthesia of the pharynx and larynx, peak concentrations of lidocaine may appear 2–4 min later [12]. Lidocaine toxicity has occurred following infiltration of the drug for laceration repair in young patients. Because the rate and extent of absorption depend on the drug and site of injection, this topic will be discussed in the PK section for each drug.

Transport of molecules across membranes: the effect of transporters

Drugs are small molecules that are susceptible to passive or active transport through biological membranes. Uptake and elimination transporters are found in all cell membranes [13,14]. Two superfamilies of transporters, the solute carrier (SLC) and ATP-binding cassette (ABC), control molecular traffic across membranes [4,15]. While SLC transporters are usually for uptake, some are involved in bidirectional transport. ABC transporters are efflux pumps that remove chemicals from the cell.

The organic anion transporting polypeptides (OATPs), the organic cation transporters (OCTs), and the organic anion transporters (OATs) are the principal solute carrier transporters. These membrane proteins are localized to the sinusoidal boundary in heart, liver, brain, kidney, and placenta. One SLC family, the multidrug and toxin extrusion transporters (MATEs), excretes oxaliplatin, cimetidine, metformin, and procainamide from cells.

ATP-binding cassette transporters comprise P-glycoprotein (P-gp), which is encoded by a variety of multidrug resistance (MDR) genes and the MDR-associated proteins. These are excretion pumps that transport endo- and xenobiotics such as unconjugated bilirubin and anticonvulsants. Like SLC transporters, these transporters are ubiquitous in the blood–brain barrier (BBB), blood–CSF barrier, gut and intestinal wall, hepatocytes, and renal tubular cells [16]. P-gp is located at the luminal membrane of endothelial and epithelial cells. P-gp appears in human brain as early as 22 weeks' gestational age (GA) and is almost totally mature at birth [17]. All these transporters are highly polymorphic. In conjunction with polymorphism of the 3A4 and 2C9/19 isoforms of the cytochrome P450 or of UDP-glucuronosyltransferase (UGT) 1A and 2B, polymorphism of P-gp increases resistance to most antiepileptic drugs (phenytoin, carbamazepine, phenobarbital, gabapentin, felbamate, topiramate, lamotrigine, valproic acid, diazepam, and lorazepam).

To date, little is known about the ontogeny of these transporters. The human fetal liver has only a small number of transporters. mRNA expression of SLC and ABC transporters increases from birth to 4 years of age and full expression is attained by 7 years [15,18]. Similar findings have been reported in the kidneys and gut.

P-gp has been detected as early as 22–26 weeks' human GA in some parts of the brainstem. By term, P-gp seems to be fully functional. Multiple drug resistance-associated protein 1 (MRP1) is detected in the fetus at 22–26 weeks' GA and has almost the same intensity as in adults. This is consistent with observations that the choroid plexus and tight junctions are mature before birth, which makes the blood–CSF barrier functional [5,16]. Lipids and possibly small hydrophobic molecules can cross the barrier with less selectivity until 6 months of age.

Disposition of drugs: transport in the blood and distribution

After either intravenous injection or administration by another route, drugs distribute within the body. Because cardiac output and the central compartment volume are larger than those of adults, distribution of drugs to target organs occurs more rapidly in young patients. Sophisticated models that tentatively explain the relationship between age, volumes, clearance, and the dose required to produce anesthesia have been described. However, population PK-PD models using age as a covariate and parameters such as the exit rate constant from the effect compartment (ke0) and the pseudo-steady-state concentration leading to half maximum effect (Cpss50 or Ce50) are now used to characterize the disposition of drugs from the central to the effect compartment and the resulting effect [19,20]. The ke0 is equivalent to the rate constant for transfer from the central compartment to the effect compartment at steady state. This parameter (or T½ke0, the corresponding half-life) is the best indicator of a drug's access rate to its target. It is directly related to time to peak action. Ce50 is the concentration of the drug in the (virtual) effect compartment and is approximated by Cpss50, the drug concentration in the effect compartment at steady state. Drugs also distribute in deeper compartments, depending on plasma and tissue protein binding, hydrophobicity, pKa, steric bulk, and clearance when steady state is not attained. This distribution process is important because it is the main factor that causes differences in delay of awakening after short or prolonged administration of drugs (volatile anesthetics, propofol). This has led to the concept of context-sensitive half-time [21]. In addition, distribution into deep compartments

(including gastric and bowel contents) may cause recirculation of drugs such as fentanyl when cardiac output and body temperature increase after surgery.

Protein binding

Many drugs are bound to serum proteins, mostly albumin (human serum albumin – HSA) and α1-acid glycoprotein (AGP). Acidic drugs such as thiopental (thiopentone) and propofol bind preferentially to HSA and basic drugs to AGP. Protein-bound molecules may or may not cross barriers depending on factors such as the nature of binding (rate of association–dissociation to the receptor) and the organ transit time [22,23]. In the liver, the presence of the space of Disse slows transit times. Clearance of drugs metabolized by the liver is frequently independent of protein binding [24]. In organs with rapid transit times, such as the brain and heart, protein binding often controls the amount of drug absorbed by the organ.

Serum albumin is the most abundant protein in plasma (approximately 0.6 mM). It contains three homologous helical domains (I–III) with binding pockets. HSA has two major high-affinity binding sites with association constants in the range 10^4 to 10^6 M^{-1} [24,25]. Site 1 binds warfarin, thiopental, propofol, and many other drugs. Site 2 binds endogenous carboxylic acids (eicosanoids, fatty acids), propofol, volatile anesthetics, and most non-steroidal anti-inflammatory drugs (NSAIDs), often in a stereospecific and allosteric manner (Fig. 10.2). Some metabolites of NSAIDs bind covalently, leading to permanent occupation of the site. Bilirubin also binds to multiple sites on HSA [26]. Drugs such as propofol can displace bilirubin, increase the amount of free bilirubin, and possibly produce kernicterus in newborns [27].

AGP, also called orosomucoid (ORM) is an acute-phase protein. At birth, AGP concentrations are about one-third to one-fourth adult concentrations and increase slightly over the next 9–12 months [28,29]. The first consequence of reduced AGP is increased free drug that can cross barriers (BBB, blood–heart), causing increased drug effects. The second consequence of the increased amount of free drug is a greater apparent total hepatic clearance than is expected for drugs with low hepatic clearance, e.g. bupivacaine. AGP has two to three high-affinity sites that mostly bind basic drugs [30,31]. However, some acidic drugs (e.g. phenylbutazone) and neutral drugs also bind to AGP. Three genetic variants (A, F1, and S) cause two main forms (F1S and A) that differently bind xenobiotics. During inflammatory processes, the AGP concentration and its affinity for drugs markedly increase. During the postoperative period, the AGP concentration almost doubles (Fig. 10.3). For drugs with low to moderate hepatic extraction ratios, such as bupivacaine, this may produce time-dependent changes in total clearance (but not in the intrinsic clearance of the free drug) after surgery (Fig. 10.4) [28]. Like most basic drugs, local anesthetics and phenylpiperidine opioids (fentanyl, sufentanil, alfentanil) are primarily bound to AGP.

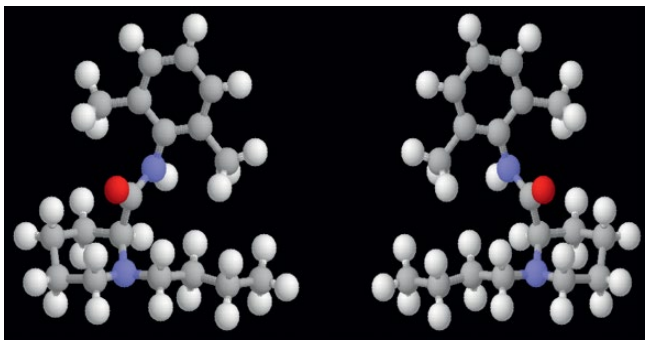

Figure 10.2 The two enantiomers of bupivacaine. The chiral carbon is at the center of the molecule. Numerous drugs such as volatile anesthetics, non-steroidal anti-inflammatory drugs, ketamine, etomidate, and local anesthetics have different stereoisomers, either true enantiomers with a chiral center or other isomers.

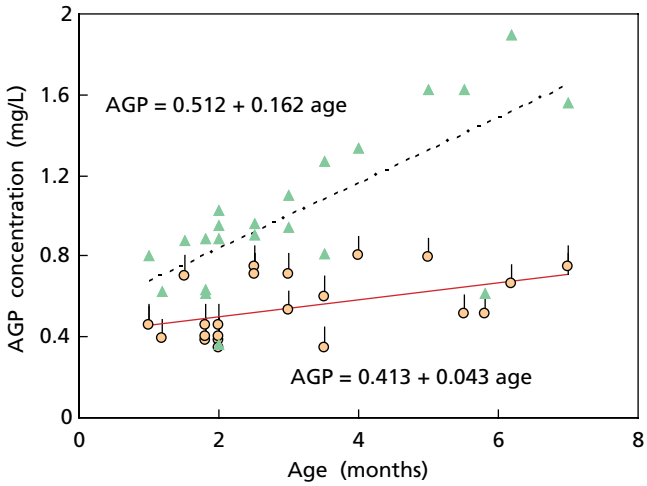

Figure 10.3 α1-Acid glycoprotein (AGP) concentrations in infants according to their age. AGP concentrations are very low at birth and progressively increase with age. The concentration of AGP increases rapidly after an inflammatory insult. Circles are individual values measured before surgery and triangles are the values measured 2 days later. AGP concentrations increased in all patients after surgery. *Source:* Reproduced from Meunier et al [28] with permission of Wolters Kluwer.

Protein–drug adducts

Binding of drugs to proteins may be entropy driven (passive phenomenon as with xenon) or enthalpy driven (usually exothermic) [32]. This causes strong binding of the drug (covalent, van der Waals forces). Covalent binding of drugs or their metabolites to tissue or plasma proteins produces mostly toxic protein–drug adducts [33]. These adducts often induce immunological reactions that cause hypersensitivity. The toxicity of halothane, paracetamol (acetaminophen), diclofenac, sulfonamides, and valproic acid is the result of adducts.

During cardiopulmonary bypass the concentration of unbound propofol increases significantly due to decreased protein binding [34]. This is probably true for most drugs with strong protein binding.

Metabolism and clearances including genetic polymorphism

Renal function

Renal function (glomerular filtration rate and tubular function) is immature at birth. Therefore, elimination of most renally excreted drugs and their active metabolites is impaired until 2–3 years of age. For example, theophylline and caffeine have very low clearances at birth. In the same way, morphine-6-glucuronide, which is an active metabolite of

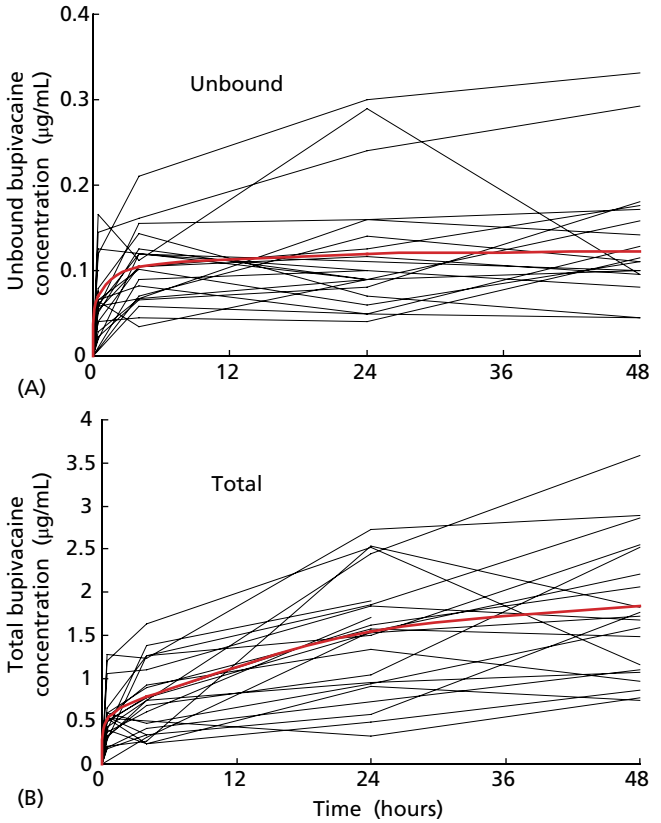

Figure 10.4 Unbound (A) and total (B) bupivacaine concentration in plasma after epidural administration (bolus at T0 followed by a continuous infusion of 0.375 mg/kg/h for 2 days). Black lines are individual data and red lines are population value fitted using NONMEM. The unbound concentration reaches steady state in less than 12 h, whereas the total concentration has not reached steady state 48 h after initiating the infusion. The continuous increase in α1-acid glycoprotein concentration caused by the inflammatory process increases protein binding. However, the unbound concentration, which is the toxic moiety, is at steady state because intrinsic hepatic clearance remains constant. *Source:* Reproduced from Meunier et al [28] with permission of Wolters Kluwer.

morphine, accumulates in premature and full-term infants, increasing the risk of respiratory depression [35,36]. Drugs such as aminoglycoside antibiotics may also be toxic. Prostaglandin concentrations are elevated in newborns to maintain an effective glomerular filtration rate. By blocking the effects of prostaglandins, NSAIDs may induce renal hypoperfusion and renal failure [3].

Hepatic metabolism [37–40]

Most drugs used for anesthesia, preoperative care, and pain control are metabolized by the liver. Hepatic metabolism of xenobiotics is by phase I and phase II reactions. Phase I reactions are characterized by microsomal oxidative metabolism that inactivates or sometimes activates the drug (Table 10.1). Phase II reactions involve conjugation and take advantage of the electrophilic properties of either the original drug or the product of phase I metabolism (Table 10.2) [39,40]. Phase II reactions occur mainly in the liver but can occur in the gut wall, the kidney parenchyma, and the lung. Enzymes involved in phase I reactions are located primarily in endoplasmic reticulum, while phase II conjugation enzyme systems are primarily cytosolic.

Cytochrome P450 is a family of enzymes located primarily at the centrilobular portion of hepatic lobules. CYP3A4 is the most abundant isoform (Fig. 10.5) [41–44]. Two factors characterize the importance of an isoform for metabolizing a given molecule: the capacity, i.e. the abundance of the enzyme; and the affinity and rate of metabolism (Km and vm in the Michaelis–Menten equation). Xenobiotics may be substrates for, inhibitors of, or inducers of the reaction and cause drug–drug interactions that have clinical consequences. Maturation of these enzymes is variable and occurs from early in intrauterine life to several years of age. For example, morphine elimination via UGT is impaired until 9 months of age [35,36,45] whereas fentanyl, which is metabolized by the CYP3A4/3A7 isoform of cytochrome P450, is adequately metabolized by very young preterm infants [46]. Ropivacaine metabolism by CYP1A2 is not fully mature before the age of 4–6 years [47].

Children are small adults

Individuals have the potential of their future in their genes. Some phenotypic expression may be absent early in life, but most genetic traits are fully expressed at birth. The most common factors influencing drug dosing are related to genetic polymorphism of metabolizing enzymes [48–54].

Polymorphism of CYP2D6 may increase rates of biotransformation of tramadol to the opioid receptor agonist O-desmethyl tramadol (M1) [55]. Codeine is also metabolized to morphine by CYP2D6 [56,57]. One death is suggested to have occurred when a breast-feeding mother extensively metabolized codeine to morphine postoperatively [58]. The increased amounts of morphine in breast milk caused severe apnea and death of the infant. Toxic events have been reported in infants and young children treated with codeine for more than one day, in children with renal failure [59], and also in children receiving tramadol after tonsillectomy [60]. On the other hand, about 5–8% of Caucasians and 20–25% of Japanese metabolize codeine poorly and do not obtain analgesic effects from the drug [61].

KEY POINTS: DEVELOPMENTAL DETERMINANTS OF PHARMACOLOGY

- Children are not small adults:
  - Their volumes, rates are different from those of adults
  - Transport of small molecules across membranes (e.g. the blood–brain barrier) is immature
- Children are small adults:
  - Genetic polymorphism is an important determinant of drug action and side effects, e.g. CYP2D6 duplication

Pharmacokinetics and pharmacodynamics of inhaled anesthetics

Gases and vapors were the first agents used for general anesthesia (ether in 1842, nitrous oxide in 1844, and chloroform in 1847). Their mechanism of action is far from fully elucidated,

Table 10.1 Hepatic metabolism of the agents used in anesthesia and perioperative care. Phase I metabolism

	Cytochrome P450 isoform					
	1A2	**2A6**	**2B6**	**2D6**	**2E1**	**3A4/5[1] (3A7)**
Early expression in liver	1 mo	1 mo	1 yr	1 w	Birth	
50% of adult activity	1 yr	1 yr		6 mo	1 yr	
90% of adult activity	4–6 yrs				4–6 yrs	
Variability between subjects due to polymorphism	Up to 60-fold			Up to 60-fold	Up to 50-fold	Up to 60-fold
Halogenated agents						
Halothane		++			++[2]	++
Isoflurane		+/–	?		+	
Sevoflurane			+/–		+[3]	
Desflurane			?		+/–[3]	
Propofol[4]			+++	I	II	I
Ketamine			+++			++ I
Midazolam			+			+++
Dexmedetomidine		++				
Opioids						
Fentanyl						+++
Alfentanil						+++
Sufentanil						+++
Tramadol				+++		+
Codeine				+++		
Amide local anesthetics						
Lidocaine	++		+/–			++
Bupivacaine	+					+++
Ropivacaine	+++		+/–			++
Acetaminophen	+				++	+
Caffeine	+++				+	+

Other isoforms involved: 2C8/9: most NSAIDs, phenytoin, barbiturates, ketamine and to a small extent caffeine; 2C19 diazepam, barbiturates, and proton pump inhibitors. CYP2C19 is subjected to important polymorphism. The isoform(s) involved in the metabolism of thiopental and etomidate remain(s) to be characterized.
(1) CYP3A7 is active in the fetus as early as 50–60 days after gestation, with a progressive switch to CYP3A4 after birth.
(2) The 2E1 isoform is responsible for the formation of toxic metabolites involved in hepatic toxicity.
(3) Desflurane is the least metabolized agent; sevoflurane metabolism is very low before the age of 4 yrs because of immaturity of CYP2E1.
(4) Propofol is also metabolized by CYP2C to a lesser extent.
+, substrate for the CYP isoform; I, inhibitor of the CYP isoform; mo, month after birth; yr, year after birth; w = week.

Table 10.2 Hepatic metabolism of the agents used in anesthesia and perioperative care. Phase II metabolism

	NAT2	**SulfoT**	**Uridine 5'-diphosphate (UDP)-glucuronosyltransferases (UGT)**							
			1A1	**1A3**	**1A4**	**1A6**	**1A8**	**1A9**	**2B7**	**2B10**
Early expression in liver	1 T	Early in the fetus	Birth	2 T		Birth			10–20%<1 T	
50% of adult activity				2 yr		6 mo			1 mo	
90% of adult activity			3–6 mo			Puberty			6 mo	
Bilirubin			+++[1]							
Morphine				+ in the neonate			+		+++	
Codeine									+++	
Buprenorphine			+	+++					+	
Propofol							++	+++		
Dexmedetomidine					+++					+++
Acetaminophen		++ in the fetus				+++		++		
Isoniazid	+++									
Sulfonamides	+++									
NSAIDs			+	++				++	+++	

Diazepam strongly inhibits the metabolism of morphine and codeine; ketamine inhibits the metabolism of morphine; ranitidine inhibits the metabolism of morphine and acetaminophen. Rifampin is an inducer of metabolism of codeine, morphine, acetaminophen, lamotrigine, propafenone. Phenobarbital (and possibly thiopental) and phenytoin are inducers of acetaminophen metabolism, which may enhance its toxicity.
(1) The lack of the 1A1 isoform induces the autosomal recessive Crigler–Najjar and Gilbert syndromes.
+, substrate for the isoform; I, inhibitor of the isoform; mo, month after birth; NAT2, N-acetyltransferase type 2; NSAIDs, non-steroidal anti-inflammatory drugs; SulfoT, sulfotransferase; T, trimester of intrauterine life; yr, year after birth.

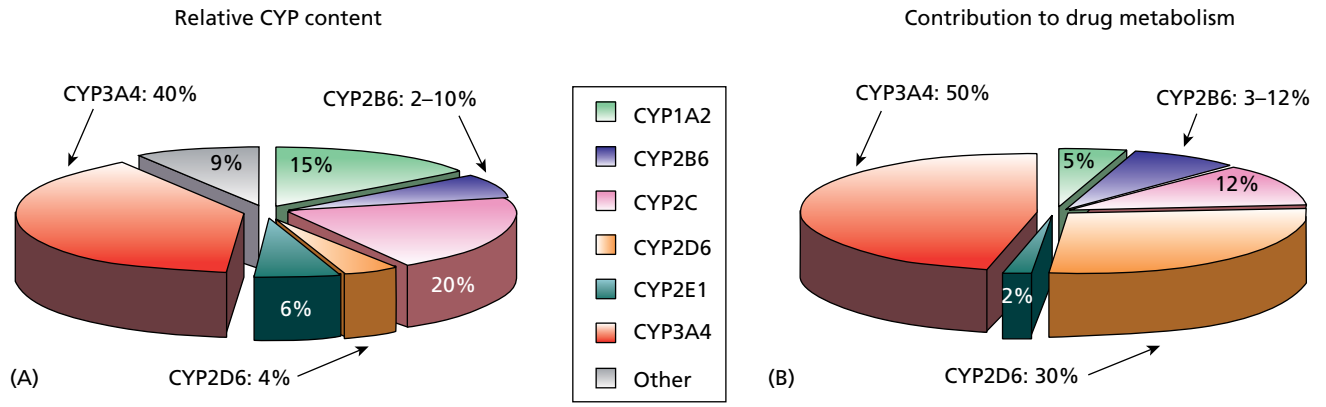

Figure 10.5 Cytochrome P450 isoforms in the liver. Relative content (A) and relative contribution for drug metabolism (B). *Source:* Reproduced from Wang and Tompkins [272] with permission of Bentham Science Publishers.

even today [62,63]. A thermodynamic effect on biological membranes has long been thought to be their mode of action. Now specific effects of these drugs on ion channels and receptors are favored. However, a body of facts leads one to think that there is a complex combination of these actions. The Meyer–Overton theory (and other related theories) is based on the observation that anesthetics non-specifically disturb the physical organization of membranes by solubilizing into lipids. There is still debate on the validity of the Meyer–Overton rule [64,65]. Interestingly, xenon, which is a rare gas, binds non-specifically to proteins, mainly by weak van der Waals forces [66,67]. A unified theory combining non-specific thermodynamic effects on the lipid bilayer and direct inhibition of excitatory neuronal channels is emerging, tentatively explaining the specific effect of anesthetics on the spinal cord [68,69]. Indeed, all anesthetic agents provoke immobility, even when noxious stimuli induce sympathetic responses. In addition, isobolographic analysis and response-surface curves of a combination of agents (both intravenous (IV) and volatile) show only additivity, which is a strong argument for a common mechanism of action [70–72].

In the usual conditions of pressure and temperature, nitrous oxide and xenon are gases, whereas halogenated anesthetic agents are in liquid form (desflurane boils at 22.8°C, thus necessitating special vaporizers) (Table 10.3). N_2O is now the single most important ozone-depleting substance emitted [73]. In addition, halogenated volatile anesthetics (and N_2O) are greenhouse gases. Twenty-year global warming potential ((GWP (20)) values and the carbon dioxide equivalent calculated at 1 minimum alveolar concentration (MAC) show a ratio of 2.2, 1, and 26.8 for isoflurane, sevoflurane, and desflurane respectively [74].

Nitrous oxide

Nitrous oxide (N_2O) is a gas with a molecular weight of 44 Da and a blood/gas distribution ratio of 0.47. At an inhaled concentration of 70%, rapid equilibrium takes place between the inspired and expired fractions of N_2O [75–77]. The kinetics of N_2O are rapid; the deep peripheral compartment is no greater than 8–10 L. Severinghaus first recognized this when he demonstrated that N_2O does not follow the Kety principle, thus leading to the first description of context-sensitive times. When administration is discontinued, elimination is rapid. Even after several hours of administration, elimination is only slightly delayed. In addition, because N_2O is rapidly diffusible, the phenomenon of diffusion hypoxia or "Fink effect" may occur when room air is administered in patients previously breathing a mixture of N_2O and O_2 [78,79]. Because of its ability to diffuse into cavities, N_2O should be used with caution when middle ear or bowel pressures are critical. N_2O has a MAC of at least 104% [80], and N_2O has an additive effect with volatile and IV anesthetics. In addition, N_2O has euphoric, neuroprotective, analgesic, and antihyperalgesic properties, probably because of its effect on the N-methyl-D-aspartate (NMDA) receptor [81,82]. It is why a 50% mixture of N_2O and O_2 is often used outside the operating room for sedation and analgesia. N_2O increases postoperative nausea and vomiting. N_2O moderately increases cerebral blood flow (CBF) and decreases vascular resistances. The net results on intracranial pressure (ICP) vary, but it usually increases [83].

Xenon

Xenon (Xe) is the heaviest non-radioactive natural noble gas (molecular weight (MW) 131.3). It is a dense monoatomic gas with a density of 5.89 and a high viscosity of 2.3 Pa/s (both under normal conditions). The high viscosity may theoretically render its use difficult in patients with increased airway resistances and in premature infants [84]. Its MAC is 70%. Xenon reaches 90% equilibrium between inspired and alveolar gas concentration after 5 min of administration. Because of its large atomic polarizability, xenon binds within cavities in all proteins [66,67,85]. This is why xenon has been considered to act by physical properties, such as the Meyer–Overton rule or the London dispersion forces (or weak van der Waals forces). Like N_2O, xenon acts as a low-affinity use-dependent NMDA receptor antagonist, but while xenon inhibits ketamine-induced c-fos expression in the rat cortex, N_2O enhances it [86,87]. In addition, xenon is a potent antinociceptive agent. This effect is thought to be independent of the opioid or adrenergic pathways. The mechanisms involved seem different from those implicated in neuroapoptosis caused by ketamine or halogenated agents.

In preliminary studies, xenon successfully protected the brains following neonatal asphyxia [88]. Another interesting property of xenon is cardiovascular stability and cardioprotection. Xenon does not alter myocardial contractility nor

Table 10.3 Gases and volatile anesthetics: physicochemical properties and pharmacokinetics

	Halothane	Isoflurane	Desflurane	Sevoflurane	N_2O	Xenon
MW (Da)	197	184	168	200	44	133
Partition coefficient (calculated from LogP)	200	126	398	631	3	–
Density (air = 1.29, helium = 0.18) (g/L, 0°C, 760 mmHg)	1.87	1.50	1.5	1.52	1.94	5.89
Viscosity (air = 1.83, helium = 1.97) (Pa/s, 25°C, 760 mmHg)	–	–	–	–	1.46	2.3
Boiling point (°C at 760 mmHg)	50	48	23	57	–88	–108
Vapor pressure (mmHg at 20°C)	244	238	669	170	57.9	–
Pressure at critical point	–	–	–	–	71.7 at 36.4°C	58 at 16.5°C
Blood/gas partition coefficient	2.40	1.40	0.45	0.65	0.47	0.12
Brain/blood partition coefficient	1.9	1.6	1.3	1.7	1.1	–
Percent metabolized	15–20	0.2	0.02	3.0	0.004	<0.001
Vss (L)#	148	69	19	38	–	–
MAC in adult (vol %)	0.76	1.15	6.0	2.0	104	70
Ce50 (%)	–	0.60–1.3	4.0–6.0	1.12–1.5	170	–
T½ ke0 (min)	–	3.2–4.3	0.9–1.3	2.0–3.5	–	–

#Vss, the total volume of distribution is for an average adult weighing 70 kg, with a cardiac output of 5 L.
T½ ke0 from BIS, Shannon or approximate entropy or from the Narcotrend give similar results.

does it markedly changes vascular tone. Xenon preconditioning before an ischemic insult has then been observed both at the neuronal and myocardial level. Like local anesthetics, xenon modulates the inflammatory response of the immune system by decreasing the production of tumor necrosis factor (TNF)-α and interleukin (IL)-6 by monocytes in response to stimulation by lipopolysaccharide (LPS) [86]. The problem of industrial production and cost will certainly limit the use of xenon in the near future.

Halogenated agents

Halogenated agents are small molecules with MW from 168 to 200 Da (see Table 10.3) [89–91]. They are mildly hydrophobic and dissolve rapidly in blood and tissue. Halothane is an alkane substituted with bromide, chloride, and fluoride. Isoflurane, sevoflurane, and desflurane are ethers, substituted with chloride and fluoride (isoflurane) or fluoride alone (desflurane and sevoflurane). Halothane, enflurane, and isoflurane are chiral drugs, i.e. they have an asymmetric carbon, and they are marketed as racemic mixtures. Sevoflurane is non-chiral. Degradation of sevoflurane with CO_2 absorbents induces the formation of compound A, which is toxic for the kidney of rats [92]. However, the risk in humans seems almost non-existent [93].

Mode of action

The principal effect of anesthetic agents is to provoke immobility through effects that occur at the spinal cord level. Apart from the Meyer–Overton theory (see section "Pharmacokinetics and pharmacodynamics of inhaled anesthetics"), the mechanism of action of halogenated agents is thought to be related to interactions with ion channels and receptors in spinal cord and brain [62,63,94]. They simultaneously enhance the activity of the γaminobutyric acid receptor, A subunit (GABAA) and glycine receptors and inhibit glutamate receptors (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainite, and NMDA receptors). They also inhibit the neuronal nicotinic receptors, a mechanism that is common with N_2O and xenon. NMDA inhibitors are known to protect against ischemia-reperfusion and to suppress the hyperalgesia induced by surgery. However, they also promote apoptosis through the mitochondrial pathway, particularly in the developing brain [95,96].

Pharmacokinetics

All halogenated agents bind to HSA in the following order: desflurane>isoflurane>halothane>sevoflurane [94,97–99]. HSA binds approximately 3 moles of anesthetic/mole of HSA.

Halogenated agents are absorbed and eliminated by the blood–alveolar interface. These agents, which are hydrophobic, distribute in deep compartments, and trace amounts can be measured in expired gases several weeks after anesthesia. Their hydrophobicity allows rapid transfer to the effect compartment and absorption by the fat. The agents with low solubility (see Table 10.3) rapidly reach saturation, i.e. pseudo-steady state [90,100]. The consequence is a more rapid induction of anesthesia and less context-sensitive increase in decrement time. Because an important amount of data are available on the solubility of these molecules in organs, as well as regional blood flows and volumes, physiological kinetic models have often been used to describe the time-course of halogenated agents in the body. Classical compartmental models are now preferred, mainly because they allow simple interpretation of basic parameters such as volumes, clearance, and half-times, and easy application to clinical situations [101–106]. The pharmacokinetics of halogenated agents is best described by first-order kinetics, using linear mammillary models. After inhalation of a gas containing the vapor, transfer from alveolar gas to blood is rapid, and distribution to peripheral compartments, including brain (effect compartment), occurs. Elimination occurs via the same route, except for the variable amount of drug that is metabolized by the liver. The alveolar fraction of vapor (F_A) is considered to reflect the arterial concentration, and the inspired fraction (F_I) the concentration in the invasion compartment. During induction of anesthesia, the F_A/F_I ratio (alveolar to inspired fraction) versus time reflects the rate of invasion (washin). After drug administration is discontinued, the ratio of alveolar fraction to alveolar fraction at the time of discontinuation (F_A/F_{A0}) reflects elimination (washout). The end tidal fraction (FET) (%) or end tidal partial pressure (mmHg) usually approximates F_A.

The uptake and elimination of volatile anesthetics depend on cardiac output and the extent of ventilation. As always in pharmacokinetics, there is no direct correspondence between physiological and kinetic compartments. The volume of the central compartment depends on cardiac output and clearance; clearance depends on both minute ventilation and cardiac output. In an analogy with hepatic clearance of drugs eliminated by liver metabolism, ventilation is equivalent to intrinsic (metabolic) clearance and cardiac output (CO) to hepatic blood flow. Because CO is a major scaling factor it would be interesting to have data relating CO and uptake and elimination in pediatrics [107]. It is also important to remember that 40% of halothane entering the body is eliminated by hepatic metabolism [101,102,108,109].

Context-sensitive decrement times

Because the kinetics is multicompartmental (steady state is not attained before several days of administration, mainly because intercompartmental clearances are very slow), the observed decline is highly context sensitive [70,104]. After a short period of administration (less than 30 min) the decline of F_A/F_{A0} of sevoflurane or desflurane is faster than that for N_2O. This is due to the fact that N_2O reaches near steady state by 20–30 min, whereas sevoflurane or desflurane are at about 60–80% of steady state by this time. After 90 min, the difference between agents becomes clinically significant (Fig. 10.6). As with the effects of minute ventilation and cardiac output on kinetics, pediatric data describing decrement times as a function of age are lacking. Moreover, most articles are now based on data files generated with the aid of software (e.g. GasMan®, Med Man Simulations, Boston, MA, USA) and do not verify their adequacy with data from patients.

Pharmacodynamics

The measure of anesthetic action has been the subject of research for more than 40 years. The initial criterion was the MAC leading to a specific effect in 50% of the patients studied [110]. The MAC is the equivalent of Ce50 for IV agents. The concept of the MAC is based on the strong assumption that alveolar concentration is almost immediately in equilibrium with the cerebral concentration and adequately reflects the concentration at the neuronal effect site. MAC is defined as the alveolar concentration of volatile anesthetic agent (in oxygen or in a mixture of oxygen and N_2O) that abolishes the movement response to skin incision in 50% of subjects tested. One may also consider other effects, such as the cardiovascular depression induced by these agents, depression which is particularly important in neonates and in infants. The MAC has a great number of variations that have appeared over time: MACINT, which is the MAC for tracheal intubation, MACBAR, which is the MAC for abolition of sympathetic response to incision (tachycardia and increase in blood pressure), MACEXT, which is the MAC for deep tracheal extubation, and others [111–115]. The MAC of isoflurane was

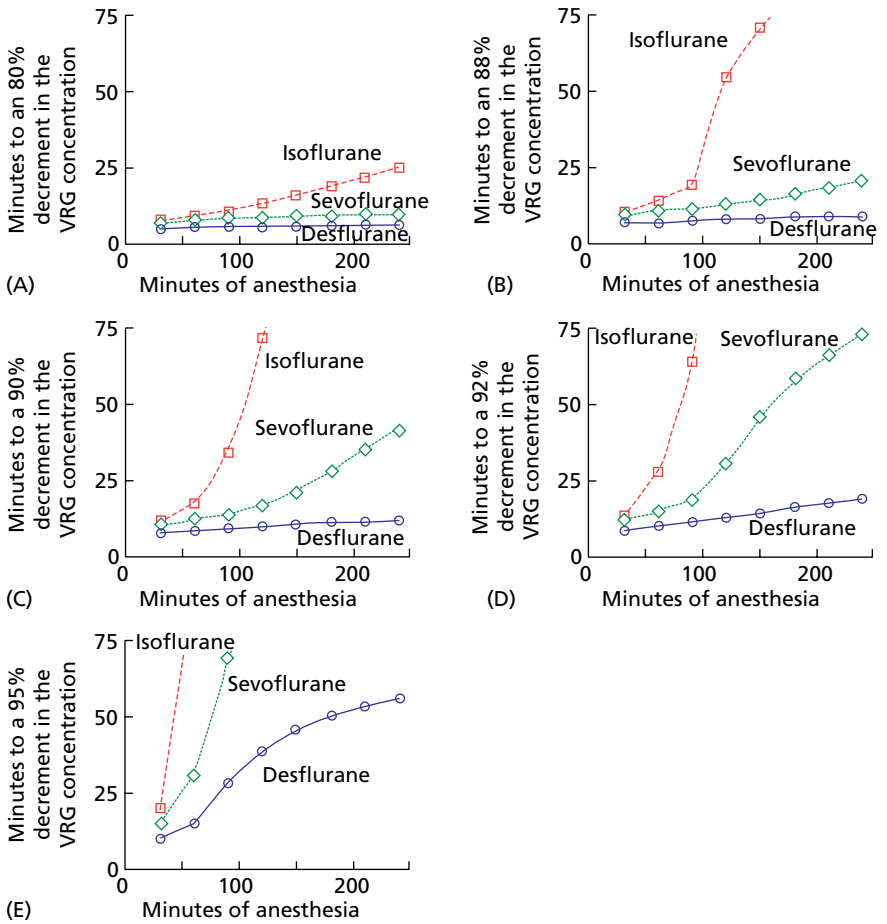

Figure 10.6 Context-sensitive decrement times in the rich vascularized compartment (VRG), i.e. brain, heart, kidney, liver, according to the duration of volatile anesthetic administration. *Source:* Reproduced from Eger and Shafer [70] with permission of Wolters Kluwer.

found to be lower in preterm babies than in term neonates. This relatively low MAC in immature babies is thought to be a general phenomenon of all volatile anesthetics, although we lack data in this age group. At birth and during the first months of life, MAC is at its peak value for all drugs (except for halothane, which attains its peak value several months after birth). After the first year of life, there is a reversal in the relationship between age and MAC; MAC decreases with age (Fig. 10.7). In summary, infants aged 6 months have a MAC 1.5–1.8 times that observed for a mean adult aged 40 years [116–119]. Also, preterm infants are supposed to be more sensitive to cardiac depression than neonates, who are also more susceptible than older children and young adults [120].

The MAC gives the probability of inappropriate anesthesia in an average patient. The possibility of modulation of anesthesia depth in line with the patient's status now exists using several indexes obtained by electroencephalogram (EEG) monitoring, such as the Bispectral Index (BIS™, Medtronic-Covidien, Minneapolis, MN, USA) and the spectral entropy or Narcotrend® Index (MonitorTechnik, Bad Bramstedt, Germany) [121–124]. In adults, numerous studies have shown that the population values of T½ke0 given by these indexes were similar and close to the values expected from clinical experience (see Table 10.3) [125–129]. However, great interindividual variability has been observed. This variability is similar to that observed with propofol, for example. In addition, the correlation between different MAC methods is difficult because, as with IV agents, all these EEG-derived algorithms are perturbed because hypnosis and analgesia are simultaneously measured. In children older than 2 years, it appears that the correlation between BIS IC50 and the different MAC measures is similar to that of adults [126,130]. To date, none of these monitors can correctly predict hypnosis in infants, perhaps with the exception of using regional and general anesthesia together (Fig. 10.8) [131–134].

Effects of volatile anesthetics on different functions

Isoflurane and desflurane are pungent and can cause airway irritation during induction of anesthesia [135]. Only halothane, which is less and less used because of its lower margin of safety compared to other agents, and sevoflurane are used for anesthesia induction. This pungency does not increase the risk of laryngospasm after induction.

Specific action on the central nervous system

Volatile anesthetics depress neuronal activity in a concentration-dependent manner. High concentrations depress EEG, and burst suppression occurs at concentrations greater than 2 MAC [136]. Sevoflurane induces epileptic activity with epileptiform discharges at concentrations usually greater than 1.5 MAC, but this also occurs at lower concentrations in some patients [137]. Convulsion-like movements may accompany these EEG signs. The morbidity of these manifestations is unknown, and no sequelae have yet been reported. However, it is recommended not to use sevoflurane concentrations in excess of 6% for induction of anesthesia and to maintain anesthesia with concentrations not higher than 1.5 MAC. Volatile anesthetics are often associated with agitation during emergence from anesthesia and for many minutes afterwards [138,139]. Emergence agitation is more frequent with newer agents such as sevoflurane. Concomitant administration of

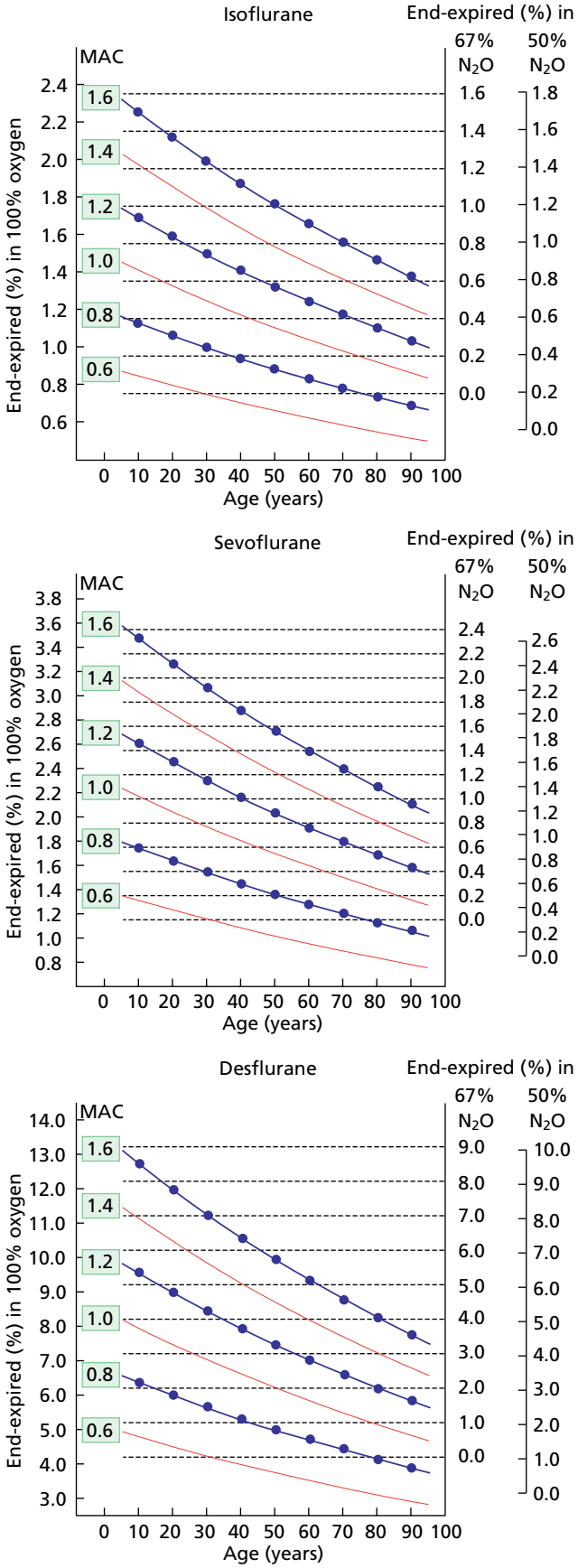

Figure 10.7 Minimum alveolar concentration (MAC) of isoflurane, sevoflurane, and desflurane according to age. Premature infants have a lower MAC than neonates. *Source:* Reproduced from Nickalls and Mapleson [119] with permission of Elsevier.

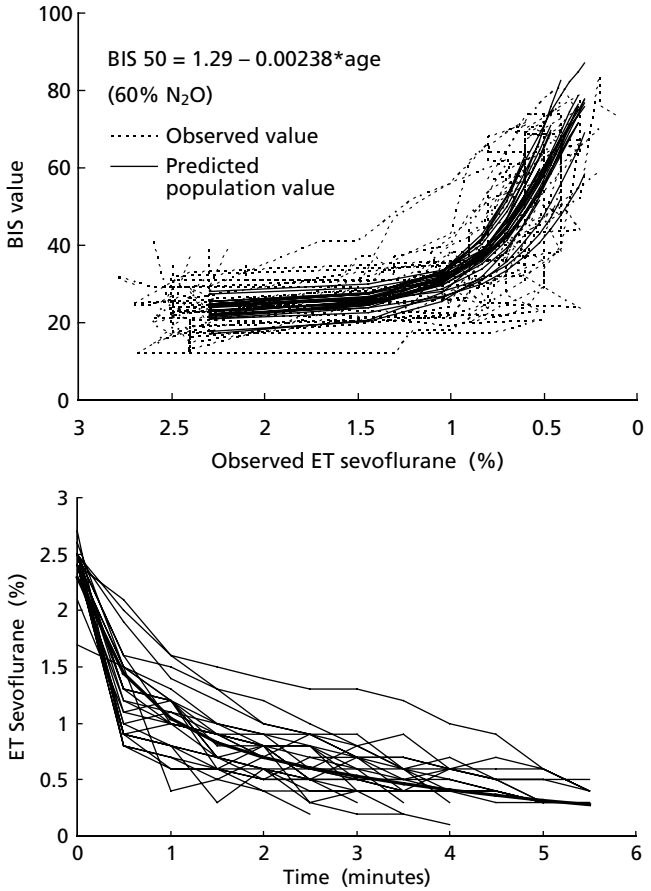

Figure 10.8 BIS values in 6 (mean) ± 3 (SD)-year-old children as a function of end-tidal (ET) sevoflurane. All patients had a regional block. Dotted lines are individual values and solid lines are Bayesian values calculated using NONMEM. Interestingly, in the absence of a nociceptive signal, the relationship between BIS value and ET sevoflurane is excellent and exhibits a negative correlation with age. *Source:* Reproduced from Lopez et al [142] with permission of Elsevier.

opioids, propofol, regional anesthesia, or ketamine may prevent emergence agitation. Dexmedetomidine should be favored as the treatment when agitation may lead to self injury [140]. Awareness is more frequent in children than in adults, but implicit memory seems to be less of a concern in pediatric patients [141,142]. Both midazolam and propofol inhibit conscious memory, but midazolam does not prevent implicit memory if present [143].

Apart from the possible neuroapoptosis induced by volatile anesthetics in infants and young children, volatile anesthetics exert a protective effect on the nervous system that is similar to that observed for the heart [144–147]. This effect seems to be independent of the inhibition of the NMDA receptor. In addition to a direct neuroprotective effect, preconditioning with isoflurane, sevoflurane, and desflurane appears efficacious in protecting against focal ischemia and apoptosis induced by ischemia or hypoxia-reperfusion. This effect seems related to the activation of various two-pore potassium channels and to the activation of inducible NO synthesis. Preconditioning seems to be particularly promising for neonatal cardiac surgery.

All volatile anesthetics increase CBF [148,149]. This increased blood flow is accompanied by a marked increase in intracerebral blood volume, which explains why increases in ICP are greater in children receiving volatile anesthesia than with IV anesthesia. Desflurane increases ICP more than isoflurane or sevoflurane. However, autoregulation is depressed in a dose-dependent manner, and the administration of less than 1–1.5 MAC seems to preserve enough autoregulation for clinical purposes, inasmuch as the main factor causing a decrease in cerebral perfusion pressure is the arterial pressure, which should be preserved [150,151].

Effect on the respiratory system [152–154]

All volatile anesthetics depress ventilation by reducing tidal volume, which is not compensated for by a parallel increase in respiratory rate. Interestingly, halothane depresses the ventilatory response to CO_2 less than the other agents. However, the important clinical issue is the response to acute hypoxia, which is depressed more by halothane than by isoflurane. Sevoflurane and desflurane are the least depressive agents. In case of a sudden decrease in PaO_2, desflurane and sevoflurane are safer agents. During one-lung anesthesia, no difference between isoflurane, desflurane, and sevoflurane has been reported. Also, no difference is reported between propofol and volatile anesthetics. At 0.5 MAC, all agents are bronchodilators. At higher concentrations, bronchoconstriction appears with desflurane at concentrations >0.5 MAC and with sevoflurane at concentrations higher than 1–1.5 MAC. Only isoflurane maintains its bronchodilating properties at 2 MAC. However, in children with airway susceptibility, for instance those with recent upper respiratory tract infection, desflurane markedly increases bronchial resistances, whereas sevoflurane exerts a bronchodilating effect [155].

Effect on the cardiovascular system [156–162]

All anesthetics depress contractility and inhibit sympathetic tone. Halothane significantly does so at 1 MAC, whereas isoflurane, desflurane, and sevoflurane only do so at concentrations above 1.5 MAC. In addition, halothane causes marked bradycardia, whereas sevoflurane has almost no effect on cardiac rhythm below 1.5 MAC. Isoflurane and desflurane have been shown to increase heart rate in adults, but an increase in heart rate is not as critical in pediatric patients. Interestingly, depression caused by halothane is poorly corrected by atropine, whereas it increases contractility in infants and children who are anesthetized with the other three agents. This difference between halothane and other agents (mainly sevoflurane has been studied) has been observed in patients without myocardial dysfunction, or with various congenital heart diseases. This is true also in patients breathing spontaneously. In addition, only halothane significantly potentiates epinephrine-induced cardiac arrhythmias. Halothane, isoflurane, and sevoflurane depress the autonomic control of arterial pressure in a similar manner. However, the bradycardia caused by halothane should be considered. Premature infants, who have an immature baroreflex, are particularly sensitive to the depression induced by anesthetics. In conclusion, halothane should be avoided when possible in infants and children, as halothane overdose has been associated with deaths in this age group. Halothane is no longer used in most countries, but is still available in some developing countries.

Isoflurane, desflurane, and sevoflurane possess cardioprotective effects, and both desflurane and sevoflurane have been

shown to decrease postoperative mortality in adults suffering from coronary artery diseases. Indeed, the cardiac depressive effect reduces oxygen demand and may protect during ischemia. However, there is evidence of a specific effect related to pre- and post-conditioning. This may be beneficial for cardiac procedures in infants and children [157,163,164].

Effect on muscle relaxation

Volatile anesthetics have an intrinsic effect on muscle relaxation [165–167]. Their prejunctional effect decreases the firing rate of motor fibers. In addition, they may also affect the sensitivity of the motor endplate. Volatile anesthetics interact with muscle relaxants. They do not interact with the kinetics of nondepolarizing muscle relaxants, but decrease Ce50 [168]. The dose of rocuronium or atracurium needed to achieve similar effect is decreased by about 25–30% in patients anesthetized with sevoflurane compared to those anesthetized with propofol [169]. At similar MACs, all volatile anesthetics enhance the action of pancuronium, vecuronium, rocuronium, atracurium, and cisatracurium to a similar degree [170].

Malignant hyperthermia (see Chapter 45)

All volatile anesthetics may induce malignant hyperthermia (MH) [171–174]. Succinylcholine increases its severity. MH is a genetic disorder of the ryanodine receptor of the skeletal muscle and has a prevalence estimated between 1:3000 and 1:8500. Indeed, the prevalence largely varies between populations. The incidence of MH associated with general anesthesia is estimated at between 1:30,000 and 1:100,000. Patients with various myopathies may be susceptible to MH. Central core disease and hypokalemic periodic paralysis are particular risks [175,176]. The usual clinical presentation is an uneventful induction of anesthesia, progressive development of tachycardia and hyperthermia, and a rise in end-tidal CO_2 tension. The associated muscle rigidity is a direct sign of impaired intracellular calcium regulation. In patients spontaneously breathing, a progressive rise in minute ventilation is also observed. Acidosis, hyperkalemia, and a serum creatinine kinase >10,000 IU/L are the main biological manifestations. If untreated, MH may be rapidly lethal. These manifestations are not always typical, and there is a risk that the diagnosis will be missed because MH may progressively develop after discharge of the patient from the operating room or because a lethal episode may occur during a future anesthetic. Dantrolene is the specific treatment (2–3 mg/kg up to 10 mg/kg as a bolus). Clinical signs determine the dose of dantrolene needed. Following treatment, the signs and symptoms of MH may recur, making it necessary to reinject dantrolene. This is why dantrolene must always be readily available. Dantrolene must be dissolved in sterile water (possibly warmed to 40°C), because dissolution is very difficult with the standard preparation. A new preparation of dantrolene, Ryanodex® (Eagle Pharmaceuticals Inc., Woodcliff Lake, NJ), is available that requires only 5 mL of sterile water to dissolve 250 mg of the drug. It is important to change the anesthesia machine and the entire circuit, to cool the patient if necessary, and to correct acidosis if necessary. The diagnosis is ascertained by a muscle biopsy, which should always be performed. Prevention of MH in susceptible subjects consists of preparing the anesthesia machine by removing the vaporizers and changing the circuit. Total IV anesthesia is used and succinylcholine is avoided.

KEY POINTS: PHARMACOKINETICS AND PHARMACODYNAMICS OF INHALED ANESTHETICS

- The mechanism of halogenated anesthetic is primarily through binding to the $GABA_A$ receptor, depressing neuronal function
- Increased minute ventilation and cardiac output will increase uptake and distribution
- MAC profile differs by agent: MAC is the highest at the age of 1–12 months for desflurane, isoflurane, and sevoflurane; MAC is lower in neonates with isoflurane and desflurane, but higher in neonates with sevoflurane

Pharmacokinetics and pharmacodynamics of intravenous anesthetics

Benzodiazepines

Benzodiazepines interact with a specific site of the GABAA receptor, increasing the affinity of the receptor for GABA [177,178]. GABAA is the principal inhibitory neurotransmitter and increases the frequency of opening of the chloride channel. Under normal conditions, chloride concentration is lower inside the cell than outside. Opening of the channel increases the concentration of chloride inside the cell and hyperpolarizes the membrane. Benzodiazepines have hypnotic and sedative properties. They are potent anticonvulsants. They are also anxiolytic and provoke antegrade amnesia. Although they are weak muscle relaxants (a central effect), they do not notably interact with peripherally acting muscle relaxants.

Pharmacokinetics

Benzodiazepines are weak bases bound to serum proteins, mainly AGP (Table 10.4) [179,180]. Only midazolam is water soluble [180]. Benzodiazepines rapidly cross the BBB and quickly access the receptor: their T½ke0 is lower than 3 min, except for lorazepam [181–184]. Conversely, the duration of action mainly depends on the affinity for the receptor. Midazolam, clonazepam, and lorazepam have an affinity constant to the receptor 20 times higher than that of diazepam, and the duration of action is as follows: diazepam 2 h, midazolam 2–4 h, clonazepam 24 h, lorazepam 24–72 h.

Benzodiazepine metabolism takes place in the liver via the CYP3A4 isoform of cytochrome P450, with the exception of lorazepam, which is metabolized by UGT [185–187]. There is no phase I metabolism. Diazepam has active metabolites, mainly N-desmethyldiazepam, which may accumulate in intensive care unit (ICU) patients with kidney failure. Midazolam has an active metabolite, α1-OH-midazolam, but the ratio between metabolite and parent drug remains constant, even in ICU patients. Because all these molecules have low hepatic extraction ratios, their elimination mainly depends on hepatic function; in the setting of liver failure, the clearance of benzodiazepines is markedly decreased. After oral administration, absorption of midazolam is rapid; its bioavailability is 50% and its T_{max}, the time-to-peak

Table 10.4 Benzodiazepines and intravenous anesthetics. Physicochemical properties and pharmacokinetics

Drug	Molecular weight (Da)	pKa	Distribution ratio (octanol/buffer)	Protein binding%		T½ (h)	CL (mL/kg/min)	Vc (L/kg)	Vss (L/kg)	T½ke0 (min)	Ce50 (μg/mL)
Midazolam	326	6.1	475	96	Adult:	3–8	1.3–4	–	1.1	3.2	–
Diazepam	284	3.3	580	98	Adult:	40	0.4–0.6	–	–	1.6	–
Thiopental	242	7.4	209	80	Adult:	12–15	3.1	0.28	2.1	1.2	–
	–	–	–	–	5 mo–4 yr:	6	6.6	0.4	2.1	–	
Propofol	178	11	6900	99%	Adult:	6–8	20	0.15	5	2.6 (LOC)–4.2(BIS50)	1.8(LOC)–5.2(BIS50)
	–	–	–	–	1 yr:	–	50	1.0	10	0.8(BIS50)	5.2(BIS50)
	–	–	–	–	5 yr:	12–15	30	0.4	8	–	–
	–	–	–	–	Premature:	–	15	1.3	6	–	–
Etomidate	244	4.5	1000	75	Adult:	3.5–4.6	10	0.3	2.5–4	1.55(BIS50)	0.53(BIS50)
	–	–	–	–	7–13 yr:	4	17	0.66	5.6	–	–
Ketamine	238	7.5	750	60	Adult S(+):	2.5–5.3	21–36	0.2–0.4	3.4	–	–
	–	–	–	–	Adult R(–):	2.6	19	0.4	3.0–8.0	–	–
	–	–	–	–	8 yr:	6–8	30	0.4	8.0	0.2	0.52 (arousal)
Dexmedetomidine	237	7.1	2.89	94	Adult:	2	9.0	0.8	1.6	6	0.00075 (Ramsey Scale 5)
	–	–	–	–	0–1 mo:	–	15.5	0.83	–	–	–
	–	–	–	–	1–6 mo:	20.1	0.76	–	–	–	0.0006–0.0008 (1 μg/kg load; 0.7 μg/kg/h infusion)
	–	–	–	–	6–12 mo:	–	18.3	0.99	–	–	–
	–	–	–	–	12–24 mo:	–	17.7	0.72	–	–	–
	–	–	–	–	2–5 yr:	–	18.3	0.96	–	–	–
	–	–	–	–	6–15 yr:	–	13.3	0.80	–	–	0.0012 (1 μg/kg load; 0.7 μg/kg/h infusion)

Ce50 is for loss of consciousness (LOC) or for a 50% decrease in the BIS value (BIS50). BIS, entropy, and various measures based on EEG give similar results.
CL, clearance; T½, terminal elimination half-life; T½ke0, rapid equilibration half-life; Vc, volume of the central compartment; Vss, steady-state volume of distribution.

concentration, occurs 40–50 min after administration. Absorption is very rapid after rectal administration. In children, T_{max} is 10 and 15 min for diazepam and midazolam respectively. After rectal administration, bioavailability is 50–80% for diazepam and 20–50% for midazolam. The intramuscular route has been abandoned because of unpredictable absorption. The volume of distribution is large (1–2 L/kg) and the terminal half-life long (see Table 10.4) [188–191]. Apart from some inhibitors of retroviral replication, such as ritonavir, few interactions between benzodiazepines and other drugs metabolized by the CYP3A4 have been described. Because of immaturity of CYP3A4, midazolam clearance is very low in preterm infants and during the first 2–3 months of life [192,193].

Pharmacodynamics

Action on the central nervous system

Benzodiazepines cause sedation through their effect on GABAA receptors. Their indications include premedication and sedation in ICUs [194]. When a benzodiazepine is used as a premedicant, a paradoxical agitation reaction sometimes occurs. However, their sedative, anxiolytic and amnesic effects make midazolam one of the preferred drugs for premedication, particularly for uncooperative children or patients who have undergone multiple procedures. However, the effect on anterograde amnesia and implicit memory remains controversial [143]. Benzodiazepines have almost no effect on CBF, ICP, or the cardiovascular system, which makes these drugs suitable for sedation in ICUs, particularly in neonates and in patients with head trauma, when long-term propofol administration is a risk [195].

Action on the respiratory and cardiovascular systems

Midazolam depresses ventilation by decreasing sensitivity to CO_2 [196]. Opioids potentiate this effect. Diazepam and midazolam produce only mild cardiovascular depression and a minimal reduction in blood pressure, due to a decrease in vascular resistance [197]. This effect is increased when the drug is administered concomitantly with narcotics or other sedatives. When given to ICU patients for several days, midazolam has no significant effect on liver or adrenal function. Tolerance and tachyphylaxis may occur, particularly with longer-term infusions (≥3 days). Benzodiazepine withdrawal syndrome occurs with high-dose/long-term midazolam infusions [198].

Dosing

For premedication in infants and children after the age of 3–6 months: midazolam 0.3–0.5 mg/kg orally (or rectally if the oral route is not possible) 30–40 min before induction of anesthesia; diazepam (if midazolam is not available) 0.1 mg/kg 60 min before surgery. As an adjunct for the induction of anesthesia, 0.15 mg/kg is given. As the sole agent for anesthesia induction, 0.3–0.6 mg/kg IV is used. The infusion dose of midazolam in critically ill patients is 0.03–0.3 mg/kg/h (30–300 µg/kg/h). The dose of midazolam is adjusted in ICU patients according to the patient's clinical condition (use of a sedation score by the attending nurse is highly recommended).

Flumazenil, a specific benzodiazepine antagonist, reverses all the effects of benzodiazepines. However, its rapid elimination kinetics makes continuous infusion of the drug necessary to maintain therapeutic efficacy [199]. The dose by IV bolus is 5–10 µg/kg every min up to 40–50 µg/kg. It may be necessary to follow this titrated dose with a continuous infusion of the drug at a rate corresponding to the titrated dose given over an hour.

Thiopental

Thiopental (thiopentone) is no longer an important drug for induction of anesthesia in younger patients, as in adults, and is not available in many parts of the world. Like propofol, thiopental modulates the GABAA and glycine receptors, but it mainly acts at the spinal cord level and preferentially on the glycine receptor [178,200–202].

Pharmacokinetics

Thiopental is a weak acid (pKa 7.6) and an octanol/buffer distribution ratio of 490 (LogP = 2.69) (see Table 10.4) [91]. It is a racemic mixture of two stereoisomers [S-(+) and R-(–)], the S-(+) isomer being twice as potent as the R-(–) isomer. Thiopental binds to HAS with an average free fraction of 15% in adults and 28% in neonates [203]. Thiopental is metabolized by the cytochrome P450 system, but the precise pathway(s) remain(s) to be characterized. Its terminal half-life is very prolonged [204–206]. After a bolus injection, the drug distributes rapidly, making its effect transient. Following a single injection, thiopental's pharmacokinetics is best described by a two-compartment linear model, with a terminal half-life of ≈12 h in adult patients. The rate of administration markedly influences the total dose needed to achieve a predetermined effect: because of rapid redistribution of the drug, the higher rate of administration leads to high, but transient peak concentration, which is unable to correctly cross the BBB; a minimum duration of plateau concentration is needed to achieve clinical efficacy. This is consistent with an equilibration half-time (T½ke0) of 2.4 min between central and effect compartment (see Table 10.4). In pediatric patients older than 6 months of age, clearance is higher than in adults, and the average T½ is 6.1 h (see Table 10.4). With prolonged administration (for example in patients with critically increased ICP), thiopental exhibits nonlinear (Michaelis–Menten) kinetics, with an apparent terminal half-life of 15 h. In neonates and young infants, kinetics are not profoundly altered but the pharmacodynamics are likely different, with an ED50 (the dose leading to loss of lid reflex in 50% of children) of 3.4, 6–7, 5.5, and 4.2 mg/kg in patients aged 0–14 days, 1–6 months, 6–12 months, and older than 1 year respectively [207,208]. Interestingly, the curve representing ED50 versus age is very similar to those of MAC versus age for halogenated agents. Studies considering allometric scaling are lacking.

Pharmacodynamics

Effect on the central nervous system

Thiopental does not increase CBF and may decrease ICP (although the cerebral perfusion pressure may not significantly change). The very prolonged elimination that is the result of Michaelis–Menten kinetics must be taken into account.

Effect on the respiratory and cardiovascular system

Thiopental depresses ventilation, likely because of decreased sensitivity to CO_2. In adults, more critical respiratory events occur in the immediate postoperative period with thiopental use than with propofol, although both cause similar changes in functional residual capacity (FRC) [209]. This increase in the number of events is likely related to the higher residual sedation associated with thiopental.

Thiopental decreases arterial blood pressure. Contrary to propofol, this decrease is not only related to decreased vascular tone but also to decreased myocardial contractile force [210]. Consequently, thiopental must be used with care in patients with cardiac failure.

Other effects

Thiopental, like other barbiturates, may induce porphyria. Its use is absolutely contraindicated in patients susceptible to such pathology. The acidity of thiopental solutions may cause necrosis at the injection site if extravascular diffusion occurs. Inadvertent arterial injection has caused severe necrosis.

Dosing

Because the risk of necrosis is high following inadvertent extravascular injection, the use of dilute solutions is recommended (2.5% in children and adults, 1% in infants). When adjuncts (opioids) are used for induction of anesthesia, the usual dose of thiopental is 2.5–3 mg/kg in neonates <10 days of age, 6–7 mg/kg in infants, and 5 mg/kg in children.

When ICU patients have thiopental infused for prolonged periods of time, thiopental kinetics become non-linear, in both adults and children. It may then be important to monitor thiopental plasma concentrations if the rate of administration exceeds 4–5 mg/kg/h.

Propofol

Propofol has largely replaced thiopental for induction and maintenance of anesthesia. The latter indication is likely related to the emergence of computer-driven systems for drug administration, since propofol kinetics and dynamics have been extensively studied [211]. Propofol enhances gating of the GABAA receptor by GABA and slows desensitization of the receptor [200,201]. In addition, propofol depresses presynaptic excitatory synaptic transmission and decreases glutamate release. Propofol also enhances the activation of the glycine receptor by glycine.

Pharmacokinetics

Propofol is a weak acid with a pKa of 11.5 and an octanol/buffer distribution ratio around 6500 [91]. Because of high hydrophobicity, propofol is "solubilized" in lipid emulsions. Propofol binds to red blood cells and serum albumin, and the free fraction is <1% [212–214]. Binding is markedly decreased in patients on cardiopulmonary bypass [215] and those in ICUs who have decreased serum concentrations of HSA. The pharmacokinetics largely varies with age,

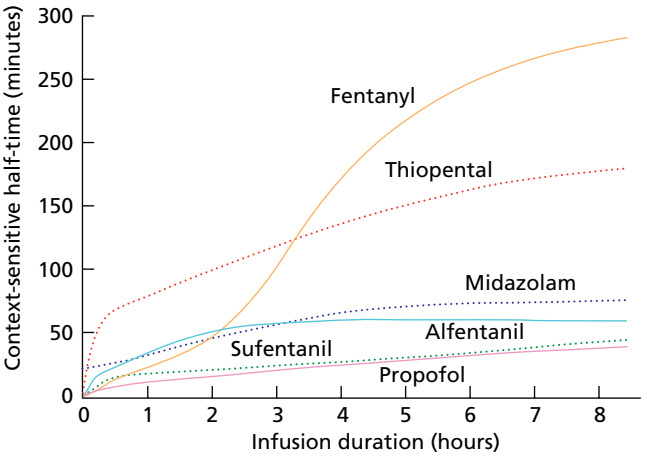

Figure 10.9 Context-sensitive decrement times of the principal agents used intravenously. Remifentanil is not depicted on this figure since its decrement times are constant. *Source:* Reproduced from Hughes et al [21] with permission of Wolters Kluwer.

explaining the differences in dosing between infants, children, and adults (see Table 10.4) [216–219]. When one compares a typical 20 kg, 5-year-old child and a typical 70 kg, 30-year-old adult, the main findings are: (1) an elimination clearance moderately higher in children than in adults; and (2) more importantly, volumes (both Vc and Vss) are between 2 and 2.5 times greater in children than in adults, and the associated intercompartmental clearances are 1.5 times greater in children than adults. When allometric scaling is performed, clearance is constant across species and age in humans: CL = 71 * (BW/70)^0.78 L/min, where BW is bodyweight and 70 the standard bodyweight for adult humans [220]. Propofol exhibits marked multicompartmental kinetics and context-sensitive decrement times (Fig. 10.9). Altered kinetics (decrease in elimination clearance) has been reported in ICU patients and in neonates [221]. In premature infants less than 38 weeks' postmenstrual age, clearance is very low since maturation of metabolism occurs at birth. Interestingly, there are almost no differences in pharmacodynamic parameters across age [222–227]. The differences are mainly kinetic, i.e. Ce50, the concentration in the effect compartment needed to achieve a desired effect, is nearly similar among infants, children, and adults. Conversely, T½ke0 and the time to peak effect are shorter in younger patients than in adults, and the difference is identical to the difference measured for volumes and intercompartmental clearances (see Table 10.4). Interestingly, the effects on ventilation and arterial blood pressure do not have the same kinetics [228,229]. In adult patients, T½ke0 for respiratory depression is 2.6 min, similar to the T½ke0 for hypnosis, whereas T½ke0 for a half decrease in systolic blood pressure from baseline to 80 mmHg is 6 and 11 min in 20- and 75-year-old patients respectively.

Pharmacodynamics

Specific action on the central nervous system

Propofol has little effect on CBF or ICP when normocarbia is present [229,230]. This is why propofol is so popular in ICUs for sedation of patients with increased ICP [231]. Propofol is also used to treat seizures, mainly in cases of status epilepticus [232].

Effect on the respiratory and cardiovascular systems

Like all hypnotic agents, propofol depresses ventilation by decreasing sensitivity to CO_2. This effect is central since the T½ke0 of respiratory depression is similar to the T½ke0 of hypnosis [232].

Propofol has a direct negative inotropic effect at very high (supratherapeutic) concentrations [210]. At therapeutic concentrations, its effect on contractility is insignificant [233]. The main cardiovascular effect of propofol is on vascular tone, probably because it inhibits the sympathetic nervous system. The prolonged T½ke0 on vascular tone strongly suggests that the effect is at least partly peripheral [227]. Propofol protects the myocardium against ischemia-reperfusion injury through its ability to inhibit the mitochondrial permeability transition pore and its antioxidant and free-radical scavenging properties [234,235].

Propofol infusion syndrome

After more than two days of infusion of propofol in ICU patients, severe toxic effects have occurred [236,237]. This "propofol infusion syndrome" is likely caused by the uncoupling effect of propofol on the respiratory chain in the mitochondria. The clinical presentation includes lactic acidosis, rhabdomyolysis, and cardiovascular collapse (bradycardia, sometimes Brugada-like ECG, asystole). Green or red urine has been described in some patients [238]. This syndrome was initially described in children and adults who had head trauma and received high-dose propofol for sedation. If sedation with propofol seems to benefit the patient, it is recommended to give <4 mg/kg/h for less than 48 h. Close monitoring of acid–base status, serum lactate, and creatine kinase concentrations should be performed. The use of propofol for total intravenous anesthesia (TIVA) for several hours has not been reported to cause adverse effects in children.

Presentation and dosing

Propofol is available as a 1% or 2% emulsion. The carrier emulsion was originally Intralipid®, but other lipid emulsions are used in generic preparations. Propofol contains EDTA, sodium metabisulfite, or benzyl alcohol as an antimicrobial agent. Pain at the site of injection is common and may be attenuated by lidocaine (0.5–1 mg/kg), either injected before the propofol or in the same syringe with the drug. Propofol should not be prepared in advance, since bacteria grow rapidly in the emulsion. Postoperative nausea and vomiting occur less frequently with propofol than with other agents (e.g. volatile anesthetics). To achieve similar plasma concentrations in children and in adults, the initial dose must be 2–3 times greater in children [239]. Because the volume at steady state is also markedly different, the initial 15–60 min of an infusion must be higher in children than in adults [240]. However, the significant hemodynamic effect of propofol must be taken into account, and balanced anesthesia with adjuncts seems preferable for induction of anesthesia. The usual doses for anesthesia induction are <1 month 2 mg/kg, 1 month to 3 years 2–3 mg/kg, 3–8 years 3 mg/kg, >8 years 2–3 mg/kg. Loss of consciousness lasts for 5–10 min after a single injection. It has also been proposed to use low doses of propofol for elective intubation in neonates [241]. The dosing scheme for continuous infusion of the drug is provided in Table 10.5.

Table 10.5 Propofol and ketamine infusion scheme

Propofol infusion dosing in infants and children. After induction of anesthesia with propofol (3–5 mg/kg), anesthesia is maintained with the following scheme. Anesthesia needs to be complemented with fentanyl/alfentanil/sufentanil or regional anesthesia (adapted from Steur et al. [240])

Age	Time (min)					
	First 10	10–20	20–30	30–40	40–100	>100
<3 mo	25	20	15	10	5	2.5
3–6 mo	20	15	10	5	5	2.5
6–12 mo	15	10	5	5	5	2.5
1–3 yr	12	9	6	6	6	6
Adult	10	8	6	6	6	4

Ketamine. Infusion scheme for children weighing 12–40 kg. Depending on the procedure, adjuncts may be given (adapted from Dallimore et al [277])

Infusion rate (mg/kg/h)					
Loading dose 2 mg/kg	0–20 11	20–40 7	40–60 5	60–120 4	>120 3.5

Etomidate

Etomidate is a carboxylated imidazole that is highly hydrophobic, has hypnotic properties, and has little effect on the cardiovascular system. It is often used for induction of anesthesia in patients with critical hemodynamic conditions, despite its suppressive effect on adrenal steroid synthesis [242,243]. Etomidate has a high degree of enantioselectivity. The R-(+) enantiomer is 10 times more potent than the S-(–) enantiomer [244,245]. The commercial preparation is the pure R-(+) enantiomer. Like propofol, etomidate interacts with the GABAA receptor, but the actions of these two drugs on the different subunits of the receptor differ [244–246]. Etomidate causes marked *in vitro* endothelium-dependent vasodilatation. However, this effect is less than that observed with propofol and is reversed by adrenergic stimulation [247].

Pharmacokinetics

Etomidate is a weak base, hydrophobic (the active molecule is "solubilized" in propylene glycol or in a lipid emulsion), and is bound to AGP. Protein binding is decreased in patients with kidney and liver failure, which may increase the sensitivity of these patients to the drug [248,249].

Etomidate is metabolized in the liver by the cytochrome P450 system, but the specific isoform(s) involved remain(s) to be characterized. CYP3A2 may be involved because etomidate decreases antipyrine clearance [250]. Clearance of etomidate is decreased in cirrhotic patients [251–253]. Metabolites are inactive. In children, the volume of the central compartment is more than twice that of adults (0.66 versus 0.27 L/kg) [254]. Clearance is also higher. However, the volume of the central compartment depends on the cardiac output.

If, indeed, children with normal cardiovascular function need a greater dose of drug for induction of anesthesia, those with impaired hemodynamics may require less [255,256].

Pharmacodynamics

Specific action on the central nervous system

Etomidate has no intrinsic action on CBF. It decreases ICP. Cerebral perfusion pressure is likely unchanged because of the etomidate-induced slight decrease in arterial blood pressure, which may explain the decrease in CBF and subsequent decrease in ICP.

Effect on the respiratory and cardiovascular systems

Etomidate induces moderate respiratory depression by reducing sensitivity to CO_2.

Etomidate is mainly used for induction of anesthesia (particularly in emergency cases) because of the hemodynamic stability observed [210,255,257–259]. Etomidate has no effect on heart rate, and contractility is only moderately impaired. *In vitro* and *in vivo* studies in animals and in humans have shown that etomidate has an intrinsic negative inotropic effect that is similar to the effects observed with ketamine and midazolam. This effect is totally reversed by β-adrenergic stimulation. More importantly, etomidate only moderately impairs vascular tone. Baroreflex control is preserved, in contrast to propofol and thiopental.

Effect on adrenal function

Etomidate blocks 11-β-hydroxylase, thus inhibiting conversion of cholesterol to cortisol [260]. After an induction dose of etomidate, adrenal suppression last for about 24 h. This effect may be clinically relevant, particularly in patients with septic shock who have compromised adrenal function.

Formulation and dosing

Two formulations are distributed, depending on the solvent used. The initial formulation uses propylene glycol (35% vol/vol), and the second uses a lipid emulsion (propofol) as the carrier. Both preparations are painful on injection, but the propylene glycol preparation is particularly irritating because of its osmolality (4640 mOsm/L).

For induction of anesthesia in the emergency department, 0.2–0.3 mg/kg is used in children with compromised cardiovascular function and 0.3–0.6 mg/kg in patients in a stable condition. Myoclonus may occur with injection of the drug. In pediatric patients, rectal induction of anesthesia is possible with a dose of 6–8 mg/kg. Continuous administration of the drug is not recommended because it suppresses cortisol synthesis.

Ketamine

Ketamine has hypnotic, analgesic, and antihyperalgesic properties and produces "dissociative anesthesia," profound analgesia, and marked sympathomimetic reactions [261]. However, ketamine has unwanted side-effects, such as hallucinations, confusion, delirium, hypersalivation, and bronchial hypersecretion. Ketamine anesthesia is characterized by rapid immobility and cataleptic appearance, mydriasis, nystagmus, and increased muscular tone. Emergence from anesthesia is characterized by a state of confusion, often with hallucinations. This state, which is amplified by light and noise, is less frequent in younger children than in adults and may be prevented by administering adjunct drugs such as benzodiazepines. Ketamine has moderate effects on the cardiovascular system. It has an asymmetric carbon, with two enantiomers R-(–)- and S-(+)-ketamine. The S-(+) enantiomer is about four times more potent than the R-(–) enantiomer [262].

Ketamine acts mainly as a non-competitive NMDA receptor antagonist. It inhibits presynaptic release of glutamate and potentiates GABAA. Ketamine also has opioid and muscarinic properties. The effects on the NMDA receptor include both the neuroprotective and proapoptotic effects of ketamine [263–267].

Pharmacokinetics

Ketamine is 50% ionized and 50% non-ionized at pH 7.4. Both the parent drug and its metabolite norketamine are bound to serum proteins, with a free fraction of 40% and 50% respectively [268]. Ketamine is metabolized by CYP2B6 and 3A4 [269–272]. N-demethylation produces norketamine, which has about 30% of the activity of ketamine. Norketamine undergoes almost the same metabolism as ketamine (hydroxylation by the CYP2B6 and glucuroconjugation) and has a terminal half-life of similar duration (≈4–6 h) [273–275]. Norketamine is then considered to be responsible for some of the effects of ketamine. Access to the receptor is very rapid, with a T½ke0 of <1 min (see Table 10.4). Drug redistribution rapidly occurs (the initial distribution half-life is <15 min), and after a single 1 mg/kg IV injection, anesthesia lasts 6–10 min. Because of the multicompartmental nature of ketamine's pharmacokinetics, decrement times are markedly context sensitive.

Pharmacodynamics [276–279]

Specific action on the central nervous system

Ketamine has specific effects on the CNS [280,281]. It enhances EEG activity and increases CBF and cerebral metabolic rate of O_2 ($CMRO_2$). Because the arterial pressure increases, there is an increase in ICP that is proportional to the increase in CBF. However, when adjuncts are used with ketamine and, more importantly, when normocarbia is maintained, ICP does not increase. Thus ketamine is often used in neurologically impaired patients. Ketamine has neuroprotective effects through its effects on the mitochondria. However, the effects of ketamine on the ATP-sensitive mitochondrial K+ channel remain a subject of debate. On the other hand, ketamine also induces apoptosis via the mitochondrial pathway. This is considered a major issue in neonates and infants. The neurotoxicity of ketamine on the brains of developing animals seems clear. Consequently, this agent should probably be used with care in younger patients.

Effect on the respiratory and cardiovascular systems

Ketamine does not depress ventilation, and the CO_2 response remains intact [282]. Tidal volume and respiratory rate are unchanged. Ketamine does not alter FRC, even at high doses, but it does induce moderate bronchodilation.

The pharyngo-laryngo-tracheal reflexes are partly conserved, leading to a relative airway protection.

Ketamine has minimal effects on myocardial contractility [283,284]. It preserves sympathetic activity and baroreflex activity [285,286]. In healthy subjects, ketamine raises arterial blood pressure slightly, increases the myocardial contractile force, and increases cardiac output. However, in patients with decreased cardiac reserve, negative inotropic effects of the drug can be unmasked when myocardial contractility fails to increase with β-adrenergic stimulation. In addition, the increase in MVO_2 may be deleterious in patients who have insufficient coronary reserve. It has been reported that ketamine inhibits ischemic preconditioning via its inhibition of ATP-sensitive K+ channels, but this is still subject to debate. The S-(+) enantiomer is undoubtedly less deleterious on both contractility and loss of ischemic preconditioning of the myocardium than the R-(–) enantiomer.

Antihyperalgesic effect of ketamine

By its anti-NMDA action, subanesthetic doses of ketamine are potently antihyperalgesic [287]. Ketamine limits opioid-induced hyperalgesia and has potent morphine-sparing effects. These effects are observed when ketamine is used early in the time-course of nociceptive stimulation, i.e. in the perioperative period. When ketamine is used only in the postoperative period, even when used with patient-controlled analgesia (PCA), the results are not so clear. In pediatric patients, these effects need to be confirmed. The use of ketamine before the age of 2–4 years is still controversial because of possible neurotoxicity.

Effects on immune function and inflammation

Like local anesthetics, ketamine has potent immunomodulatory and anti-inflammatory properties. Ketamine decreases nuclear factor κ B (NFκB) activation and TLR4 expression and is more frequently used in septic and trauma patients [288]. These anti-inflammatory properties have not been shown in pediatric patients. Further studies are needed to assess the beneficial effect of ketamine in septic or cancer patients.

Formulations and dosing

Ketamine has various formulations. The initial preparation of the racemic mixture contains benzethonium chloride as a preservative. Both the R-(–) enantiomer and the preservative are neurotoxic. In numerous countries, the S-(+) enantiomer without preservative is available because it is less toxic. However, even the pure S enantiomer may be neurotoxic at high concentrations, and its use is not recommended as an adjuvant for epidural injection.

Numerous routes for ketamine delivery are used. For IV induction of anesthesia, 1–2 mg/kg is used. For maintenance anesthesia, 2–4 mg/kg/h of ketamine is infused. However, because of the context-sensitive half-time of the drug, it may be better to use an adapted regimen (see Table 10.5). Ketamine may also be injected intramuscularly at a dose of 5–8 mg/kg. The onset of anesthesia is slower (5–10 min) and its duration is prolonged (20–30 min). Ketamine may also be given rectally at the same dose. Ketamine is also increasingly used for procedural sedation, particularly in the emergency department, using 1–1.5 mg/kg IV or 4–5 mg/kg intramuscularly (IM) [289,290]. The low-dose regimen used to prevent postoperative hyperalgesia consists of an IV loading dose of 0.15–0.30 mg/kg before surgery and a continuous infusion of 0.1–0.3 mg/kg/h for 24 h. As an adjunct to PCA, the dose is 1 mg ketamine per mg of morphine. However, most pediatric studies do not show a benefit to low-dose ketamine.

Dexmedetomidine

Dexmedetomidine is an imidazole derivative sedative/hypnotic agent that acts at CNS α_2-adrenergic receptor binding sites as a highly selective agonist, with a 1600:1 α_2:α_1 selectivity (by comparison, clonidine is 200:1 α_2:α_1 binding). Dexmedetomidine produces hypnosis and anxiolysis by binding presynaptic α_2 receptors in the locus coeruleus, and analgesia by binding to α_2 receptors in the spinal cord [291]. It was approved by the US Food and Drug Administration (FDA) in 1999 for use as an ICU sedative in ventilated adults, and a second indication was approved in 2007 for procedural sedation in spontaneously ventilating adults. Dexmedetomidine is now available in European and most other countries; however it is not labeled for use in children in any country despite its widespread use in children. Dexmedetomidine use has increased greatly in the past decade as a sedative in the ICU setting, an adjunct to general anesthetic techniques including volatile anesthetics and TIVA, a procedural sedative alone or in combination with other drugs, a premedication, a prevention or treatment for postanesthetic delirium, and an adjunct for caudal or epidural analgesia [292].

Pharmacokinetics

In children, IV dexmedetomidine is 93% protein bound, the rapid redistribution phase after an IV loading dose is about 7 min, clearance is approximately 15 mL/kg/min, and the terminal elimination half-life is about 2 h [293]. Eighty-five percent of the drug undergoes glucuronidation in the liver by UDP-glucuronidyl transferase, and 15% by cytochrome P450 2A6, into inactive metabolites, with a very small fraction excreted unchanged in the urine and stool. Using allometric size modeling, clearance is about 300 mL/min/70 kg in term neonates, and increases to about 600 mL/min/70 kg by about 1 year of age to over 700 mL/min/70 kg in older children [294]. Dexmedetomidine can be delivered by non-IV routes, and its bioavailability is intranasal 65%, orogastric 16%, buccal 84%, and IM 100%.

Specific action on the central nervous system

Presynaptic α_2 receptor binding in the locus coeruleus results in decreased norepinephrine release, producing sedative effects that mimic natural sleep, as evidenced by EEG studies in children that document a state similar to non-rapid eye movement sleep [293]. Plasma levels of about 600 pg/mL or higher produce significant sedation in children. Dexmedetomidine reduces CBF proportionally to cerebral metabolic rate, and does not appear to affect ICP. The drug preserves both somatosensory and motor-evoked potentials. When administered via the epidural space, dexmedetomidine has analgesic and antinociceptive properties in children.

In preclinical animal models, dexmedetomidine does not cause neuroapoptosis, and either completely or partially

blocks neuroapoptosis by volatile anesthetic agents, ketamine, and propofol [295]. This property has made dexmedetomidine a leading candidate drug for study as an alternative regimen for the issue of potential anesthetic neurotoxicity (see Chapter 46). Dexmedetomidine also has neuroprotective effects in cerebral ischemia and inflammation in preclinical models [296,297]. When used as an ICU sedative, dexmedetomidine is associated with a lower incidence of delirium in children [298].

Effect on the respiratory and cardiovascular systems

A major advantage of dexmedetomidine for sedation is that it maintains normal respiratory patterns, minute ventilation, and upper airway patency at normal sedative doses. This property facilitates earlier extubation for procedures such as cardiac surgery in infants [299]. This advantage is also seen in pediatric patients with obstructive sleep apnea, where upper airway patency is maintained with less airway support compared to propofol when used for imaging studies [293].

Because of its effect to decrease sympathetic outflow from the CNS and in the peripheral nervous system, dexmedetomidine administration results in lower heart rate (HR) and mean arterial pressure (MAP) compared to baseline, with the effect generally proportional to the loading dose and infusion rate [293,300]. Decreases of up to 20–30% may be observed with rapid loading doses in less than 5 min, especially in the absence of surgical stimulation. Slower loading over 10 min lessens the magnitude of the decrease in HR and BP. Glycopyrrolate may be used to prevent or treat dexmedetomidine-induced bradycardia, although there are reports of systemic hypertension when this combination of drugs is used. High or repeated loading doses of dexmedetomidine may cause transient hypertension, presumably from binding of peripheral arteriolar α_1 receptors [293].

Dexmedetomidine lengthens all electrophysiological intervals in the cardiac conduction system, and can result in second- or third-degree heart block or junctional bradycardia [301]. In the setting of pediatric cardiovascular surgery, dexmedetomidine should be avoided in patients with these dysrhythmias. Dexmedetomidine should be used only with great caution in patients receiving digoxin, β-adrenergic blocking or calcium channel blocking drugs. Conversely, dexmedetomidine administration is associated with a lower incidence of atrial and ventricular tachydysrhythmias after cardiac surgery in children [302].

Formulation and dosing

Dexmedetomidine is freely water soluble and has a pKa of 7.1. Each mL of the undiluted solution contains 118 µg of dexmedetomidine hydrochloride (equivalent to 100 µg dexmedetomidine base) and 9 mg of sodium chloride in water. The solution is preservative free and contains no additives or chemical stabilizers [303].

As a sedative agent in the ICU setting, or as an adjunct to general anesthetic techniques, an IV loading dose of 0.5–1 µg/kg over 10 min, followed by an infusion of 0.3–1 µg/kg/h is sufficient in most settings, taking into account that other agents, i.e. benzodiazepines and opioids in the ICU, and volatile agents or regional anesthesia in the OR, will be used. Doses in neonates must be reduced by 50%, accounting for reduced hepatic metabolism [294]. As a sole IV sedative for procedural sedation for MRI, loading doses of 2–3 µg/kg, with or without infusion of 1–2 µg/kg/h, have been described as effective in children without cardiovascular disease. As an intranasal sedative or premedication, doses of 2–3 µg/kg are effective [292,304].

Dexmedetomidine has been described as a useful agent to prevent or treat tolerance and withdrawal syndromes from prolonged use of benzodiazepines or opioids in the ICU setting. Conversely, prolonged ICU administration of dexmedetomidine greater than 7 days has also been associated with a withdrawal syndrome that includes agitation, hypertension, and tachycardia [292].

Neuroapoptosis related to general anesthesia

At birth, the central nervous system is not fully developed and external interventions may alter this fragile organ. For example, detrimental plasticity has been described at the spinal cord level in neonates suffering from intense, prolonged pain [305]. In the same way, general anesthesia may induce neuroapoptosis in the developing brain [306] (Fig. 10.10).

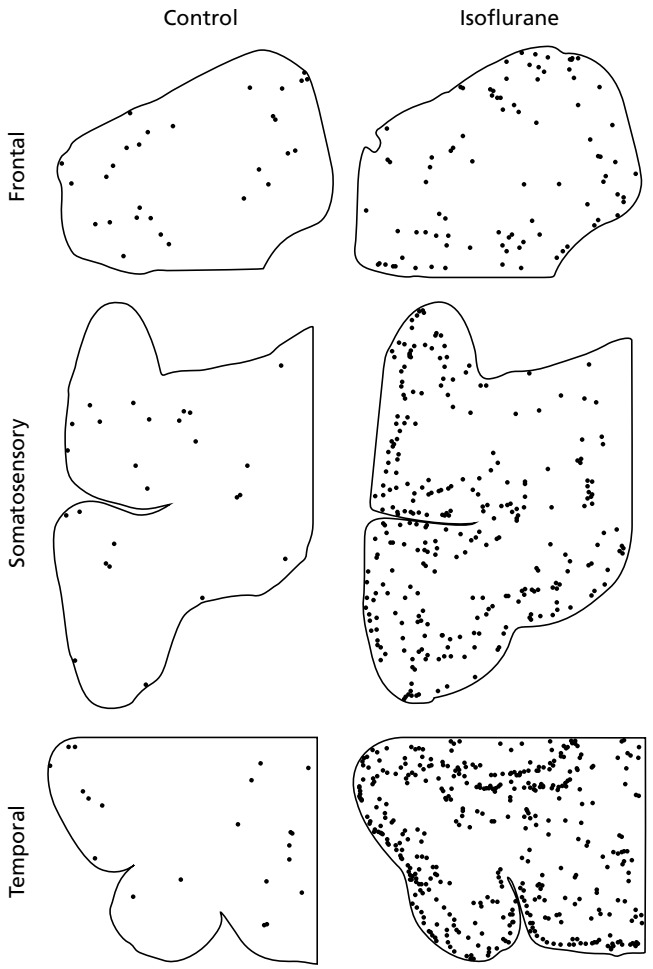

Figure 10.10 Brain sections of the neocortex in the rhesus macaque (computer reconstruction. It is clear that the number of apoptotic cells (black dots) is markedly increased in the animals exposed to 0.7–1.5 vol% end-tidal isoflurane for 5 h. *Source:* Reproduced from Brambrink et al [309] with permission of Wolters Kluwer.

To date, no clinical trial has been able to demonstrate any cognitive impairment in patients who had anesthesia in early life, but all regulatory agencies and anesthesia societies warn against unnecessary anesthesia in children up to 3 years of age. In 1999, a landmark study by Ikonomidou and colleagues demonstrated that blockade of NMDA receptors in the developing animal led to neuronal apoptosis [307]. Since then, numerous drugs have shown potential for neuroapoptosis in the developing brain, including ketamine and halogenated anesthetics, but also propofol and midazolam [95,96,265,308–310]. However, many of these animal studies have been conducted in extreme conditions, i.e. with associated hypoxia or decrease in blood pressure, which may add their confounding effects [311]. Dexmedetomidine has recently been proposed as a neuroprotectant drug, but clinical studies are needed to ascertain the results of animal studies [312]. At present, we may recommend postponing non-urgent procedures requiring general anesthesia. If the procedure is non-elective, awake regional anesthesia or regional anesthesia under light general anesthesia is certainly a good choice. If general anesthesia is mandatory, balanced anesthesia with opioids is certainly to be favored.

KEY POINTS: PHARMACOLOGY OF INTRAVENOUS AGENTS

- Propofol binds to $GABA_A$ receptors and is a versatile agent for induction and maintenance. Its effects to decrease vascular tone and interfere with mitochondrial function at high and prolonged doses are the drug's major drawbacks
- Etomidate is an imidazole derivative that binds to GABAA receptors. It is essentially devoid of cardiovascular effects, but even a single dose causes reversible adrenal suppression
- Ketamine binds to NMDA receptors and is a useful agent for induction and for IV sedation. Excessive salivation and dysphoria upon emergence are its major side-effects
- Dexmedetomidine binds to presynaptic α_2 receptors and has been used increasingly as an ICU sedative, an adjunct to general anesthesia, and for procedural sedation. It is the only commonly used IV sedative/hypnotic that does not cause neuroapoptosis in preclinical models

Opioids

Opioids interact with specific opiate receptors (μ, δ, κ). Their major sites of action include the spinal cord, the medulla, and the periaqueductal grey matter [313,314].

Two main families of opioids are currently available: long-lasting hydrophilic drugs, mainly used for postoperative or chronic pain relief, and short-acting drugs of the phenylpiperidine chemical family, used preferentially for perioperative analgesia. However, short-acting drugs are being used more and more commonly outside the operating room. These are almost pure μ receptor agonists. Except for remifentanil, the liver metabolizes phenylpiperidines.

Phenylpiperidines

Pharmacokinetics

Phenylpiperidines are weak bases that bind to AGP [29,315,316]. They are exclusively metabolized in the liver by the CYP3A4 isoform, with the exception of remifentanil, which is degraded in plasma by non-specific cholinesterases [317–319]. These cholinesterases are ubiquitous; their deficiency is lethal. Thus, all patients are able to metabolize remifentanil. Clearance of remifentanil is very rapid in neonates. The drug's clearance decreases slightly thereafter (Table 10.6). These molecules have no active metabolites. Fentanyl, alfentanil, and sufentanil undergo hepatic metabolism, which rapidly matures (Fig. 10.11) [46]. Sufentanil is a suitable choice for opioid administration by target-controlled infusion (TCI) because it has shorter, more predictable context-sensitive half-times than fentanyl or even alfentanil (see Fig. 10.9) [320]. The decrement times of remifentanil are very short and almost constant, whereas the decrement times of fentanyl markedly increase with duration of administration [21].

Effect on the central nervous system

None of these agents has a deleterious effect on cerebral hemodynamics, provided the CO_2 tension is normal. With normal $PaCO_2$, neither CBF nor ICP is increased [321–323].

Effect on the respiratory and cardiovascular systems

All opioids depress ventilation. Muscle rigidity may be a problem in younger patients, especially when the drug is rapidly injected [324]. At equipotent doses, all phenylpiperidines reduce FRC to the same extent [325,326]. When injected slowly, these agents do not significantly decrease chest wall compliance, which allows them to be used in ICUs. Interestingly, muscle rigidity has been described following remifentanil injection in the mother [327].

All phenylpiperidines have depressant effects on myocardial contractility and vascular tone [161,328–331]. They provoke marked bradycardia. Atropine does not totally restore myocardial contractility. Remifentanil causes more bradycardia than the other drugs, but at equianalgesic doses all four drugs probably have similar effects. The incidences of respiratory depression, nausea and vomiting, pruritus, and rarely urinary retention are similar for all opioids [313].

Fentanyl

Fentanyl is the oldest of these agents [46,332–336]. Its half-life is very long, particularly when it is used to sedate patients in ICUs. Fentanyl's hepatic extraction ratio is greater than 70–80% in children. Soon after birth, fentanyl's clearance from the body exceeds 50% of hepatic blood flow (see Fig. 10.11). Unfortunately, fentanyl's important volume of distribution and slow intercompartmental clearance leads to rapid increases in context-sensitive decrement times with increased duration of administration. Moreover, fentanyl is secreted into gastric fluid, and recirculation of the drug from gastric contents and deep compartments can occur long after recovery from anesthesia. The usual dosing is 2–4 μg/kg as a bolus injection and 1–2 μg/kg for reinjections. The same dose

Table 10.6 Opioids and acetaminophen. Physicochemical properties and pharmacokinetics

Drug	Molecular weight (Da)	pKa	Distribution ratio (octanol/buffer)	Protein binding %		T½ (h)	CL (mL/kg/min)	Vc (L/kg)	Vss (L/kg)	T½ke0 (min)
Fentanyl	336	8.4	860	70–85		6–8	10–20	–	4–5	5
Alfentanil	–	6.5	130	65–90		1–2	10–15	–	0.4–1	1.5
Sufentanil	387	8.0	1750	80–90		2–3	4–9	–	2–3	2–4
Remifentanil	–	7.1	18	–		0.1	90–46	–	0.45–0.24	<1
Morphine	285	8.0#	6	30–35		1.5–2	30–40	–	2–4	100
Tramadol	263	9.4	250	20	Adult:	5.5	6.3	–	2.7–4.1	–
					2–8 yrs:	2.8–3	10.3	–	2.2	100–200
					Neonate:	–	5.7	–	–	–
Codeine[1]	299	8.2	12			1.7	8.5	–	–	–
Acetaminophen	151	9.5	3		Adult:	2	3.8	0.5	0.9	–
					2–15 yrs:	2	3.3	0.34	0.82	–
					Preterm babies and neonates (IV) CL = 0.5–1.5 mL/kg/min (27–46 week PMA)	–	–	–	–	–

CL, clearance; T½, terminal elimination half-life; Vc, volume of the central compartment; Vss, steady-state volume of distribution. 1 Codeine is metabolized to morphine, which is the active molecule.

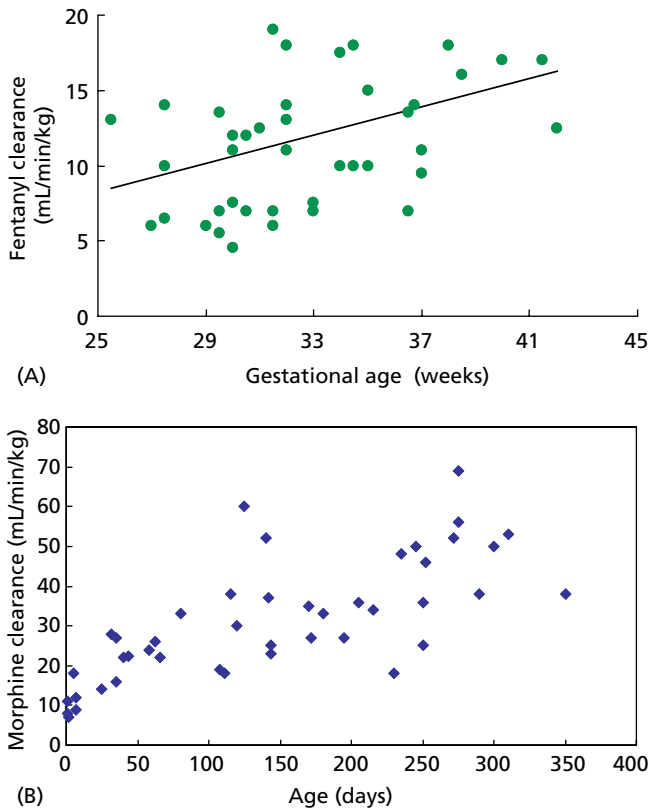

Figure 10.11 (A) Fentanyl and (B) morphine clearance as a function of age. In the younger premature infants, fentanyl clearance is relatively high (about half the liver blood flow). Maturation occurs rapidly and is almost complete at 42 weeks. Morphine clearance, on the other hand, is low at birth and maturation is complete only at the end of the first year of life. *Source:* Reproduced from (A) Saarenmaa et al [46] and (B) Lynn et al [45] with permission of Elsevier.

1–2 µg/kg/h is used for continuous IV infusion. Continuous infusion of fentanyl is not recommended during surgery if the plan is to extubate the trachea shortly after surgery. The time to peak effect is 5–6 min.

Alfentanil

Alfentanil has a short half-life, limited distribution into deep compartments, and high clearance (see Table 10.6) [335,337,338]. After an IV bolus dose of drug, alfentanil's peak effect occurs in 1–2 min. Following a prolonged infusion, decrement times increase moderately. The usual bolus dose of 10–20 µg/kg is followed by reinjections of 5–10 µg/kg for procedures of short duration.

Sufentanil

Sufentanil's half-life is of intermediate duration [335,337, 339–343]. Its effect is prolonged the least by prolonged administration, which is why its use has become very popular. Sufentanil's time to peak effect is 2–4 min. The usual bolus dose is 0.2–0.4 µg/kg at the time of anesthesia induction, followed by either reinjections (0.1–0.25 µg/kg) or an infusion of 0.1–0.5 µg/kg/h.

Remifentanil

Remifentanil is a very potent opioid that has a rapid onset (<1 min) and a very short half-life [337,344–349]. Its decrement times are constant. The context-sensitive half-time, i.e. 50% decrement time, is close to 4 min no matter how long the drug is administered. When given with propofol (3–4 mg/kg) or sevoflurane (0.5–1 MAC), excellent intubating conditions are produced in children in 20–30 sec after a bolus of 2–3 µg/kg. However, bolus doses of remifentanil are not recommended in neonates and infants because these patients may develop significant bradycardia and hypotension [327,328]. When given with 0.5–1 MAC of volatile anesthetic, a continuous infusion of 0.15–0.25 µg/kg/min (in neonates and infants) or 0.50 µg/kg/min (in children) gives excellent analgesia and stability, even for neonates who are more susceptible to the HR and blood pressure effects. However, care should be taken to (1) provide quality analgesia upon awakening and in the postoperative period because the analgesic effects of remifentanil are very short once the

drug infusion is discontinued, and (2) look for occurrence of the postoperative hyperalgesia syndrome, which follows the administration of large doses of opioids. Remifentanil and sufentanil are the drugs of choice for TIVA. The usual dose of remifentanil is 0.10 µg/kg/min in infants and 0.25 µg/kg/min in children.

Morphine

Morphine is a natural alkaloid derived from *Papaver somniferum*. It is an ampholyte, with a MW of 285 (free base), pKas of 9.85 and 7.87, an octanol:water distribution ratio of 1.42 at physiological pH, and is 35% protein bound to HSA. Morphine has four isomers, with little difference between them (codeine has the same isomeric distribution and morphine-6-glucuronide (M-6-G), the active metabolite of morphine, has two isomers).

Pharmacokinetics

Morphine (like hydromorphone) does not undergo phase 1 metabolism by cytochrome P450, but undergoes direct phase 2 metabolism by the 2B7 and to a lesser extent the 1A3 isoforms of UGT [37,39,350,351]. About 40% of morphine metabolism is extrahepatic, explaining why clearance is markedly greater than hepatic blood flow [352]. However, in patients with either a prothrombin time >40% above normal or a liver mass that decreases hepatic function by 50%, dosing must be halved (titration is unchanged) [353–355]. Although less than 10% of morphine is transformed to M-6-G, it has major importance because M-6-G has 2–8 times the potency of morphine and because its clearance is critically low [356,357]. In cases of renal failure, M-6-G elimination is impaired, and the risk of respiratory depression increases when the creatinine clearance (CrCL) is below 30 mL/min/1.73 m^2 [358]. Because the production of M-6-G is delayed, its concentration rises long after morphine administration is discontinued (Fig. 10.12). In patients with a CrCL of 15–30 mL/min/1.73 m^2, the dose of morphine should be halved. Drugs other than morphine should be given if the CrCL is <15 mL/min/1.73 m^2. Naloxone is efficacious for the treatment of narcotic-induced respiratory depression, but at times it must be infused for hours or even days. Peritoneal dialysis is poorly efficacious for removal of morphine, but hemodialysis (and usually hemofiltration) removes M-6-G. However, M-6-G may accumulate between dialysis sessions. Fentanyl and sufentanil are eliminated by hemofiltration and require the use of alternative agents in ICU patients undergoing hemofiltration.

Phase 2 metabolism is immature at birth and slowly increases during the first 6–9 months of life (see Fig. 10.11) [36,45]. This fact, together with the opioid receptor immaturity during the same period of time, explains why morphine dosing is different in young infants than in older infants and children (see Table 10.6) [35,36,359–362].

Morphine is hydrophilic and does not easily cross biological membranes. Morphine's effect concentration peaks 20 min after an IV injection (see Fig. 10.12). However, morphine concentration in the effect compartment reaches 80% of the peak concentration 6 min after an IV bolus. It remains above this concentration for 80 min. Morphine's duration of action is much longer than that of fentanyl or sufentanil.

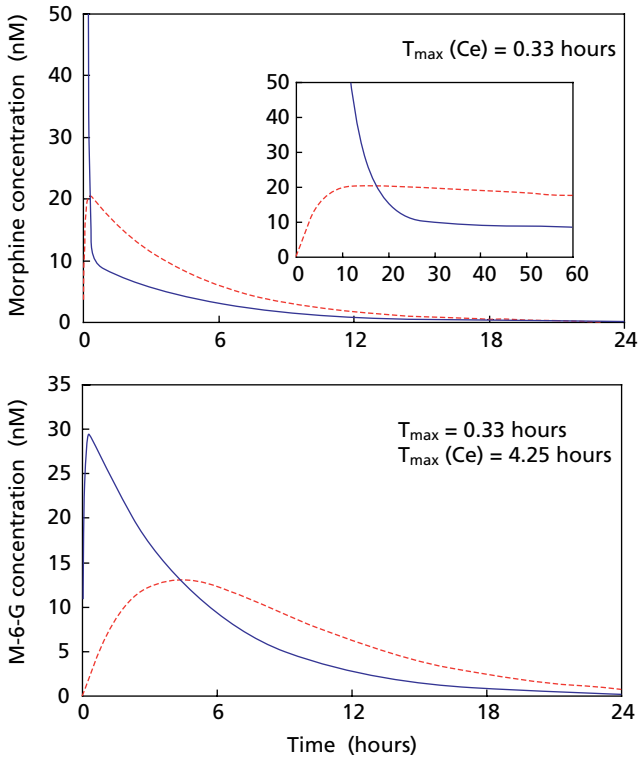

Figure 10.12 Morphine (*top*) and M-6-G (*bottom*) concentrations in the central compartment (*solid lines*) and in the effect compartment (*dotted lines*) after a single IV injection of morphine. After an IV bolus injection, morphine concentration peaks at 20 min because this hydrophilic drug slowly crosses the blood–brain barrier. M-6-G, which is more hydrophilic, peaks more than 4 h after the morphine injection. This phenomenon explains why the effect of oral morphine is delayed (part of the effect is due to M-6-G because of the first-pass effect). Adapted from Mazoit et al [356].

Pharmacodynamics

Respiratory depression is a frequent side-effect of opioids in neonates and infants. Respiratory rates decrease progressively, and respiratory depression increases. Depression is more associated with episodes of desaturation than with hypercarbia because of the associated sedation. However, sedation is difficult to appreciate in infants because they normally sleep much of the time. Monitoring by transcutaneous pulse oximetry is recommended for young infants, but clinical observation is also necessary, often in the postanesthesia care unit (PACU) or ICU. Apart from respiratory depression, the other side-effects of morphine include nausea and vomiting, urinary retention, pruritus, and constipation after 2–3 days of drug administration. Dexamethasone, droperidol, or a 5-HT3 receptor inhibitor like ondansetron best prevents postoperative nausea and vomiting (PONV).

Dosing

Morphine should be titrated in infants and young children. In neonates and infants younger than 3 months of age, a continuous IV infusion of the drug is usually sufficient. The doses are

between 10 and 30 µg/kg/h and are adjusted according to desired effect and the respiratory rate. Infants <3 months of age are very sensitive to the respiratory depressive effect of morphine. In infants older than 3–6 months and children <10 kg BW, IV titration of the drug is begun by injecting a loading dose of 50 µg/kg in those aged <12 months or 100 µg/kg thereafter. The loading dose is followed by 25 µg/kg every 5 min until the desired effect is reached. Children <40 kg usually receive 75 µg/kg every 5 min until the effective dose is reached. Children weighing more than 40 kg may receive the adult regimen, i.e. 3 mg as a bolus every 5 min. Before the age of 6–7 years, it is not appropriate to use a PCA device with the parents injecting the boluses because of safety issues. Even after this age, this method has its limits, and only a few teams continue to practice parent-controlled analgesia. Continuous infusions of opioids have shown similar benefits and similar limits as PCA, i.e. the lack of efficacy on pain with movement. The infusion regimen is between 20 and 40 µg/kg/h. After the age of 6 or 7 years, children are able to understand the principle of PCA. The dosing and rules of administration for children are similar to those for adults, i.e. boluses of 15–20 µg/kg every 5–10 min. Use of a continuous infusion of morphine along with the PCA has long been used, but this practice may induce respiratory depression. In patients receiving a continuous infusion of drug, nurse-controlled analgesia allows the injection of small boluses of drug and/or the modification of the infusion rate of morphine by increments or decrements of 5 µg/kg and is used in numerous centers. This is a good practice, provided all team members (including doctors and nurses) are well trained and follow rigorous protocols.

When pumps for continuous drug infusion or for PCA are not available, the intramuscular or (better) subcutaneous route can be used, but when this is done, the blood concentrations exhibit peaks and valleys. The oral route is also possible. However, when this route is used, the hepatic first-pass effect needs to be taken into account because part of the morphine dose is metabolized before reaching the general circulation. Only 10% of the metabolites are active (M-6-G). The concentration of M-6-G in the effect compartment is not significant before 6–9 h after initial administration of the drug (see Fig. 10.12). The oral dose of morphine is 0.2–0.4 mg/kg, with a maximum dose of 20 mg every 6 h.

Other opioids

Tramadol

Tramadol, a centrally acting analgesic, is a racemic mixture of cis and trans isomers that have few differences in activity, binding, or metabolism. It is a weak µ opioid receptor agonist that inhibits norepinephrine and serotinin reuptake [363–365]. The (+) enantiomer has greater affinity for the µ receptor and preferentially inhibits serotonin uptake while enhancing serotonin release. The (–) enantiomer preferentially inhibits norepinephrine reuptake by stimulating α_2-adrenergic receptors. The O-desmethyl metabolite (M1) is active and (+)M1 is the principal active molecule.

Pharmacokinetics

Tramadol is metabolized primarily by the CYP2D6, which is immature at birth [53,54,363,364]. Formation of M1 is impaired *in utero* and has important polymorphisms. The affinity of M1 for the µ receptor is 300–400 times greater than that of tramadol [365]. Both forms have similar half-lives [366–368]. Because M1 is at least as efficacious as the parent drug, there is a lag-time between its administration and effect. This is why the tramadol dose–effect relationship is flat and why it provides inadequate analgesia when injected immediately after surgery [369]. Hepatic failure markedly decreases the clearance of tramadol. Renal failure slightly decreases its clearance, but markedly decreases M1 clearance. CYP2D6 polymorphism may lead to inadequate analgesia in 5–6% of Caucasians because tramadol metabolism and M1 formation are reduced. In contrast, ultra-fast metabolizers of tramadol are at risk of respiratory depression. This wide variation in metabolism has resulted in the FDA issuing a warning that tramadol is contraindicated and should not be used in children less than 12 years of age for pain treatment, nor in children 12–18 years of age after tonsillectomy [370–372]. After oral administration, bioavailability of the drug is 70–90%. The T_{max} is 1–2 h, depending on the formulation (drops are more rapidly absorbed).

Pharmacodynamics

Respiratory depression with tramadol is less common than with morphine. Other side-effects include nausea, vomiting, dizziness, sweating, dry mouth, and drowsiness. However, like codeine, tramadol may induce severe poisoning in ultra-fast metabolizers [60].

Dosing

Tramadol is mainly used to treat mild to moderately severe postoperative pain and for intraoperative analgesia, although its analgesic properties are weaker than those of phenylpiperidines or morphine. Giving 2–3 mg/kg IV at the beginning of surgery can provide effective postoperative analgesia for many patients. Continuous infusions of tramadol are not recommended because the lag-time for M1 formation is long. Oral tramadol 1–3 mg/kg is given every 6–8 h.

Codeine

Codeine is a natural alkaloid from opium. It mainly acts by producing morphine, which is a minor metabolite (≈5–6% of codeine is transformed into morphine in most Caucasian subjects) [56,60]. The main metabolite, codeine-6-glucuronide, does not appear to be active. Because of CYP2D6 polymorphism, there are large variations in morphine production. For example, about 20–25% of East Asians do not metabolize codeine to morphine; 5–6% of Caucasians fail to do so. In those adults who metabolize codeine extensively, the absorption of 50 mg codeine leads to morphine and M-6-G production with C_{max} = 27 ± 23 and 41 ± 33 nM at T_{max} = 0.7 and 1.8 h respectively. The corresponding areas under the curve (AUC) compare with those obtained after 3–6 mg of oral morphine. However, some ultra-fast metabolizers have CYP2D6 gene duplication and may produce exaggerated amounts of morphine [57]. Fatalities have been reported in babies breastfed by their ultra-fast metabolizing mothers, in infants and young children treated with codeine for more than 1 day, or children with renal failure in whom M-6-G production was dramatically increased [58,59,373]. Codeine was also the subject of an FDA warning that the drug is contraindicated in children less than 12 years and in obese adolescents 12–18 years of age [370].

Dosing

Codeine is sometimes used in combination with acetaminophen. In children older than 6 months of age, dosing is 1 mg/kg/6–8 h. For day case surgery, parents should be warned against the possible lack of effect or the very rare possibility of overdosage with drowsiness or even coma and bradypnea [374].

Acetaminophen (paracetamol)

Acetaminophen has anti-inflammatory, antipyretic, and analgesic properties. Its mechanism of action is central and partly unknown [375,376]. Acetaminophen inhibits the COX-3 variant of cyclo-oxygenase. In addition, an active metabolite (p-aminophenol) may exert an effect through cannabinoid receptors.

Acetaminophen is poorly soluble in water. Mixing acetaminophen with mannitol and cysteine improves its solubility and stability. The time to peak plasma concentration is 30–60 min and 1–2 h after oral and rectal administration respectively (see Table 10.6) [377–382]. Bioavailability after oral administration is 85–95% and is usually <80% after rectal administration. Metabolism of the drug is by CYP2E1, CYP1A2, and CYP3A4 in the liver (see Table 10.1). N-acetyl p-benzoquinone imine (NAPQI) is a toxic metabolite that causes hepatotoxicity by binding to cellular proteins and forming drug adducts [33,383]. Paracetamol appears to be less metabolized in early infancy, but clearance rapidly increases after birth [381]. Neonatal icterus reduces clearance by 40%.

Exposure to acetaminophen in infancy and early childhood has been claimed to increase the incidence of asthma, but recent studies did not confirm the risk [384,385]. Intravenous paracetamol is also increasingly used to induce ductus arteriosus closure [386].

Dosing

Acetaminophen is available as tablets, an oral solution, suppositories, and a solution for IV infusion. The latter formulation is not available in all countries. For IV and oral administration, dosing is 10 mg/kg/6 h in premature infants and in neonates. Dosing is 15 mg/kg/6 h from 1 month to 2 years and 20 mg/kg/6 h from 2 to 15 years. By the rectal route, the first dose is 40 mg/kg.

Sucrose and other sweet-tasting solutions

These have shown antinociceptive properties in premature babies and neonates [387]. They are now commonly used, often in conjunction with comforting measures, to treat procedural pain and are recommended during awake regional anesthesia such as spinal anesthesia.

KEY POINTS: OPIOIDS

- Phenylpiperidine metabolism is almost fully mature in premature babies, hence increasing numbers of pediatric ICUs use fentanyl or sufentanil routinely for sedation
- Morphine metabolism is immature at birth and morphine clearance slowly increases during the first year of life. However, morphine remains the drug of choice in the postoperative period
- Codeine and tramadol mainly act via their metabolites. Some patients are ultra-fast metabolizers and are at risk of life-threatening complications. Codeine should therefore be avoided in children under 12 years, and particularly after discharge from hospital and in patients with sleep apnea syndrome

Muscle relaxants and reversal agents

The main two classes of muscle relaxants are depolarizing and non-depolarizing. Suxamethonium is the only depolarizing muscle relaxant still in use. Non-depolarizing agents include non-steroidal and steroidal agents. Both classes are non-competitive antagonists of acetylcholine (ACh).

Neuromuscular transmission

Muscle contraction is elicited by release of ACh in the synaptic cleft of the neuromuscular junction [388,389]. Calcium-dependent mechanisms are responsible for release of ACh from stores in presynaptic vesicles. In the synaptic cleft, ACh is rapidly degraded by acetylcholinesterases. There is also reuptake of some of the Ach by the motor nerve endings. Ach works by stimulating opening of muscle nicotinic acetylcholine receptors (nAChR), which allows sodium and calcium to enter the cells. The signal is further transmitted by sodium channels ($NA_V1.4$) [390], which are particularly abundant around endplates. $NA_V1.4$ density is lower in neonatal muscle. Seventeen subunits assemble numerous nAChR subtypes. Two variants of muscle type receptors, the adult $\alpha_1\beta_1\varepsilon\delta$ and the fetal $\alpha_1\beta_1\gamma\delta$, are present in humans (Fig. 10.13). During the first 2–4 years of life, the adult subtype progressively replaces the fetal subtype. Fetal receptors respond more slowly to ACh. Interestingly, fetal subtypes are re-expressed in ICU patients during prolonged periods of immobilization and inflammation. Neonates, infants, and young children also release less ACh into synaptic clefts than adults. However, the response of infants and children to muscle relaxants depends

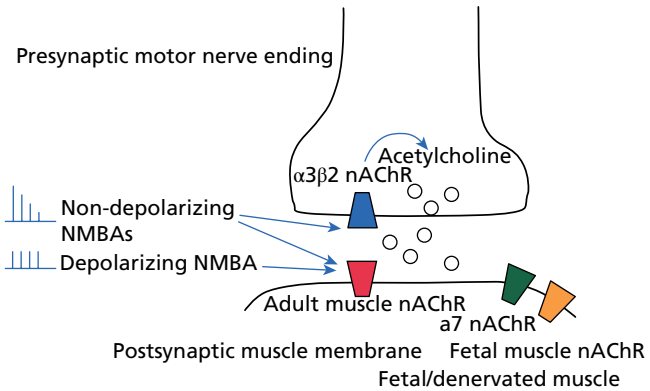

Figure 10.13 A schematic representation of the neuromuscular junction. The effect of neuromuscular blocking agents (NMBA) on the postsynaptic and presynaptic nicotinic acetylcholine receptor (nAChR) is depicted. The fetal muscle type nAChR has a lower affinity and rate of response than the usual adult receptor. *Source:* Reproduced from Fagerlund and Eriksson [389] with permission of Elsevier.

on numerous factors, such as the pharmacokinetics of the muscle relaxant and the binding capacity of the receptor. For example, the volume of distribution of succinylcholine and most non-depolarizing agents is increased in infants.

Monitoring neuromuscular blockade [391]

The only way to directly and reliably determine and prevent residual muscular blockade is by neuromuscular stimulation by acceleromyography. Acceleromyography measures the contraction of muscles in response to stimulation of their motor nerve. Single twitch measures the response height elicited by a single impulse. The train-of-four (TOF) measures the response to four successive supramaximal stimuli at 0.5 s intervals, and the height of the fourth to the first response is determined (T4/T1 ratio, that measures the amount of fade after repetitive stimulations). This ratio measures the decrease in response (fade) to repeated stimuli and is a measure of the amount of fade. Tetanic stimulation, the result of high-frequency stimulation, causes tetanic muscle contraction. Double-burst stimulation (DBS) consists of two short tetani (three impulses at 50 Hz) separated by an interval long enough to allow relaxation (usually 750 ms). Post-tetanic stimulation is the response to a single twitch or a TOF after a tetanic facilitation. Presynaptic neuronal nAChR is not inhibited by succinylcholine. Fade observed with non-depolarizing agents is related to the effect on presynaptic receptors; succinylcholine has no effect on these receptors, thus no fade is observed with this agent. This may explain why there is a lack of effect with TOF and tetanic fade [392]. All non-depolarizing drugs, on the other hand, inhibit neuronal nAChR and exhibit fade. The most common monitoring sites are the adductor pollicis (thumb), the orbicularis oculi (eyelid), and the corrugator supercilii (superciliary arch). The last is used to test for blockade of the laryngeal adductor muscles. The time course of blockade of the different muscles varies (Fig. 10.14) [393–396]. The abdominal wall and laryngeal muscles exhibit rapid onset and offset of neuromuscular blockade compared to the adductor pollicis. In addition, laryngeal adductors require higher doses of non-depolarizing drugs to achieve complete blockade than the adductor pollicis. The diaphragm is the muscle most resistant to blockade; its onset and recovery from blockade are similar to those of the adductor pollicis.

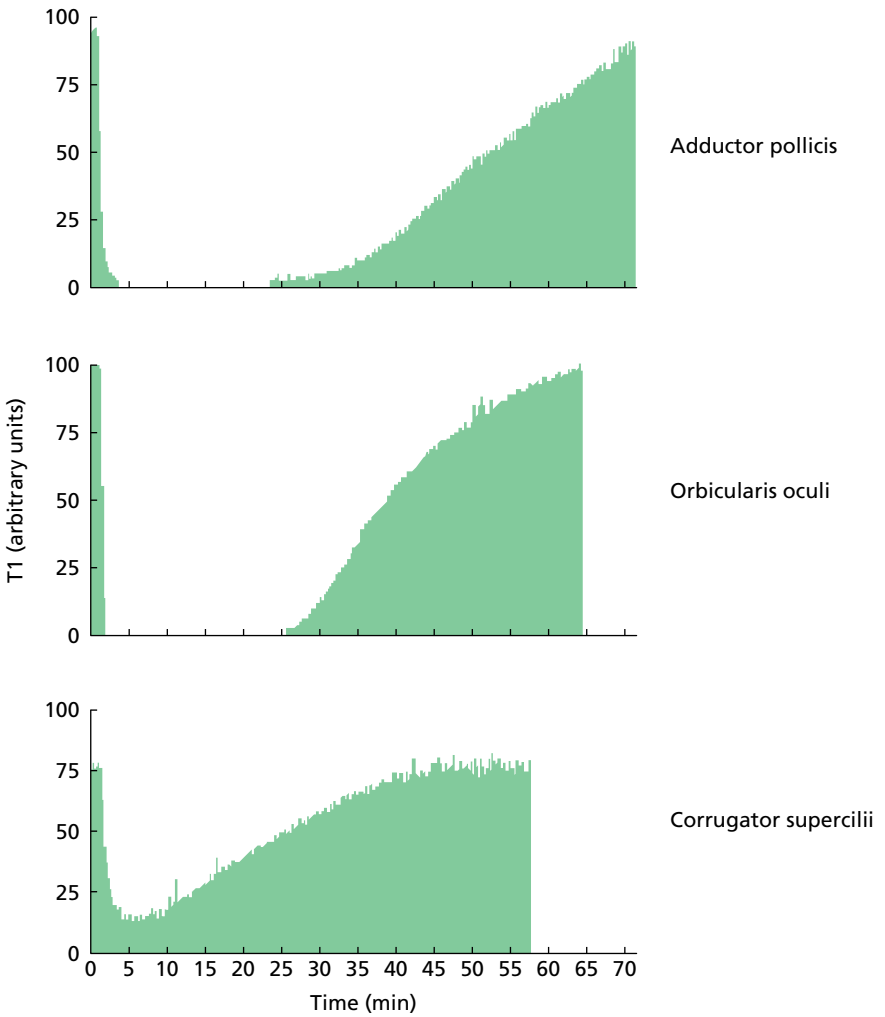

Figure 10.14 Difference in pharmacodynamics of muscles after injecting rocuronium into a patient. Train-of-four stimulations were repeated every 15 s and the T1 response is depicted in the figure. Clearly, the corrugator supercilii has a shorter delay of response, but is more resistant. Its kinetics is close to that of the laryngeal muscles. This is in perfect accordance with the 2–4-fold difference in T½ke0 reported for the adductor pollicis and laryngeal muscles after vecuronium or rocuronium injection. *Source:* Reproduced from Plaud et al [393] with permission of Wolters Kluwer.

Table 10.7 Muscle relaxants and reversal agents. Physicochemical properties and pharmacokinetics

Drug	Molecular weight (Da)	Distribution ratio (Octanol/ buffer)	Protein binding %	T½ (min)	CL (mL/kg/ min)	Vc (mL/kg)	Vss (mL/kg)	T½ke0		Ce50 (ng/mL)
								Adductor pollicis	Larynx (min)	
Succinylcholine	290	$7\ 10^{-5}$	20	1.01	37	9	40	12	–	746
Pancuronium	–	–	–	107	1.81	–	275	5.1	–	–
Vecuronium	558	0.15	70	–	4.9	40	200	5.8	1.2	166
Rocuronium	546	0.02	45	71	3.2	47	210	4.4	2.7	820–1420
		Infant (1–10 mo)	–	–	35	230	2.8	–	650	–
			Child (2–6 yrs)	46	7.1	35	165	3.6	–	–
Atracurium	929	$1\ 10^{-4}$	37	–	–	–	–	6.8	–	–
Cisatracurium	929	$1.9\ 10^{-4}$	20	26	4.1	35	94	3.9–9.8	–	98–153
			Child (1.5–6 yrs)	–	6.8	87	207	6.0	–	129
Mivacurium	1029	$3\ 10^{-3}$	30							
			Cis-cis	68	3.8	–	227			
			Cis-trans	2.0	106	–	278			
			Trans-trans	2.3	57	–	211			
Neostigmine	223	32		110	9.2–10	80	1700–1860			
Edrophonium	166	63		126	8.3–12.1	50	810–900			
		Infant (3–7 mo)	73	17.8	150	1180	–			
		Child (1–4 yrs)	99	14.2	170	1220	–			
Sugammadex	2178			136	75–138	50	160–200	1.0 (rocuronium)	–	720
								1.7 (vecuronium)	–	62

Ce50, pseudo-steady-state concentration leading to half maximum effect; CL, clearance; T½, terminal elimination half-life; T½ke0, rapid equilibration half-life; Vc, volume of the central compartment; Vss, steady-state volume of distribution.

The differences in T½ke0 at different sites reflect differences in muscle physiology (Table 10.7 and Fig. 10.14). Low degrees of neuromuscular blockade cause sufficient pharyngeal dysfunction to allow easy tracheal intubation [397]. Consequently, the corrugator supercilii is the best indicator of ease of tracheal intubation, and the adductor pollicis is the best indicator of early recovery from the block. One response out of four (TOF) means that the muscular force is <10% of control. When the fourth response reappears, the force of the tested muscle has reached at least 25% of control. In clinical practice, the recovery of T4/T1 to >90% indicates that non-significant residual block remains. Reversal of muscle blockade is usually only possible if two of four responses of the TOF are present.

Succinylcholine

Despite succinylcholine (SCh) being the only depolarizing muscle relaxant available, its precise mechanism of action remains unclear. Its injection induces massive exocytosis of Ach and muscle fasciculation. The ensuing paralysis involves complex mechanisms that include desensitization of the receptor and inactivation of the sodium channels. SCh has a rapid onset and short duration of action, which makes it the agent of choice for rapid sequence induction.

SCh has low affinity for the presynaptic nAChR and causes a phase I block (decreased twitch amplitude, absence of fade, absence of post-tetanic potentiation). Large doses of SCh cause tachyphylaxis and a phase II block that resembles a non-depolarizing block.

Pharmacokinetics

Succinylcholine has two molecules of ACh linked by an ester bond. It is highly hydrophilic (see Table 10.7) [398]. Like cocaine, heroin, and ester local anesthetics, SCh is hydrolyzed in serum, red blood cells, and liver by non-specific esterases (butyrylesterases or pseudocholinesterases) [399,400]. There are many plasma cholinesterase genotypes that are responsible for wide variations in plasma cholinesterase activity. Some patients have reduced blood pseudocholinesterase activity. More than 20% of Caucasians are heterozygous for the main atypical variant. Patients with this variant have elimination half-lives that are nearly double those of patients without the variant. Patients who are homozygous for the abnormal variant may remain paralyzed for hours to days following a single injection of SCh. Determining the dibucaine number is the test for lack of pseudocholinesterase. However, lack of sensitivity, specificity, and cost make its routine use unlikely. Eskimos and Australian aborigines share the same genotype and have greater risk for prolonged paralysis with SCh.

Succinylcholine rapidly accesses the neuromuscular junction. It is rapidly degraded due to its small volume of distribution and to elimination from both the central and peripheral compartments (see Table 10.7) [401]. The elimination half-life of SCh is 1 min. However, the T½ke0 for blockade of the adductor pollicis is 12 min and is similar to that for non-depolarizing agents. The short onset of the drug's effect is aided by the high dose injected. Unfortunately, no recent data for infants and children are available [402–404]. Infants require 3 mg/kg and children 2 mg/kg to produce the same intubating conditions. It is highly probable that these differences in

drug dosage are the result of different volumes of distribution in the two groups. SCh is very hydrophilic. PK-PD data are needed in newborns, infants, and children, and should be correlated using allometric scaling.

Pharmacodynamics

Succinylcholine has numerous side-effects that have caused some anesthesiologists to abandon its use.

Effects on the central nervous system

Succinylcholine is said to increase ICP. However, recent studies have shown that this is not the case if normocapnea is maintained. It has also been thought to increase intraocular pressure by causing contraction of the extraocular muscles. Recent evidence has shown that intraocular pressures do not increase when the trachea is rapidly intubated and the lungs are ventilated [405].

Effects on the cardiovascular system

Succinylcholine can cause either tachycardia or bradycardia, but bradycardia seldom occurs with the first dose of ACh. It occurs much more commonly after a second or third dose of the drug. Bradycardia is easily prevented by atropine [406]. Although not well documented, SCh-induced fasciculations are said to increase cardiac output and $CRMO_2$. This effect does not appear to have clinical relevance.

Potassium release, effects on muscles, and malignant hyperthermia

Potassium release

Succinylcholine causes potassium release that usually is minimal and has no clinical consequence, unless the patient is hyperkalemic. Patients with Duchenne muscular dystrophy and other myopathies, paralysis (usually of spinal origin), rhabdomyolysis, and burns have a significant risk for developing arrhythmias with SCh due to receptor upregulation and phenotype changes in denervated muscle [407,408].

Masseter rigidity and malignant hyperthermia

Succinylcholine may cause masseter spasm and incomplete relaxation of the jaw, particularly when it is given during halothane anesthesia. Some authors argue that this occurs because the dose of SCh was inadequate. SCh can trigger malignant hyperthermia (see section "Pharmacokinetics and pharmacodynamics of inhaled anesthetics" and Chapter 45). This is more likely when it is used with halothane or sevoflurane.

Non-depolarizing muscle relaxants

Non-depolarizing muscle relaxants compete with ACh at both muscle and neuronal nAChR. Non-depolarizing relaxants are either aminosteroids (pancuronium, vecuronium, and rocuronium) or benzylisoquinoliniums (atracurium, cisatracurium, and mivacurium) [409]. All of these drugs produce a block of <40 min duration. Mivacurium's duration of action is the shortest.

Pharmacokinetics

All neuromuscular relaxants are highly water-soluble and have small volumes of distribution [398]. They are best described by two- or three-compartment linear kinetics (see Table 10.7) [410–419]. The volume of the central compartment is no larger than the plasma volume, and the volume of distribution at steady state (Vss) is equal to one-quarter the body weight. Clearance of non-depolarizing muscle relaxants is usually relatively low, except for mivacurium, which is hydrolyzed by the same cholinesterases as SCh.

Metabolism

Aminosteroids are principally eliminated unchanged in urine and bile by carrier-mediated processes [420,421]. Transport is by OCTs and, to a lesser extent, by P-gp. Pancuronium has major renal transport and limited hepatobiliary transport [422]. As much as 25% of a dose of pancuronium can be recovered as the 3-hydroxy metabolite, which has blocking properties half as potent as those of pancuronium. Patients with renal and/or liver failure have delayed elimination of pancuronium. Vecuronium is excreted unchanged in urine and in bile (>50% is transported in bile) [423]. Patients who have cholestasis have reduced clearance of vecuronium. Renal failure has less effect. However, patients with end-stage renal failure also exhibit decreased clearance of vecuronium and a slightly higher sensitivity to the drug than normal subjects. Small amounts of 3-desacetyl vecuronium, a moderately active metabolite, were found in plasma after prolonged administration of vecuronium. Rocuronium, a derivative of vecuronium, has a rapid onset and duration of action that are similar to those of vecuronium. Rocuronium is excreted unchanged in urine and feces; its metabolism is minimal. Rocuronium's elimination is only slightly impaired by renal failure. Excretion by transporters is less impaired than that by metabolism. For example, patients with cirrhosis have greater volumes; patients with cholestasis and jaundice have decreased clearance. The order of clearance is pancuronium < vecuronium ≈ rocuronium, which explains their durations of action.

Atracurium has ten stereoisomers [424]. The 1R-cis, 1'R-cis isomer is called cisatracurium. Both atracurium and cisatracurium are spontaneously degraded in plasma by Hofmann elimination and to a small degree by carboxylesterase activity. The Hofmann reaction is rate limited and temperature and pH dependent. The main end-product of atracurium and cisatracurium is laudanosine, which is toxic and may cause seizures. However, serum concentrations of laudanosine are always below the toxic threshold. Because cisatracurium is 3–5-fold more potent than atracurium, cisatracurium causes less histamine release and has less potential for causing convulsions.

Mivacurium is hydrolyzed in plasma by the same pseudocholinesterases that hydrolyze SCh [425,426]. It is a mixture of stereoisomers; the cis-trans and the trans-trans both have similar potency. A third isomer, the cis-cis, accounts for <6% of the total amount of metabolites and is about one-thirteenth as potent as the other two isomers. Unfortunately, the cis-cis isomer is poorly cleared; its T½ is about 20–30 times longer than that of the other two isomers. Patients who are heterozygous for plasma cholinesterase (those with the atypical AA variant, i.e. 20% of the Caucasian population) clear the major isomers 50% less well and have a prolonged T½ [400]. Patients who are homozygous for AA or other variants can have prolonged

neuromuscular blockade. Clearance of mivacurium is moderately decreased by renal failure [426].

Pharmacodynamics

For neuromuscular blocking agents, ke0 is strongly correlated with logD, the distribution coefficient. Highly hydrosoluble molecules rapidly access their receptors, producing a rapid onset of action. Ce50 is inversely correlated to logD and to molecular weight (MW). Highly hydrosoluble molecules, and those with low MW, are more potent [398]. The duration of action depends on the rate of receptor access (T½ke0) and on affinity for the receptor. Interestingly, there is a great difference between the different sites of action. T½ke0 is much slower for adductor pollicis muscles than for the laryngeal muscles [393,395]. Drug access to the laryngeal muscles is 4–6 times more rapid than to the adductor pollicis and the diaphragm. The onset of action is dose dependent. Drugs with relatively short durations of action, such as rocuronium, may require relatively large doses of drug for the onset of action to be rapid. Rocuronium has the shortest T½ke0 and a rapid onset of action. Because of its intermediate duration of action, it is possible to use high doses of rocuronium to provide excellent intubating conditions 1 min after its injection.

Specific effect on organs

Non-depolarizing agents have little effect on CBF or ICP. Atracurium, cisatracurium, and mivacurium release histamine, which, when injected rapidly, can induce bronchoconstriction, hypotension, and tachycardia [427]. Pancuronium (and occasionally rocuronium) blocks muscarinic receptors and induces moderate tachycardia.

Interactions

Volatile anesthetics and neuromuscular blocking drugs interact [428–430]. The mechanism for this potentiation remains unclear, but is likely an additive effect on the nAChR [422]. For example, sevoflurane shortens the onset and prolongs the duration of a rocuronium-induced block in children. T½ke0 and Ce50 are decreased by 60%, and the recovery time to T1 = 5% is prolonged by 25%. Acid–base disturbances, hypokalemia, and hypothermia may prolong the duration of action of muscle relaxants. Numerous drugs (volatile anesthetics, antimicrobials such as gentamicin, lithium, and calcium-channel blockers) interact with neuromuscular blocking agents and enhance the block. Magnesium sulfate potentiates the action of non-depolarizing agents by decreasing Ach release. Resistance to neuromuscular blocking drugs can be caused by phenytoin, carbamazepine, and other anticonvulsants. Giving SCh after a non-depolarizing agent prolongs the block.

Allergy to muscle relaxants

Neuromuscular blocking agents can cause severe anaphylaxis, which is different from the release of histamine commonly observed when atracurium, cisatracurium, or mivacurium are injected rapidly [431–433]. Anaphylaxis is rare in neonates and infants. The incidence of anaphylaxis increases with age and reaches its maximum in 30–60-year-old patients. Based on skin tests, rocuronium is said to cause more allergic reactions than the other drugs, but skin testing may not be the best way to determine this. Grade III (bronchospasm ± urticaria) reactions occur in about 75% of cases.

Dosing

Tracheal intubation

The intubating dose of SCh is 1 mg/kg in adults, 3 mg/kg in infants, and 2 mg/kg in children. The intramuscular dose of SCh for emergency tracheal intubation is 5 mg/kg [434].

The intubating dose for rocuronium is 0.6 mg/kg in both infants and children. This dose produces excellent intubating conditions in <1 min. Older children often require the adult dose 1.2 mg/kg for rapid sequence induction of anesthesia. This dose of drug provides excellent intubating conditions, but its duration of action is prolonged.

Pancuronium 0.08–0.1 mg/kg has an onset time of between 3 and 5 min and duration of action of more than 60 min. The reinjection dose of 0.02 mg/kg is given when T2 of the TOF returns. *Vecuronium* 0.1–0.2 mg/kg has an onset time of between 1 and 3 min and duration of action of 30–40 min. The reinjection dose is 0.1 mg/kg. A continuous infusion at 1–1.2 µg/kg/min is used for maintenance. *Rocuronium* 0.4–0.6 mg/kg has an onset of between 1 and 2 min and duration of action of 40–60 min. The reinjection dose is 0.1–0.15 mg/kg. A continuous infusion of 5–15 µg/kg is often used for maintenance. *Atracurium* 0.4–0.8 mg/kg has an onset of between 2–3 minutes and duration of action of 40–60 min. The reinjection dose is 0.1–0.2 mg/kg. A continuous infusion of 5–15 µg/kg/min is used for maintenance. *Cisatracurium* 0.1–0.2 mg/kg has an onset of between 2–3 min and duration of action of 40–60 min. The reinjection dose is 0.03–0.5 mg/kg. A continuous infusion of 1–3 µg/kg/min is used for maintenance. *Mivacurium* 0.2 mg/kg has an onset of between 1–3 min and duration of action of <30 min.

Reversal agents

Two different classes of antagonists are used to reverse neuromuscular blockade: the quaternary ammonium reversible acetylcholinesterase inhibitors, and sugammadex.

Acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors (neostigmine and edrophonium) are quaternary ammoniums and are hydrophilic, ionized compounds.

Pharmacokinetics

Neostigmine and pyridostigmine are tertiary ammonium compounds that bind covalently to acetylcholinesterase and form inactive carbamylated complexes that degrade slowly (T½ ~30 min) [435]. Edrophonium forms a weak complex that degrades more rapidly, which explains why its effects are shorter than those of neostigmine. Its half-life is shorter than that of either neostigmine or edrophonium. Neostigmine is rapidly metabolized at the neuromuscular junction by acetylcholinesterases and by erythrocytes. The nearly inactive metabolites are conjugated and eliminated by the kidney [436]. Edrophonium is metabolized to an inactive glucuronide conjugate. Interestingly, although the pharmacokinetics of both drugs are poorly understood, their terminal half-lives

are longer than those of all neuromuscular blockers, including pancuronium (see Table 10.7) [437,438]. In anephric patients, elimination of neostigmine is impaired (T½ = 181 versus 80 min). The time to reach T1, T4/T1 and T2 is always shorter in children than in adults. Moreover, recovery occurs more quickly with edrophonium in children than with neostigmine [439–446]. This is true for all blocking agents studied. Neostigmine is about 12–18 times more potent than edrophonium. In pediatric patients, the doses of edrophonium required for either 50% or 80% recovery of twitch height are comparatively greater (on a weight basis) than in adults. It is unclear if this is true for neostigmine.

Pharmacodynamics

Acetylcholinesterase inhibitors have numerous side-effects that are mostly related to their muscarinic effects [427]. These include bradycardia, salivary and intestinal secretions, miosis, and bronchoconstriction. Atropine or glycopyrrolate administration can prevent or reverse these effects. In pediatric patients, atropine-induced tachycardia is rarely a problem, but bradycardia may be a problem, particularly in neonates and infants. Edrophonium causes less bradycardia than neostigmine and is preferred in pediatric patients. The bronchoconstriction induced by these drugs may be a problem, particularly in patients with asthma.

Dosing

In infants and children, the dose of neostigmine required to reverse the block varies between 0.03 and 0.07 mg/kg, depending on the neuromuscular blocking agent used. The author recommends a bolus of 0.05 mg/kg. The drug's peak effect occurs 10 min after injection. Edrophonium 0.75–1 mg/kg is given as a bolus. Its peak effect occurs 2–3 min after injection. Atropine 10–-15 µg/kg should be given *before* either drug to prevent bradycardia. Glycopyrrolate 4 µg/kg in children and up to 8 µg/kg in neonates and infants effectively prevents bradycardia.

Sugammadex

Sugammadex is a cyclodextrin that can encapsulate aminosteroid neuromuscular blockers. It has an outer hydrophilic structure and an inner hydrophobic core. The drug was designed to specifically encapsulate rocuronium and vecuronium and to a lesser extent pancuronium. Sugammadex has no effect on benzylisoquinoliniums (atracurium, cisatracurium, and mivacurium). No serious side-effects have been reported, but anaphylaxis is possible.

Pharmacokinetics

Sugammadex is eliminated unchanged by the kidney [447]. Its half-life exceeds that of all neuromuscular blockers [448,449]. Its clearance is 75–138 mL/min, which approximates the glomerular filtration rate (GFR). In patients with renal failure, the decrease in sugammadex clearance is similar to the decrease in renal clearance [450]. The affinity of sugammadex for vecuronium and rocuronium differs. T½ke0 for vecuronium is twice that of rocuronium (see Table 10.7). This difference in the rate of access is consistent with the difference in Kd, the equilibration dissociation rate constant (0.1 µM for rocuronium versus 0.175 µM for vecuronium). However, the binding capacity is similar for both drugs (the ratio of Ce50 for the sugammadex effect site is similar to the ratio of Ce50 for neuromuscular junction effect site). After a dose of rocuronium, 2 mg/kg of sugammadex is injected at reappearance of T2. The time to 90% recovery of TOF occurs after 0.6 min in infants, 1.2 min in children, and 1.2 min in adults. Doses >2 mg/kg do not hasten recovery.

Dosing

For routine reversal of a block after reappearance of T2, 2 mg/kg of sugammadex is adequate [451]. However, in an emergency (e.g. failure to intubate the trachea after a large dose of rocuronium), sugammadex doses as high as 12 mg/kg may be required.

Anticholinergic agents

Two anticholinergic agents are clinically available, atropine and glycopyrrolate [452–458]. These are non-selective competitors for ACh at the muscarinic receptors and have little or no action on nicotinic receptors.

Atropine is a natural alkaloid of *Atropa belladonna*. It is a tertiary amine with a pKa of 9.9. Atropine is highly ionized at physiological pHs and rapidly diffuses in water compartments (Vd 4.9 L/kg). Atropine has a chiral carbon (the R form is almost inactive).

Glycopyrrolate is a synthetic quaternary ammonium salt that is totally ionized at physiological pHs. Its volume of distribution is small, 0.60 L/kg. In adults, the terminal half-life of atropine is 3–4 times longer than that of glycopyrrolate (2.3–3.7 versus 0.8 h). In infants and children, glycopyrrolate's T½ is very short (20 min) due to its greater clearance (22 mL/kg/min (infants and children)versus 9 mL/kg/min (adults)). Atropine's clearance is 15.4 mL/kg/min in adults. The larger volume of distribution in neonates and infants makes the T½ longer than in adults. Atropine is metabolized in the liver; one of its metabolites, 1-hyoscyamine, is active. Glycopyrrolate is not extensively metabolized and is rapidly excreted unchanged in urine. Elimination of glycopyrrolate is impaired by renal failure. Unlike atropine, glycopyrrolate does not cross the blood–brain barrier.

Anticholinergic agents increase heart rate, inhibit secretions, and induce bronchodilation. Atropine induces mydriasis while glycopyrrolate does not. At very low doses, both drugs can cause bradycardia. Glycopyrrolate's heart rate effects are delayed compared to those of atropine (2–3 min versus 1 min). Toxicity (tachycardia, restlessness and excitement, hallucinations, delirium, and coma with paralysis) occurs at supratherapeutic doses of atropine. Hypotension and circulatory collapse may also occur.

Dosing

The IV dose of atropine is 10–15 µg/kg. That of glycopyrrolate is 4 µg/kg for children and up to 9 µg/kg for infants 1 month to 2 years old. Some preparations of glycopyrrolate contain benzyl alcohol, which is toxic to neonates and infants and should not be repeated.

Following intramuscular injection, T_{max} occurs in 15–30 min. However, drug absorption by this route varies widely. IM doses are similar to or slightly higher than IV doses.

KEY POINTS: MUSCLE RELAXANTS AND REVERSAL AGENTS

- Succinylcholine has a very large volume of distribution in infants. The intubating dose is 3 mg/kg before 1 year and 2 mg/kg from 1 to 6–8 years
- The dose of neostigmine required to reverse the block is 0.05–0.07 mg/kg in infants and children
- Atropine (10–15 µg/kg) or glycopyrrolate (5–10 µg/kg) must be administered *before* reversal in infants (bradycardia induces a major fall in cardiac output in infants)
- Aminosteroid relaxants are mostly excreted unchanged by membrane transporters, which are not all fully mature at birth and during the first years of life. Atracurium and cisatracurium are degraded by the Hofmann reaction, which is temperature dependent
- Sugammadex is a newer cyclodextrin reversal agent specific for vecuronium and rocuronium. Large doses up to 12 mg/kg can be used for emergency reversal of dense neuromuscular blockade

Local anesthetics

Local anesthetics (LA) block propagation of impulses along nerve fibers by inactivation of voltage-gated sodium channels, which initiate action potentials [459]. Some toxins (tetrodotoxin (TTX)) act on the outside of cells to block action potentials; local anesthetics have their effects on the cytosolic side of phospholipid membranes. Two main chemical compounds have been synthesized and used clinically as LAs, amino esters (2-chloroprocaine, procaine, tetracaine) and amino amides (lidocaine, bupivacaine, ropivacaine). Amino esters are degraded by pseudocholinesterases in plasma; they undergo minimal hepatic metabolism. Amino amides are more stable and are metabolized exclusively by the liver.

Pharmacokinetics [460]

Local anesthetics (LAs) are weak bases with molecular weights of 236–288 Da (Table 10.8). The pKa of all LAs is between 7.6 (mepivacaine) and 9.1 (chloroprocaine). At a pH of 7.40, 60–85% of the molecules are ionized and diffuse in the body's water compartments. LAs are also soluble in lipids and cell membranes. Bupivacaine is 10 times more soluble in membranes than lidocaine; ropivacaine is twice as soluble as lidocaine. With the exception of lidocaine, all amide LAs possess an asymmetric carbon. Although the physicochemical properties (pKa, distribution ratio) of the isomers are identical, the enantiomers have different affinities for the biological effectors (channels, receptors, proteins). Ropivacaine and levobupivacaine are pure S-(–) enantiomers. LAs are marketed as hydrochloride salts in water at pHs of 4–5 to prevent them from coming out of solution. The salts precipitate when bicarbonate is added to the solution to increase its pH.

Like most weak bases, amide LAs bind to serum proteins and red cells. This may be clinically important, especially in neonates and young infants. Neonates who have hematocrits >45% may have less unbound drug. In serum, LAs bind to both AGP and albumin. Despite its low concentration in serum (less than 1 g/L in adults), AGP is the major protein that binds LAs. During the first 6–9 months of life, AGP concentrations progressively increase and reach adult levels by 1 year of age (see Fig. 10.3) [28]. When this occurs, the free fraction of LAs decreases [461]. The decrease in free fraction may protect from LA toxicity. However, the concomitant decrease in hepatic clearance of free drug may leave clearance unchanged (see Fig. 10.4). LAs also bind to HSA, but with a very low affinity. It is only because HSA is the most abundant protein in serum that its binding capacity is significant.

Absorption

After application of topical anesthesia to the upper airway via atomizer, LAs are rapidly absorbed and can cause toxicity, particularly in children under 4 years of age. This is why it is important to use devices that deliver no more than 10 mg with each activation [462]. EMLA® (eutectic mixture of local anesthetics) cream contains equal amounts of lidocaine and prilocaine and is not absorbed in significant amounts, except in premature babies [463]. Prilocaine produces methemoglobinemia in neonates and infants, especially if they are also treated with trimethoprim–sulfamethoxazole [464]. The cream may not work in premature babies because of their very high skin blood flow.

Table 10.8 Physicochemical properties of local anesthetics

Drug	Molecular weight (Da)	pKa*	Distribution coefficient†	Protein binding	Onset of action	Duration of action	Potency‡
Esters							
Procaine	236	8.9	1.7	6%	Long	1 h	0.5
Chloroprocaine	271	9.1	9.0	?	Short	½ h–1 h	0.5–1
Amides							
Lidocaine	234	7.8	43	65%	Short	1 h 30–2 h	1
Prilocaine	220	8.0	25	55%	Short	1 h 30–2 h	1
Mepivacaine	246	7.7	21	75%	Short	1 h 30–2 h	1
Bupivacaine**	288	8.1	346	95%	Intermediate	3 h–3 h 30	4
Ropivacaine	274	8.1	115	94%	Intermediate	3 h	3.5–4

* pKa at 37°C.
** Bupivacaine = levobupivacaine.
† Octanol:buffer partition.
‡ Potency is relative to lidocaine.

Amide LAs have a bioavailability of 1 (metabolism is exclusively hepatic). Since these drugs are hydrophobic, they bind to tissues, which delays their absorption. This delay varies depending on the local conditions. For example, absorption occurs more rapidly after an ilio-inguino-iliohypogastric block than after a caudal block. In adults, 3 h after an epidural injection, only 70% of a dose of lidocaine and 50% of a dose of bupivacaine or of ropivacaine is absorbed, which is a safety factor [465]. From adult studies it is clear that the speed of drug absorption decreases from head to foot and from the thoracic to the caudal portion of the epidural space. Lidocaine and bupivacaine concentrations peak about 30 min after caudal or lumbar injection in infants and adults. The T_{max} for ropivacaine is much longer in infants than in children and in children than in adults, probably because CYP1A2, which metabolizes lidocaine and ropivacaine, is immature before 4–7 years of age [466]. This phenomenon is less important with levobupivacaine because levobupivacaine is metabolized by CYP3A4/7 [467].

Epinephrine reduces the peak concentrations of LAs. The usual concentration used in clinical practice is 5 mg/L (1/200,000), which is optimal in adults. It is possible that this concentration of epinephrine may decrease spinal cord blood flow in some infants and produce neurological deficits. Therefore, some authors suggest using no more than a 1/400,000 concentration of epinephrine in infants <1 year of age, since this concentration is also efficacious [468].

Distribution

The volume of distribution of LAs at steady state (Vss) is slightly less than 1 L/kg (Table 10.9) [469–478]. Because drug absorption is delayed, volumes calculated after administration by non-intravenous routes are markedly overestimated. Terminal half-lives are also increased compared to values obtained after an IV injection. Total body clearance of the drug is only measured accurately following extravascular administration, but sampling must take place over a prolonged period of time. It is highly probable that LAs distribute into large volumes in neonates, infants, and adults, thus preventing high serum drug concentrations from occurring after a single injection. However, this is not the case following several injections. Ropivacaine's volume of distribution is smaller than that of bupivacaine in adults and probably in pediatric patients. At similar doses, the C_{max} of ropivacaine is higher than that of bupivacaine, despite ropivacaine's delayed T_{max}.

Elimination

Liver cytochrome P450 enzymes metabolize all amide local anesthetics. Bupivacaine is predominantly metabolized into pipecoloxylidide (PPX) by CYP3A4/7 [479]. Ropivacaine is predominantly metabolized to 3′- and 4′-OH-ropivacaine by CYP1A2 and to a minor extent to PPX by CYP3A4 [47]. These enzymes are not fully mature at birth and have important differences in their developmental expression. The extraction ratios for lidocaine (0.65–0.75) are relatively high. Lidocaine is flow limited rather than rate limited for its elimination. Therefore, any decrease in cardiac output decreases hepatic clearance of lidocaine. The resultant increase in plasma concentration of LA may be toxic. Bupivacaine and ropivacaine, on the other hand, have a relatively low hepatic extraction ratio (0.30–0.35) and are rate limited for their elimination. Thus, hepatic clearance and free fraction are major determinants of total clearance. After surgery, serum AGP concentrations increase, which increases protein binding. This decreases

Table 10.9 Bupivacaine, levobupivacaine, and ropivacaine pharmacokinetics after different routes in infants and children compared to adults

		fu	Vss# (l L/kg)	CLT/f (mL/min/kg)	CLU/f (mL/min/kg)	T½# (h)
Bupivacaine						
IV adults		0.05	0.85–1.3	4.5–8.1	≈100	1.8
Epidural adults		–	–	4–5.6	–	5.1–10.6
Infants caudal single shot		0.16 (0.05–0.35)	3.9	7.1	–	–
Children (5–10 years)		–	2.7	10		–
Infants epidural prolonged		(0.06–0.24)*	–	5.5–7.5*	36–73	–
		(0.03–0.18)‡		3.5–4‡	36–73	
Levobupivacaine						
IV adults		0.045	0.72	4.2	116	2.6
Caudal, infants 0.6–2.9 months		0.13	2.87	6.28	51.7	–
Ropivacaine						
IV adults		0.05	0.5–0.6	4.2–5.3	≈100	1.7
Epidural adults		–	–	4.0–5.7	≈70	2.9–5.4
Caudal single shot	Neonates	0.07	–	–	50–58	–
	Infants	0.05–0.10	2.1	5.2	–	–
	Children	5.2 (1.3–7.3)	2.4	7.4	151	–
Epidural prolonged	Neonates	–	2.4	4.26	–	–
	Infants	–	2.4	6.15	–	–
	Children	0.04	–	8.5	220	–

fu, free fraction; Vss, volume of distribution at steady state; CL/f, total body clearance over bioavailability (T, total fraction, U, unbound fraction); T½, terminal half-life. For adults, a mean BW of 75 kg has been assumed.

#Apparent value, T½ and volumes measured after non-intravenous injections are overestimated because of a flip-flop effect (i.e. because absorption lasts longer than elimination).

* After 3 h infusion.

‡ After 48 h infusion, CLT decreases with time because protein binding increases.

total clearance but not intrinsic clearance. This resets the total serum concentration, without changing the unbound concentration (see Fig. 10.4). Bupivacaine clearance is low at birth and increases slightly during the first 6–9 months of life. Ropivacaine clearance, which is also low in neonates and infants, increases during the first 2–6 years of life [28,461,462,466,467,474–478]. Despite the low clearance, ropivacaine concentrations remain below toxic levels, even in younger patients.

Pharmacodynamics

Local anesthetics cross membranes as free bases (unionized). Inside the cells, they become ionized and bind to specific amino acids within sodium channel pores and mechanically block the pores [479]. LAs also block potassium and calcium channels, but this requires slightly higher drug concentrations than those needed to block sodium channels. Voltage-gated potassium channels initiate repolarization. Some of these channels (including the hERG (human ether-à-go-go related gene) channel) are responsible for genetically induced arrhythmias, such as the long-QT, short-QT, or Brugada syndromes. These channels are blocked by LA concentrations just slightly higher than those needed to block sodium channels [480,481]. Unlike the CNS and heart, peripheral nerves only express a small number of potassium channels. Both sodium and potassium channel blockade are stereospecific. The S enantiomers induce a lesser block than the R enantiomers. LAs bind to L-type calcium channels, but it is unclear if blockade of these channels affects the cardiotoxicity of long-lasting LAs.

Nerve fibers are either myelinized or unmyelinized. The action potential of unmyelinated fibers propagates continuously. After initial depolarization, the sodium channels become unreceptive to stimulation (refractory period), which prevents backward propagation of impulses. Sodium and potassium channels are evenly distributed along the fibers. Conduction velocity of small fibers is low. Myelin insulates myelinated nerves, and this layer is interrupted regularly by the nodes of Ranvier. Sodium channels are concentrated at the node of Ranvier in concentrations of ≈200,000 channels/cm^2 [482,483]. Potassium channels are distributed along the myelin sheet with a higher concentration present in the juxtaparanodal region. The sudden depolarization of the node induces an electrical field, which extends to 2–3 nodes. Action potentials "jump" rapidly from one node to the next. Because the distance between nodes is greater in heavily myelinated fibers (there are 3–4 nodes/cm in Aα fibers and 20–30 nodes/cm in Aδ fibers), the conduction velocity is faster in motor and small sensory fibers than in fibers that conduct pain signals. Because the electrical field extends over a relatively long distance, nerve fibers must be "bathed" over a relatively long distance by LAs. This progressive extinction of the signal is called decremental conduction. Fortunately, the phasic block that is induced by the high firing rate of nerves reinforces the block. Small Aδ lightly myelinated fibers are blocked by less drug than is needed to block heavily myelinated fibers. This phenomenon, called *differential nerve block*, is explained by differences in internode distance between fibers [484]. It is unknown to what extent concentration gradients across the myelin sheath also participate in this phenomenon. Myelinization begins during the third trimester of pregnancy and is incomplete at birth. After birth, myelinization increases

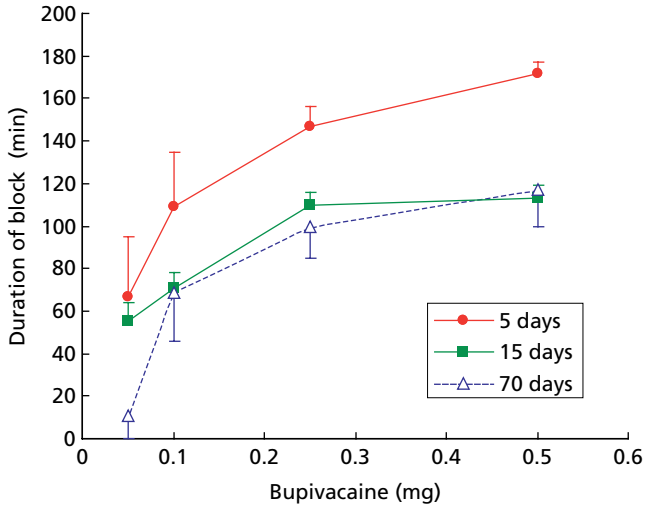

Figure 10.15 Duration of sciatic nerve blocks in rats after an injection of bupivacaine. The block is more protracted in newborn than in older rats. Duration of the block in 2- and 10-week-old rats was similar despite a marked difference in size and weight. It appears that the distance between nodes of Ranvier, which is fixed at its adult value by the age of 1–2 weeks, is the main determinant of the motor blockade. *Source:* Reproduced from Kohane et al [485] with permission of Wolters Kluwer.

rapidly and is almost complete by 3–4 years of age [483]. In rats, the nodes of Ranvier are fully mature at 2–3 weeks of age. Interestingly, the internode distance is similar between 2-week-old and adult rats. This may explain why infants and young children require larger volumes of LAs per kilogram than older children or adults (Fig. 10.15) [485]. Fortunately, lower concentrations of LA are needed to cause the block. Infants and children need larger volumes of solution with lower concentration of LAs to achieve blocks of similar intensity and duration as adults. Surprisingly, infants require larger doses of LAs for spinal anesthesia. Despite this, the duration of the spinal block is shorter. Some authors have attributed this difference to a larger volume and a more rapid turnover of CSF in neonates and infants than in older children and adults. Unfortunately, the pharmacokinetics of LAs in the CSF is particularly unknown in pediatric patients. The brain CSF volume and CSF turnover are lower in neonates and infants than in children and adults (see Fig. 10.15) [486,487]. The major factor responsible for this rapid effect seems to be pharmacodynamic. The intensity and duration of the block depend on number of nodes of Ranvier blocked (differential block). The distance between nodes is fixed soon after birth [482,483]. When this occurs, the short duration of spinal anesthesia in infants is not surprising.

Effects on the central nervous and cardiovascular systems

Like all inhibitors of sodium channels, low doses of LAs are anticonvulsive, which is why lidocaine is still used to treat intractable epilepsy in children [488]. However, the therapeutic ratio is low and the margin of safety does not favor lidocaine. At higher doses LAs may produce convulsions and coma. At similar concentrations to those that cause convulsions, long-lasting LAs can induce cardiac arrhythmias. With the exception of nodal conduction, which depends on calcium channels, impulse conduction in the heart depends on sodium

channels. This is why lidocaine is a chief class Ib antiarrhythmic agent. LAs prolong the refractory period, but the balance between the increase in effective refractory period and the decrease in the ventricular conduction velocity does not favor LAs. Long-lasting LAs, such as bupivacaine, profoundly decrease ventricular conduction velocity [489]. This phenomenon is markedly amplified by tachycardia [490]. In neonatal and adult animals, the intensity of the block is similar at similar heart rates [491]. However, because neonates and infants normally have higher heart rates than adults, they are more sensitive to local anesthetic-induced blocks than adults. LAs also impair myocardial contractility. However, to obtain the same decrease in contractile force, it is necessary to infuse 10 times more bupivacaine than is required to impair ventricular conduction. Apart from the effect of the central block-induced sympathetic blockade, LAs have direct vasoactive properties. The S enantiomers (ropivacaine and levobupivacaine) have mild vasoconstrictive properties. These properties have been advocated as the cause of ischemia after penile block, but a direct relationship between ropivacaine and ischemia in this report seems doubtful [492].

Stereospecificity

Mepivacaine, prilocaine, bupivacaine, and ropivacaine have an asymmetric carbon. Because binding to serum proteins, hepatic enzymes, or ion channels may be asymmetrical, different stereospecific properties are expected. Protein binding, pharmacokinetics, and nerve blocks have little stereoselectivity, which is why levobupivacaine has almost the same blocking properties as its racemic counterpart. In the heart, conduction is markedly stereospecific, whereas contractility is unaffected by stereoselectivity.

Local anesthetics have anti-inflammatory properties and inhibit platelet aggregation [493]. They decrease leukocyte priming and the production of free radicals [494–496]. Systemically administered lidocaine has antinociceptive effects, particularly on neuropathic pain [497]. Consequently, LAs are now used preoperatively to prevent postoperative hyperalgesia in adults [498]. Interestingly, LAs can prevent and even treat complex regional pain syndrome in adults and children by limiting the neuropathic inflammatory processes [499,500].

Toxicity of local anesthetics

At the site of injection, the minimum concentration required to produce a nerve blockade is 300–1500 μM for lidocaine and 100–500 μM for bupivacaine. In adults these concentrations of lidocaine occasionally cause cauda equina syndrome but are more likely to cause transient neurological symptoms following spinal anesthesia. LAs can also be toxic to muscles, bupivacaine being the most toxic [501,502]. Muscle toxicity is not enantioselective. Care should be taken when regional anesthesia is provided for eye surgery in adults, for children with myopathies (bupivacaine is an *in vitro* model of Duchenne myopathy), and perhaps for children with mitochondrial myopathy. Peripheral blocks are more dangerous than central blocks because it is easier to inject drug directly into muscle with peripheral blocks.

After both local and regional anesthesia, the blood concentration of LAs rises rapidly and can cause neurological or cardiac toxicity. Neurological toxicity occurs in about one case per 1000 patients [503]. Because of their low protein binding and intrinsic clearance, infants are more prone to LA toxicity than adults. General anesthesia may conceal the early signs of LA toxicity in children. In addition to pharmacokinetic factors, the rapid heart rate of children increases LA toxicity [491]. Ropivacaine and levobupivacaine (S-(–) enantiomers) are appropriate choices for younger patients because both drugs should produce less tonic block. Even if toxic events occur with ropivacaine, small doses of epinephrine should cause rapid recovery. Impaired ventricular conduction is the primary manifestation of LA toxicity. QRS widening, bradycardia, and torsades de pointe are followed by ventricular fibrillation and/or asystole [504]. The slight decrease in myocardial contractility caused by LAs is usually not a major problem. Treatment includes oxygenation, cardiac massage, correction of acidosis, and epinephrine (which is given in small incremental boluses beginning with 2–4 μg/kg) [505]. If ventricular fibrillation persists, defibrillation (2–4 joule/kg) is performed. Although resuscitation measures must be initiated immediately, the specific treatment of LA toxicity is rapid administration of Intralipid®. Numerous case reports have shown that rapid bolus injections of a lipid emulsion reverse the toxic effects of LAs [506–508]. Because one mole of Intralipid® binds >3000 times more molecules of bupivacaine than a mole of buffer, the volume of distribution suddenly increases [509]. However, a recent experiment performed in volunteers has shown that, if this lipid sink effect exists, the benefit remains less than initially expected [510] (Fig. 10.16). A direct effect of lipids on myocardium has also been advocated to explain the effect of this lipid rescue [511]. In addition, the effect is lower in less hydrophilic drugs such as ropivacaine as compared to bupivacaine or levobupivacaine [510]. Similarly, long-chain emulsions are preferable to medium- or short-chain emulsions.

The recommended dose of 20% Intralipid® for pediatric patients is 5 mL/kg by IV bolus. If cardiac function does not return, this dose (up to 10–12 mg/kg) is repeated. Rather than institute a maintenance infusion of Intralipid®, patients are closely monitored and given more Intralipid® as needed. The lipid emulsion decreases LA elimination, thus the cardiac effects may recur later.

Prevention of toxicity includes slow injection of small amounts of drug and frequent catheter aspiration. Some authors recommend injecting a solution that contains epinephrine. Continuous administration of LAs for postoperative pain is better than bolus injections because the latter may cause peaks and valleys of drug concentration and pain relief. If the catheter migrates into a blood vessel, continuous administration is safer. In older children, patient-controlled regional anesthesia (PCRA, see Chapter 37) works well. Also, the size of the boluses is small enough to avoid toxicity.

Adjuvants

Adjuvants are often used to prolong the duration of analgesia.

Epinephrine (5 μg/mL = 1/200,000) decreases C_{max} without affecting the time to peak concentration. In <6-month-old infants, 2.5 μg/mL 1/400,000 epinephrine has been recommended [468]. However, the drug is less efficacious with long-acting S-(–) enantiomers and has limited use with these solutions. Plain solutions of LAs *must* be used for penile, interdigital, and eye blocks.

Clonidine 1–2 μg/kg, either IV or in the epidural space, prolongs the duration of caudal blocks [512]. More than 2 μg/kg

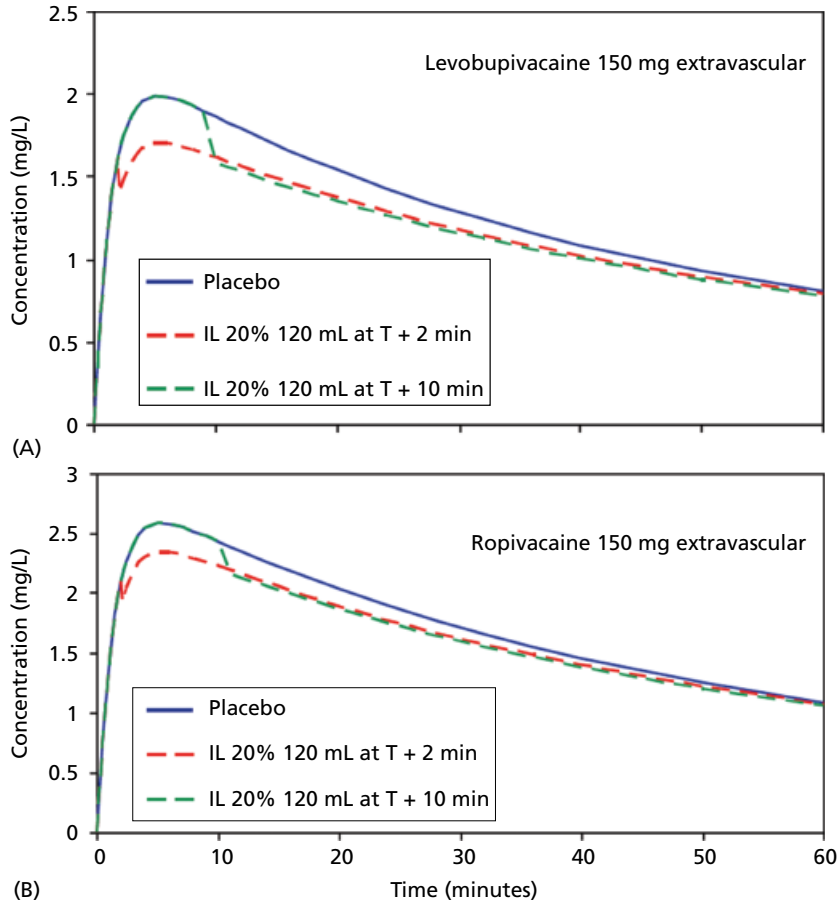

Figure 10.16 Simulations of the plasma concentration observed after extravascular injection of 150 mg levobupivacaine (A) or ropivacaine (B) followed by a bolus of 120 mL Intralipid® 20% (IL). These simulations were generated using the kinetic data obtained from 16 volunteers receiving the drugs as a short infusion and Intralipid® or placebo in a cross-over manner. Intralipid® rapidly decreases the peak concentration, but the effect is moderate. *Source:* Reproduced from Dureau et al [510] with permission of Wolters Kluwer.

may lead to hypotension. Clonidine is not recommended for infants <3 months of age because it can cause apnea in this age group.

Some clinicians use *ketamine* as an adjuvant for epidural block [513]. Both the R-(–) enantiomer and the preservative are highly neurotoxic. Even the S(+) enantiomer can be toxic. Thus it may be wise to avoid the use of ketamine as an adjuvant for epidural blocks [514,515].

Opioids are often used as adjuvants for epidural block. After 6–9 months of age, adding opioids to LAs prolongs epidural analgesia for up to 24 h. Hydrophobic agents (fentanyl, sufentanil) must be placed at the metameric level where the pain will occur [516,517]. Preservative-free morphine easily spreads rostrally and can be placed at a lower metameric level, but the risk of respiratory depression is theoretically higher. The bolus dose of morphine is 25–30 µg/kg in the epidural space, which is followed by a continuous infusion of 1 µg/kg/h. When continuous epidural administration of fentanyl or sufentanil is combined with local anesthetics, the doses are 0.2 µg/kg/h and 0.1 µg/kg/h respectively. Morphine 5–10 µg/kg can be used as the sole agent for spinal analgesia during general anesthesia.

Formulation and dosing

Plain solutions of amide LAs are preservative free; only epinephrine-containing solutions include metabisulfite [518]. The S enantiomers (ropivacaine and levobupivacaine) are safer and cause similar quality and duration of analgesia and less motor blockade than a racemic mixture of bupivacaine. When regional analgesia is used during general anesthesia, low concentrations of LAs (2–2.5 mg/mL, i.e. 0.2–0.25%) are used. The maximum dose is 2–2.5 mg/kg for the initial caudal injection, 1.2–1.7 mg/kg for lumbar or thoracic epidural injections, 0.5 mg/kg for peripheral blocks. Continuous infusion of LAs for postoperative analgesia uses low concentrations of drug (0.625–1 mg/mL) at a maximum rate of 0.20 mg/kg/h in neonates, 0.30 mg/kg for 1–6 months old, and 0.40 mg/kg beyond 6 months of age.

KEY POINTS: LOCAL ANESTHETICS

- The amide local anesthetics levobupivacaine and ropivacaine should be favored because these molecules are less toxic to the heart and because they induce less motor block than racemic agents
- In case of local anesthetic systemic toxicity with cardiac toxicity, the usual resuscitation maneuvers with lipid rescue are the basis of therapeutic intervention
- In infants older than 3 months, clonidine is commonly used as an adjuvant for caudal epidural anesthesia

Anesthetic pharmacology in obese children

The prevalence of obesity, defined as a body mass index (BMI) greater than the 95th percentile for age and gender in children 2–19 years of age in the US, has increased from 13.9% in 2000 to 17.2% in 2014 [519]. Recommendations for anesthetic drug dosing in obese children based on evidence are limited to a handful of studies. Clinical trials for dosing recommendations for drug labeling almost always exclude morbidly obese patients. Further clouding the issue, many recommendations for drug dosing are based on lean body weight (LBW), that is, the weight excluding all fat weight, which of course is unrealistic for most all patients. The ideal bodyweight (IBW), which is the BMI at the 50th percentile for age and gender, is also discussed in some dosing schema.

In children, propofol is the best-studied agent for PK and PD data for dosing recommendations in obese patients. For induction using propofol, a dose based on the IBW, rather than total body weight (TBW), seems to be most appropriate based on both processed- EEG and clinical signs (loss of eyelid reflex) [520,521]. However, for maintenance infusion, dosing based on an allometric function with an exponent of 0.75 provided the best fit to achieve and maintain a plasma concentration of about 3 μg/mL, which is associated with adequate depth of anesthesia by processed EEG criteria. This dosing regimen for a TBW 130 kg, 1.66 m adolescent, with an IBW of 78.7 kg would be 1.4 mg/kg TBW propofol for induction, followed by an infusion of 155 μg/kg/min for 20 min, 120 μg/kg/min for 20 min, and finally 85 μg/kg/min for a 60 min anesthetic.

For other anesthetic drugs, e.g. opioids, thiopental, and etomidate, pediatric data are lacking but in adults most authorities recommend that LBW be utilized as the basis for dosing [522]. For muscle relaxants, again there are no published pediatric data, but for succinylcholine, whose pharmacodynamic properties are determined by the volume of the extracellular fluid compartment, TBW should be the basis for dosing. For the other non-depolarizing muscle relaxants, either LBW or IBW is recommended. For all drug dosing in obese patients, the principle of titrating to effect is crucially important, given the paucity of data in children and the variation in the PK/PD data in adults [522].

CASE STUDY

A full-term newborn weighing 3520 g was scheduled for esophageal atresia (type 3) repair 16 h after birth. Cardiac, abdominal, and renal echography were normal. A small amount of stridor was noticed. An ENT surgeon was asked to evaluate the child and perform laryngoscopy prior to surgery. All blood tests were normal for age, except the activated coagulation test, which was slightly prolonged (45 s versus 35 s for control). Factors VIII and IX were subsequently found to be normal, as was a preoperative thromboelastogram. The physical examination showed an apparently healthy boy who was spontaneously breathing and had mild stridor. A peripheral venous catheter was in place. A suction catheter was present in the upper esophagus to aspirate saliva. Anesthesia was induced with sevoflurane (6% inspired) with spontaneous ventilation. The ENT surgeon sprayed the larynx with 10 mg of 2% lidocaine without epinephrine. No airway abnormality was found, and the trachea was intubated. Following tracheal intubation, the patient was given sufentanil (0.5 μg) and atracurium (1 mg) over 1 min. The lungs were mechanically ventilated. An epidural was performed using levobupivacaine. Because lidocaine had been administered 30 min earlier for examination of the larynx, the initial bolus of LA was reduced (5 mg or 2 mL of a 2.5 mg/mL solution). The bolus was immediately followed with a continuous infusion of 0.85 mg/h, i.e. 1.4 mL/h of a 0.0625% solution. Anesthesia was maintained with sevoflurane 1.5–2% (0.5–0.6 MAC without N_2O). Surgery was uneventful and the trachea was extubated after reversal of the muscle relaxant (neostigmine 350 μg, atropine 75 μg). In addition to the epidural, intravenous acetaminophen (50 mg bolus plus 25 mg every 6 h) was given. Unfortunately, the epidural catheter was dislodged 5 h after surgery. The anesthesiologist prescribed a continuous IV infusion of morphine 40 μg/h, but because drugs already given through the epidural catheter would provide pain relief for 1–2 more hours, no loading dose of morphine was given. Six hours later, the patient's respiratory rate progressively decreased to 16 bpm. The infusion of morphine was decreased to 30 μg/h and the respiratory rate returned to normal. The remainder of his postoperative course was uneventful.

1. Because lidocaine was used for the laryngeal examination, a smaller dose of LA was given into the epidural space. Lidocaine is rapidly absorbed following topical application to mucous membranes and may interact with levobupivacaine given for blocks.
2. Sevoflurane was used to induce anesthesia because it, plus the topical anesthesia, provided excellent conditions for the laryngopharyngeal examination. Following tracheal intubation, a phenylpiperidine opioid and a muscle relaxant were slowly injected to prevent a "stiff" chest from developing. The drugs were also injected slowly to prevent the profound hypotension that sometimes occurs when sufentanil and atracurium are injected rapidly.
3. The epidural was performed (1) to provide postoperative analgesia, allow rapid tracheal extubation, and avoid postoperative mechanical ventilation, and (2) to reduce the amount of halogenated agents used and prevent their possible deleterious CNS effects. At this age, MAC is higher than that of adults. However, MAC may differ for different variables (e.g. hemodynamic variables). Balanced anesthesia with opioids and regional anesthesia is a good choice. Levobupivacaine was chosen over ropivacaine because levobupivacaine is metabolized by CYP3A4/3A7, which is more mature at birth. Ropivacaine

is metabolized by CYP1A2, which is immature until 4 years of age. Pure S enantiomers (ropivacaine and levobupivacaine) are less toxic and induce less motor blockade, a significant problem in infants. Because the volume of distribution of hydrophilic local anesthetics is large in neonates and infants, the initial bolus dose/kg is usually the same as in older children. Since LA toxicity is additive, and because a topical spray of lidocaine was used less than 1 h before the epidural block, limited amounts of levobupivacaine (1.4 mg/kg) were injected into the epidural space. This initial bolus was followed by a continuous infusion of the drug. The infusion dose was reduced because the volume of distribution would be filled after 4–5 half-lives; at that point clearance rapidly becomes the only factor governing drug concentration. Because clearance of the unbound fraction (CLu), which is responsible for LA toxicity, is low at birth and progressively increases with age, the dose varies with age. Fortunately, infants less than 4–6 months old have excellent pain relief with smaller doses of LAs.

4. Postoperative pain control is critical, not only to relieve the pain but to also reduce respiratory complications (hypoventilation). In addition to regional anesthesia, this patient received paracetamol (acetaminophen). Because metabolism of this drug is reduced during the first month of life, the child was given about half the dose of paracetamol given to older patients. No loading dose was given.

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 11
Fluids, Electrolytes, and Nutrition

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Introduction

Fluid and electrolyte management is an essential component of the care of hospitalized pediatric patients. Fluids and electrolytes, like anesthetics, must be titrated to effect based on clinical assessment and an in-depth knowledge of a wide range of organ systems. The objective of this chapter is to enhance understanding of the mechanisms underlying fluid and electrolyte regulation, examine management of their disturbances, and illustrate related anesthetic implications in children.

Physiology

Renal physiology

The kidneys are important for regulating fluid and electrolyte homeostasis. Each kidney contains 1.0 to 1.3 million nephrons, the functional units of the kidney. The afferent arteriole carries blood into the glomerulus while the efferent arteriole carries blood away. The glomerulus, a specialized cluster of capillaries, is responsible for filtration of water, amino acids, and free ions from the plasma. This tuft-like network of branching capillaries is contained within a cup-like sac called Bowman's capsule. Filtered fluid flows across the glomerular basement membrane into Bowman's capsule, to the proximal convoluted tubule, through the loop of Henle, to the distal convoluted tubule, and then exits the nephron as urine via the collecting duct. Through complex mechanisms of resorption and secretion across the renal tubules, filtered fluid is altered significantly as it traverses the renal tubular system (Fig. 11.1). Embryologically, development of the renal system begins as early as the third week of gestation. By the 10th week, the glomeruli within the nephron function and produce urine. Nephrogenesis, the formation of the functional units of the kidney, is complete by 34–36 weeks' postconceptual age. Although the term neonate has a full complement of glomeruli, the glomerular filtration rate (GFR) is only about 30% of the normal adult rate, even when adjusted for body surface area. During the first year of life, the GFR increases dramatically due to increases in glomerular and tubular size. When infants are born before 34 weeks of gestation, the formation of new nephrons continues after birth. Thus, some of the increase in the GFR in these infants will be due to the addition of more glomeruli [1–4].

The GFR is regulated by the balance of Starling forces across the capillary wall, total surface area of the capillaries, permeability of the glomerular wall, and renal blood flow. In general, fetal and neonatal renal function is characterized by low renal blood flow and a low GFR that are caused by high renal vascular resistance, low systemic blood pressure, and a smaller capillary surface area for filtration. Renal vascular resistance decreases rapidly after birth, and systemic blood pressure and capillary surface area increase as the infant ages [5]. Neonates double GFR by 2 weeks of age and triple it by 3 months. GFR reaches adult levels by 2 years of age. The GFR of premature infants is even lower at birth and increases more slowly than that of their full-term counterparts [6].

Full-term infants can conserve sodium despite a low GFR. As GFR and the filtered sodium load increase, the proximal tubule is able to increase sodium resorption [7]. Preterm infants exhibit prolonged glomerular–tubular imbalance, with GFR exceeding the tubule's ability to reabsorb sodium due to proximal convoluted tubule immaturity. Additionally, the distal convoluted tubule does not respond to aldosterone. Consequently, preterm infants are at risk for excessive sodium excretion and hyponatremia. Sodium reabsorption increases with age; at 30 weeks' postconceptional age a neonate excretes 5% of the filtered sodium load, while a full-term neonate excretes only 0.2% of the filtered sodium load [8].

Creatinine and/or creatinine clearance (either calculated directly from 24-h urine collection or indirectly from a formula) are commonly measured or calculated as a means of

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

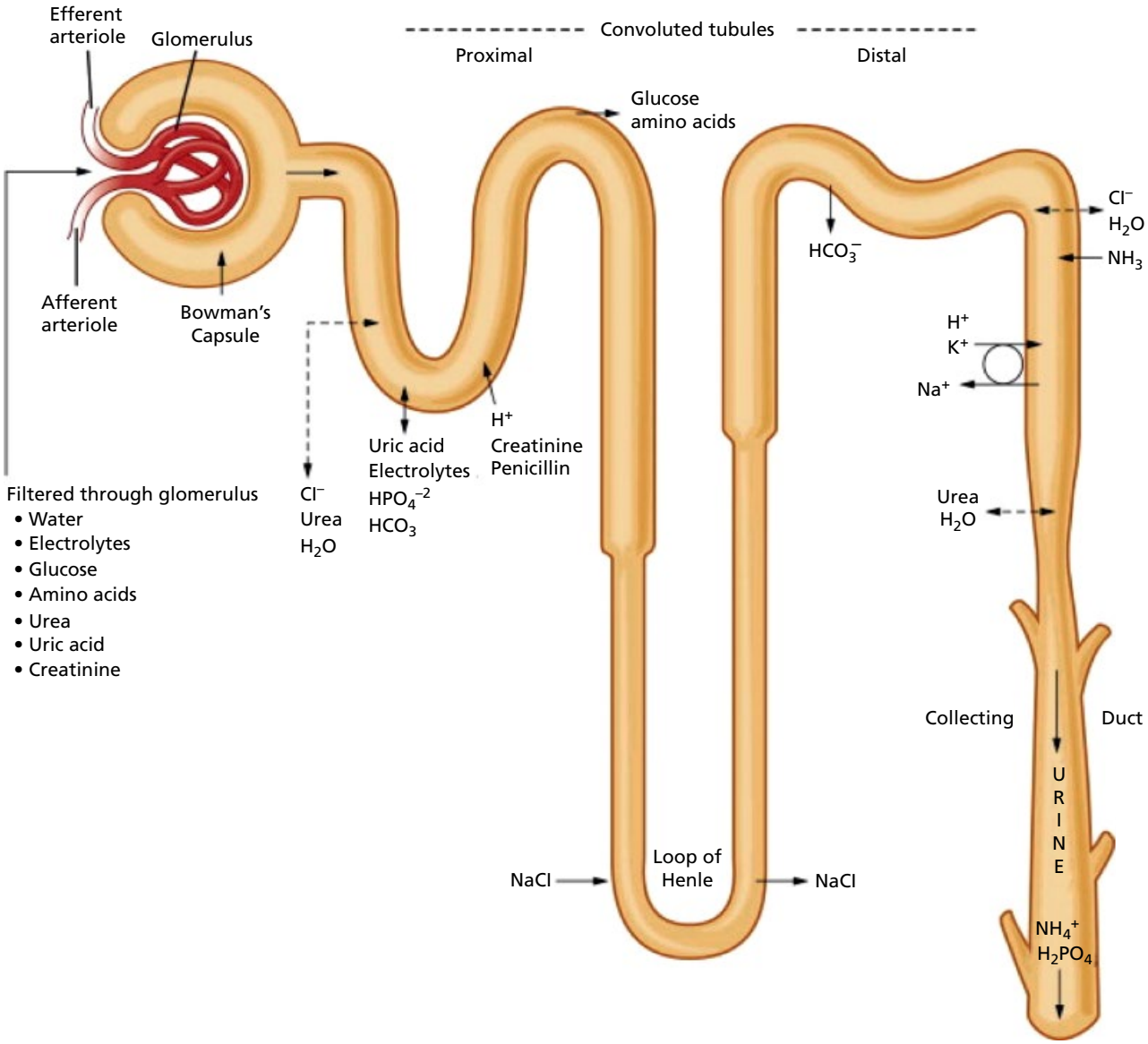

Figure 11.1 Structure of the nephron. *Source:* Reproduced from Egan and Hemmings [4] with permission of Elsevier.

estimating GFR. This relationship is complicated and unreliable in neonates and infants. In most infants, the plasma creatinine concentration actually increases after birth. In fact, the more preterm the infant, the higher the rise in plasma creatinine before it begins to decline to a steady-state level [2,9]. Chapter 9 presents additional information about the developmental physiology of the renal system.

Body fluid homeostasis

Conceptually, the internal environment of the body is an interconnected group of anatomical compartments among which fluids distribute. Water is the primary fluid found in the human body and accounts for 50–80% of total bodyweight. Total body water (TBW), defined as the amount of sodium-free water in the body, is distributed across two main compartments that are separated by the cell membrane: the extracellular fluid (ECF) compartment and the intracellular fluid (ICF) compartment (Fig. 11.2). The variation in water content depends on tissue type: muscle contains 75% water, whereas adipose tissue contains only 10% water. TBW decreases with age, mainly because of loss of water from the ECF compartment. For preterm and low-birth-weight infants, TBW is 80% of total bodyweight. For term infants up to 6 months, TBW equals 75% of total bodyweight. In infants greater than 6 months of age, as well as in children and adolescents, TBW is estimated at 60% of body weight [10–15]. TBW decreases and constitutes a smaller percentage of bodyweight during dehydration.

Intracellular fluid represents about two-thirds of TBW, which is equivalent to 30–40% of total bodyweight. In preterm infants the proportion of ECF is much greater than that of the ICF and reaches 60% of TBW at term [16]. In the neonate, the normal postnatal diuresis causes an immediate decrease in the ECF volume. This decrease in ECF volume is followed by continued expansion of the ICF volume because of cellular growth. The change in TBW distribution, as a function of weight, continues postnatally such that by around 3 months of life the intracellular compartment is larger than the extracellular compartment. This shift is beneficial because it allows fluid to be mobilized from ICF in periods of dehydration in

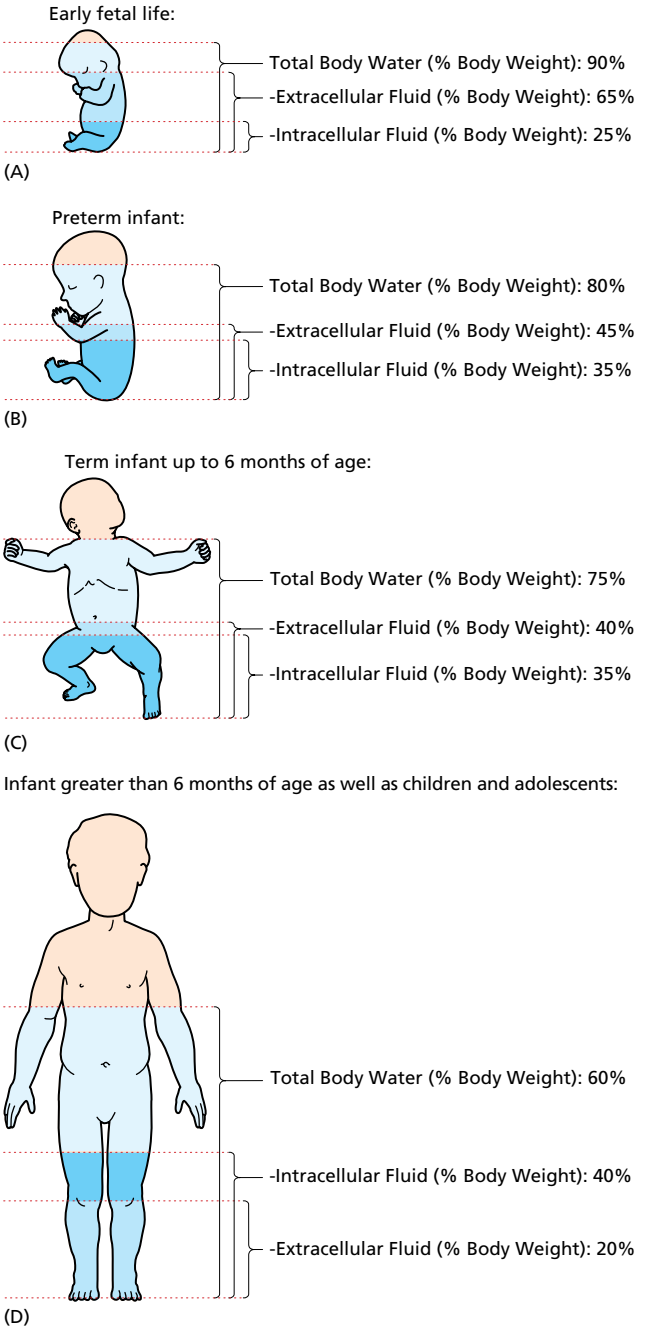

Figure 11.2 Schematic representation of body fluid compartments as a percentage of body weight in (A) early fetal life, (B) the preterm infant, (C) the term infant up to 6 months of age, (D) infants more than 6 months of age, children, and adolescents. ECF, extracellular fluid; ICF, intracellular fluid; TBW, total body water.

order to replenish intravascular volume. The non-neonate is better able than the neonate to maintain intravascular volume lost from fasting, fever, diarrhea, or other causes. The adult ratio of extracellular water (ECW) to intracellular water (ICW) is achieved by about 1 year of age (Fig. 11.3).

The ECF consists of both the plasma volume and the interstitial fluid volume. The plasma volume is relatively small, which is important to consider in the context of intravenous fluid therapy. This compartment remains constant throughout life, comprising ~5% of bodyweight. It is the milieu in which blood cells, platelets, and proteins are suspended. The interstitial fluid volume accounts for 15% of bodyweight and

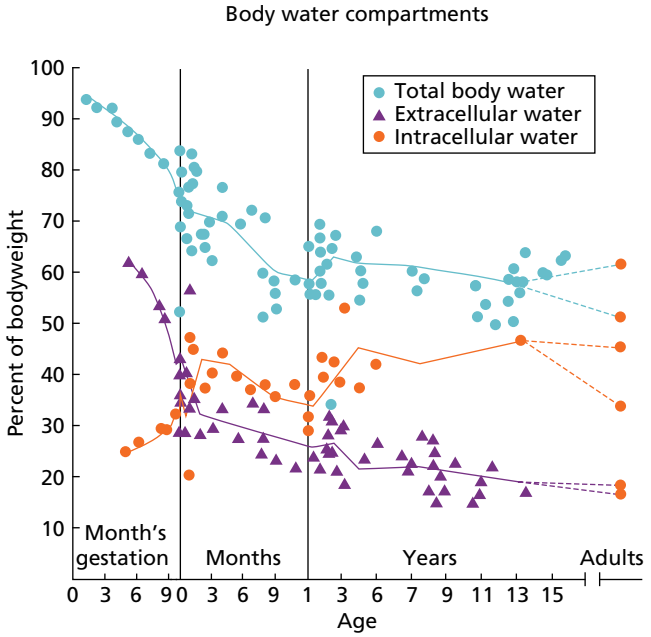

Figure 11.3 Body compartments: fetus to adult. Total body water, extracellular water, and intracellular water as a percentage of bodyweight. *Source*: Reproduced from Friis-Hansen [10] with permission of American Academy of Pediatrics.

has a solute composition almost identical to that of intravascular fluid, except for a lower protein concentration.

The solute composition of the ICF and ECF is different. Sodium and chloride are the dominant cation and anion in the ECF, respectively. Potassium is the most abundant cation in the ICF, and its concentration within the cells is approximately 30 times higher than in the ECF. Proteins, organic anions, and phosphate are the most plentiful anions in the ICF (Table 11.1) [17]. For all practical purposes, the electrolyte values in the neonatal period are the same as in the child and adult with the exception of potassium, which can be about 1–2 mmol/L higher than average for the first 2 days of life [18]. The difference in the distribution of cations – sodium and potassium – is due to the activity of the Na^+/K^+-ATPase pump, which extrudes sodium from cells and moves potassium into cells. In contrast, the dissimilarity between the anions in the ICF and the ECF is determined largely by the presence of intracellular molecules that do not freely cross the cell membrane.

Table 11.1 Composition of body fluid compartments

	Extracellular fluid	Intracellular fluid
Osmolality (mOsm)	290–310	190–310
Cations (meq/L)	155	155
Sodium (Na^+)	142	10
Potassium (K^+)	4.0	140
Calcium (Ca^{2+})	2.4	0.0001
Magnesium (Mg^{2+})	1.2	58
Anions (meq/L)	155	155
Chloride (Cl^-)	103	4
Bicarbonate (HCO_3^-)	28	10
Phosphates	4	75
Sulfate (SO_4^{-2})	1	2
Organic acids	6	–
Protein	5	40

Source: Data from Hall [17] with permission of Elsevier.

It is important to remember that the serum concentration of a measured electrolyte does not always reflect the body content. This is because of the larger volume of ICF compared with ECF and the variation in electrolyte concentrations between these two compartments. For example, the intracellular potassium concentration is much greater than the serum concentration. A shift of potassium from the intracellular space can maintain a normal serum potassium or even cause an elevation in serum potassium, despite massive losses of potassium from the intracellular space. This is most evident in diabetic ketoacidosis, a state of significant potassium depletion that is often masked by transmembrane shifts of potassium from the ICF to the ECF.

The mathematical relationship (Starling equation) describing net water movement across a membrane between these compartments includes factors for oncotic and hydrostatic pressures on either side of the membrane (e.g. interstitial and intravascular space):

$$J_V = K_F\left(\left[P_C - P_I\right] - \delta\left[\pi_C - \pi_I\right]\right)$$

where J_v = the net flow across the membrane, K_F = fluid filtration coefficient of the membrane, P_C = capillary hydrostatic pressure, P_I = interstitial hydrostatic pressure, δ = solute reflection coefficient (permeability of solute across a specific membrane), π_C = capillary oncotic pressure, and π_I = interstitial oncotic pressure. Fluid moves as a function of the product of the permeability of the membrane and net driving pressure (hydrostatic pressure minus oncotic pressure) (Fig. 11.4). Disturbances of this relationship (e.g. when membrane trauma decreases the reflection coefficient for proteins) may cause the interstitial compartment to expand and edema to develop. In the normal patient, oncotic and hydrostatic pressures are balanced. With various disease states, the interstitial space expands at the expense of the intravascular space. For example, increased capillary permeability during sepsis (trapping protein in the interstitial space, increasing π_I) or increased venous pressure with positive pressure ventilation (increasing P_C) may produce edema and/or decrease intravascular volume.

Osmolality

An understanding of osmotic shifts between the ECF and ICF is fundamental to understanding the physiology of fluid balance. Osmolality is defined as the concentration of all of the solutes in a given weight of water. Due to permeability of the cell membrane to water, iso-osmolality, or osmotic equilibrium, is generally maintained between compartments. If the osmolality in one compartment changes, then water movement leads to a rapid equalization of osmolality. This can lead to significant shifts of water between the intracellular space and the extracellular space [19,20]. Plasma osmolality is tightly regulated and maintained at 285–295 mOsm/kg. It can either be measured directly or estimated by the following formula [21]:

$$\text{Osmolality} = 2\times[\text{Na}] + [\text{glucose}]/18 + [\text{BUN}]/2.8$$

Glucose and blood urea nitrogen (BUN) are measured in mg/dL. Division of these values by 18 and 2.8, respectively, converts the units into mmol/L. Multiplication of the sodium value by 2 accounts for its accompanying anions, principally chloride and bicarbonate. The calculated osmolality is usually slightly lower than the measured osmolality.

Urea normally contributes little to plasma osmolality. Urea is not confined to the extracellular space because it readily crosses the cell membrane, and its intracellular concentration approximately equals its extracellular concentration. Whereas an elevated sodium concentration causes a shift of water from the intracellular space, with uremia there is no osmolar gradient between the two compartments and, consequently, no movement of water. Therefore, the effective osmolality can be calculated as follows [21]:

$$\text{Effective osmolality} = 2\times[\text{Na}] + [\text{glucose}]/18$$

The effective osmolality (also called the tonicity) determines the osmotic force that is mediating the shift of water between the ECF and the ICF. Effective osmolality differs from measured osmolality in that it accounts only for osmotically active impermeable solutes rather than all osmotically active solutes, including those that are permeable to cell membranes. There are many mechanisms that influence ECF volume and osmolality including antidiuretic hormone (ADH) and thirst, renal regulation of sodium, the renin–angiotensin–aldosterone system, and atrial natriuretic peptide.

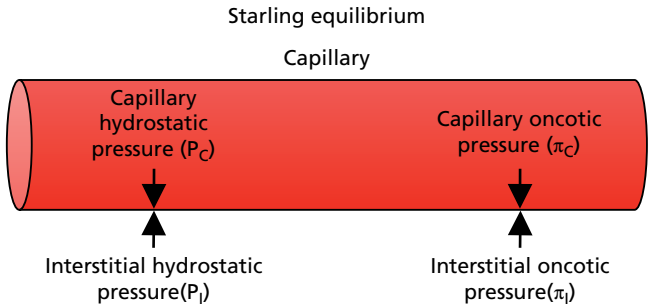

Figure 11.4 The Starling hypothesis states that fluid flux at the capillary level is controlled by a balance between hydrostatic pressure and osmotic pressure gradients between the capillaries and interstitial spaces.

Regulation of extracellular fluid volume and osmolality

Antidiuretic hormone and thirst

Osmoreceptors in the hypothalamus can detect as little as a 1% change in plasma osmolality [22]. When an elevated effective osmolality is sensed, ADH is secreted by neurons in the supraoptic and paraventricular nuclei of the hypothalamus [23,24]. The prohormone of ADH migrates along the nerve axons to the posterior pituitary gland, where it is stored as arginine vasopressin. It is released through exocytosis [25]. Circulating ADH binds to its V_2 receptors in the collecting duct cells of the kidney, and, via the generation of cyclic adenosine monophosphate, causes insertion of water channels (aquaporin-2) into the renal collecting ducts [26]. This produces increased permeability to water, permitting resorption of water into the hypertonic renal medulla. As a result, urine concentration increases and water excretion decreases. Urinary water losses are not completely eliminated because there is obligatory excretion of urinary solutes, such as urea

and sodium [27]. ADH secretion virtually disappears when the plasma osmolality is low, allowing excretion of maximally dilute urine. The consequent loss of free water (water without sodium) corrects the plasma osmolality.

The minimum urine osmolality is approximately 30–50 mOsm/kg [28,29], placing an upper limit on the kidney's ability to excrete water. Sufficient solute must be present for water loss from the kidneys. The maximum urine osmolality is approximately 1200 mOsm/kg [28]. Obligatory solute losses dictate the minimum volume of urine that must be produced, even when maximally concentrated. Obligatory water losses increase in patients with high salt intake or high urea losses, as may occur after relief of a urinary obstruction or during recovery from acute tubular necrosis. An increase in urinary solute and subsequent water losses occurs with osmotic diuresis, which occurs classically from glycosuria in diabetes mellitus and after mannitol administration. There are developmental changes in the kidney's ability to concentrate the urine. The maximum urine osmolality in a newborn, especially a premature newborn, is less than that in an older infant or child [30]. This limits the ability to conserve water and makes such a patient more vulnerable to hypernatremic dehydration.

A secondary stimulant for ADH release is a perceived decrease in intravascular volume, as sensed by baroreceptors in the left atrium, aortic sinus, and carotid sinuses. Hypovolemia, as well as hypotension, stimulates a nonosmolar release of ADH. In fact, volume depletion takes precedence over osmolality in the regulation of ADH. In other words, brisk ADH release can occur in the volume-depleted or hypotensive child even when the plasma osmolality is as low as 260–270 mOsm/L [31].

Inappropriate ADH release is associated with many other clinical scenarios, resulting from both hemodynamic and nonhemodynamic stimuli (Box 11.1). The pediatric surgical patient is at risk for increased ADH given the pain, stress, opioids, hypovolemia, and/or hemorrhage associated with the perioperative period [32,33].

Thirst is also regulated by hypothalamic osmoreceptors. These receptors are distinctly different from those that determine ADH secretion. By linking to the cerebral cortex, osmoreceptors stimulate thirst when serum osmolality increases. Thirst is not physiologically stimulated by plasma osmolality until it reaches 290 mOsm/kg, a level at which ADH levels are sufficient to induce maximal antidiuresis [34]. Additionally, thirst is frequently a response to an absence of ADH (central diabetes insipidus) or lack of responsiveness to ADH (nephrogenic diabetes insipidus), which results in the production of copious, dilute urine. Those who cannot perceive thirst develop profound problems with fluid balance. Although the mechanisms are not all clearly understood, angiotensin II, which is increased during volume depletion, and baroreceptors are also known to stimulate thirst [35].

Renal regulation of sodium

As stated previously, sodium, the principal extracellular cation, is the primary determinant of osmolality and therefore critical to the maintenance of intravascular volume. The principal extracellular anion, chloride, is also necessary, but for simplicity, sodium balance is considered the main regulator of volume status. Given the need for equal numbers of cations and anions, body content of sodium and chloride usually changes proportionally. There are, however, some situations in which chloride depletion is the dominant derangement causing volume depletion (metabolic alkalosis with volume depletion). Other situations also exist, such as volume depletion with metabolic acidosis, where sodium depletion may exceed chloride depletion.

Because there is little homeostatic control of sodium intake, the kidney determines sodium balance. Sodium homeostasis is maintained by altering the percentage of filtered sodium that is resorbed along the nephron. Normally, the kidney excretes <1% of the sodium filtered at the glomerulus. In the absence of disease, extrarenal losses and urinary output of sodium match intake, with the kidney having the capacity to adapt to large variations in sodium intake. Urinary sodium excretion, which is regulated by both intrarenal and extrarenal mechanisms, can be reduced to virtually undetectable levels when necessary. The most important determinant of renal sodium excretion is the effective intravascular volume of the child. The effective intravascular volume is the volume status that is sensed by the body's regulatory mechanisms.

Sodium resorption occurs throughout the nephron (see Fig. 11.1). While the majority of filtered sodium is resorbed in the proximal tubule and the loop of Henle, the distal tubule and the collecting duct are the main sites for precise regulation of sodium balance. Approximately 65% of the filtered sodium is reclaimed in the proximal tubule, which is also the major site for resorption of bicarbonate, glucose, phosphate, amino acids, and other substances that are filtered by the glomerulus [36]. The transport of all these substances is linked to sodium resorption by cotransporters, or a sodium–hydrogen exchanger in the case of bicarbonate. This link is clinically important for bicarbonate and phosphate because their resorption parallels sodium resorption. In patients with metabolic alkalosis and volume depletion, correction of the metabolic alkalosis requires urinary loss of bicarbonate, but the volume depletion stimulates sodium and bicarbonate retention, preventing correction of the alkalosis. Volume expansion causes increased urinary losses of phosphate, even when there is phosphate depletion [37]. Resorption of uric acid and urea occurs in the proximal tubule and increases when sodium retention increases. This arrangement accounts for the elevated uric acid and BUN measurements that often accompany dehydration, which is a stimulus for sodium retention in the proximal tubule [38]. The cells of the proximal tubule are permeable to water; thus, water resorption in this segment parallels sodium resorption.

The loop of Henle is, in terms of absolute amount, the second most important site of sodium resorption along the nephron [39]. The Na^+/K^+, $2Cl^-$ cotransporter on the luminal side of the membrane reclaims filtered sodium and chloride, whereas most of the potassium is recycled back into the lumen. This is the transporter that is inhibited by furosemide and other loop diuretics, which are highly effective at increasing sodium excretion. The ascending limb of the loop of Henle is not permeable to water, permitting sodium retention without water. ADH stimulates sodium retention in this segment; this arrangement helps create a more hypertonic medulla, which maximizes water conservation when ADH acts in the medullary collecting duct. Because loop diuretics inhibit sodium retention in this segment, their use causes a less

Box 11.1: Clinical settings associated with increased antidiuretic hormone production

Hemodynamic stimuli

Hypovolemia
- Vomiting
- Diarrhea
- Diuretics
- Renal salt wasting
- Hypoaldosteronism

Hypervolemia
- Nephrosis
- Cirrhosis
- Congestive heart failure
- Hypoalbuminemia

Hypotension

Non-hemodynamic stimuli

CNS disturbances
- Meningitis
- Encephalitis
- Stroke
- Brain abscess
- Head injury
- Hypoxic brain injury

Pulmonary disease
- Pneumonia
- Asthma
- Tuberculosis
- Empyema
- Chronic obstructive pulmonary disease
- Bronchiolitis
- Acute respiratory failure
- Atelectasis
- Positive pressure ventilation

Cancers
- Lung
- Brain
- CNS
- Head
- Neck
- Breast
- Gastrointestinal tract
- Genitourinary tract
- Leukemia
- Lymphoma
- Thymoma
- Melanoma

Medications
- Cyclophosphamide
- Vincristine
- Morphine
- Selective serotonin reuptake inhibitors
- Carbamazepine

Other
- Nausea
- Emesis
- Pain
- Stress
- Postoperative state
- Cortisol deficiency

CNS, central nervous system.

Source: Adapted from Bailey et al [32] with permission of Wolters Kluwer.

hypertonic medulla, preventing excretion of maximally concentrated urine in the presence of ADH.

Sodium retention in the distal tubule is mediated by the thiazide-sensitive Na^+, Cl^- cotransporter [40]. This segment of the nephron is relatively impermeable to water, and along with sodium and chloride retention, the distal tubule is important for delivery of fluid with a low sodium concentration to the collecting duct. This allows for excretion of water without sodium in patients who stop secreting ADH because of low plasma osmolality. Thiazide diuretics, by inhibiting sodium and chloride retention in this segment, prevent the excretion of water without electrolytes – partially explaining the severe hyponatremia that occasionally develops in patients receiving chronic thiazide diuretics.

The collecting duct, the final segment of the nephron, is important for the regulation of excretion of water, potassium, acid, and sodium. Even though the amount of sodium resorbed in this segment is lower than in any other segment, this is the critical site for the regulation of sodium balance. Sodium resorption occurs via a sodium channel that is regulated by aldosterone. When these channels are open under the influence of aldosterone, almost all of the sodium can be resorbed. The uptake of sodium creates a negative charge in the lumen of the collecting duct, which facilitates the secretion of potassium and hydrogen ions. The potassium-sparing diuretics, amiloride and triamterene, block these sodium channels, and the inhibition of sodium uptake decreases potassium excretion. The potassium-sparing diuretic spironolactone blocks the binding of aldosterone to its receptor; thus, it indirectly decreases the activity of the sodium channels. As highlighted previously, the collecting duct is important for the regulation of water balance because it responds to ADH by inserting water channels that increase the permeability to water, and the hypertonicity of the renal medulla allows for maximal concentration of the urine [4].

The amount of sodium filtered at the glomerulus is directly proportional to the GFR. If sodium resorption in the nephron were constant, complete resorption of sodium with a small decrease in the GFR and significant renal sodium wasting with a small increase would result. This does not occur, however, because sodium resorption in the nephron is proportional to sodium delivery, a principle called glomerular tubular balance.

Renin–angiotensin–aldosterone system

The renin–angiotensin–aldosterone system is also an important regulator of renal sodium excretion. The juxtaglomerular apparatus produces renin in response to decreased effective intravascular volume. Specific stimuli for renin release include decreased perfusion pressure in the afferent arteriole of the glomerulus, decreased delivery of sodium to the distal nephron, and β_1-adrenergic agonists, which increase in response to intravascular

volume depletion [41,42]. Renin, a proteolytic enzyme, cleaves angiotensinogen to produce angiotensin I. Angiotensin-converting enzyme then converts angiotensin I into angiotensin II [43]. The actions of angiotensin II include direct stimulation of the proximal tubule to increase sodium resorption and stimulation of the adrenal gland to increase aldosterone secretion. Through its actions in the distal nephron – specifically, the late distal convoluted tubule and the collecting duct – aldosterone increases sodium resorption. Aldosterone also stimulates potassium excretion, increasing urinary losses. Along with decreasing urinary loss of sodium, angiotensin II acts as a vasoconstrictor, which helps maintain adequate blood pressure in the presence of volume depletion [44].

Atrial natriuretic peptide

Volume expansion stimulates the synthesis of atrial natriuretic peptide (ANP), a polypeptide produced by the atria in response to atrial wall stretch. Along with increasing the GFR, ANP inhibits both renin secretion and aldosterone synthesis, which subsequently facilitates an increase in urinary sodium excretion. ANP also guards against excessive plasma volume expansion in the face of increased ECF volume by shifting fluid from the vascular to the interstitial compartment. ANP inhibits vasoconstriction induced by angiotensin II and norepinephrine and acts in the brain to decrease the desire for salt and inhibit the release of ADH. Thus, the net effect of ANP is a decrease in blood volume and blood pressure through natriuresis and diuresis [45].

Blood volume

The circulating blood volumes of neonates, infants, and children were determined in the late 1960s to mid 1970s and remain the accepted norms for estimating a wide variety of clinically important conditions and guiding therapies, such as blood loss and transfusion of blood products [46,47]. The blood volume gradually decreases (as a function of weight) with growth and development. Thus, in low-birthweight, preterm, or critically ill infants, values as high as 100 mL/kg have been measured. Blood volume increases slightly during the first few months of life, reaching its peak at 2 months of age (approximately 86 mL/kg), then returns to near 80 mL/kg and finally stabilizes at 70 mL/kg by the end of the first year of life. An estimate of the circulating blood volume is presented in Table 11.2.

Table 11.2 Estimate of circulating blood volume

Age	Estimated blood volume (mL/kg)
Premature infants	90–100
Term infants	80–90
Infants <1 year	75–80
Children	70–75
Adults	65–70

KEY POINTS: PHYSIOLOGY OF FLUID AND ELECTROLYTE REGULATION

- Immature renal development in the preterm infant can lead to excessive sodium excretion and hyponatremia
- Numerous hemodynamic and non-hemodynamic stimuli for antidiuretic hormone secretion (ADH) place virtually all hospitalized patients at risk for the development of hyponatremia
- Sodium is the dominant extracellular cation and is the primary determinant of osmolality and therefore critical to the maintenance of intravascular volume. The resorptive capabilities of the kidney determine sodium balance
- The renin–angiotensin–aldosterone system's regulation of renal sodium excretion plays a key role in maintaining adequate blood pressure in the presence of volume depletion
- Atrial natriuretic peptide (ANP) is a key regulator of sodium resorption in states of hypervolemia and its secretion ultimately results in reduction of intravascular volume and systemic blood pressure
- The circulating blood volume in preterm neonates is as high as 100 mL/kg. By the end of the first year of life, the circulating blood volume decreases to adult values of approximately 70 mL/kg

Intravenous fluid therapy

Historical perspective

Intravenous (IV) fluid therapy for the ill child was first reported in 1831 by Dr Thomas Latta in his resuscitation of patients dehydrated by cholera. Instead of infusing fluid into the colon, Latta decided to "throw it immediately into the circulation" [48]. Between 1882 and 1885 the British physiologist Dr Sydney Ringer conducted his so-called "extravital investigations" and developed a fluid that enabled a frog's heart to continue beating outside the body by using a solution comparable to blood plasma [49]. Around 1900, the Dutch physiologist Dr Hartog Jacob Hamburger developed "physiological" or "normal" saline, i.e. 0.9% sodium chloride [50]. In retrospect, the adjectives "physiological" and "normal" are misnomers. In fact, the chloride concentration of 0.9% NaCl is supraphysiological with a chloride concentration of 154 mmol/L versus a serum concentration of 100 mmol/L [51]. In 1918, Blackfan and Maxcy reported instilling 0.8% isotonic saline intraperitoneally to successfully treat an infant with diarrheal dehydration [52]. In 1931, Karelitz and Schick used an IV solution of 5% dextrose combined with either isotonic saline or Ringer's solution to "detoxify" dehydrated children [53]. In 1932, the American pediatrician Dr Alexis Hartmann modified Ringer's solution by adding the buffer lactate [54]. The fluids developed by Latta, Ringer, Hamburger, and Hartmann all qualify as crystalloids, water with electrolytes forming a solution that is capable of crystallizing. In contrast to crystalloids, colloids are fluids in which insoluble particles are suspended and not in solution. The naturally occurring colloid albumin was first used to treat trauma casualties, including burn patients after the Pearl Harbor attack in 1941 [55]. Contributions by Gamble in the 1940s detailed the anatomy of fluid and electrolyte compartments and the role of the kidney in fluid maintenance [56]. In 1950, Darrow and Pratt described the effects of potassium loss and developed regimens for replacing electrolyte deficits in children with diarrhea [57].

In 1957, Malcolm Holliday and William Segar coauthored a report that first estimated "the maintenance need for water in parenteral fluid therapy" [58]. The data from this article evolved into the "4–2–1" formula widely used to calculate the rates of hourly maintenance IV fluid requirements for hospitalized children. The authors simplified the calculation of fluid requirements by correlating insensible loses to the metabolic rate of healthy children at rest and during normal activity. They noted that the requirements for water paralleled those for energy, and that metabolic rate correlated to weight. Holliday and Segar assumed the energy requirements of a "hospitalized patient" to be "roughly midway between basal and normal levels" and constructed a curve of caloric requirement versus weight (Fig. 11.5) [58]. The basal metabolic rate and estimated total energy expenditure with normal activity curves were based on data from studies by Talbot published in 1925 [59]. Based on these plots, the authors proposed daily fluid requirements for patients weighing 0–10 kg to be 100 mL/kg, for patients 11–20 kg 1000 mL + 50 mL/kg for each kilogram between 11 and 20 kg, and for patients weighing more than 20 kg 1500 mL + 20 mL/kg for each kilogram over 20 kg. This construct was further simplified into the "4–2–1" rule. The rule suggested an hourly maintenance IV fluid rate for hospitalized children of 4 mL/kg/h for the first 10 kg of weight, 2 mL/kg/h for the next 10 kg, and 1 mL/kg/h for each kg thereafter (Table 11.3). In 1988, Lindahl found that energy expenditure in anesthetized children was 50% lower than that calculated by Holliday and Segar, but he calculated that 166 mL of water were required to metabolize 100 calories under anesthesia [60]. Thus, there was good agreement in fluid requirements between those proposed by Holliday and Segar and those by Lindahl.

In their article, Holliday and Segar further proposed that electrolytes in IV fluids should mimic those found in human milk [58]. They estimated the amount of sodium, potassium, and chloride in 100 mL of human milk and used those concentrations to determine daily requirements based on the volume of maintenance fluid. They recommended 3 meq/kg/day for sodium and 2 meq/kg/day for both potassium and chloride. This led to the practice of adding 0.2% saline to 5% dextrose for routine IV fluid. In the conclusion of their paper, the authors emphasized that their data were meant to provide only maintenance needs for water and warned against using these data to guide repair of deficits or replacement of continuing abnormal losses of water.

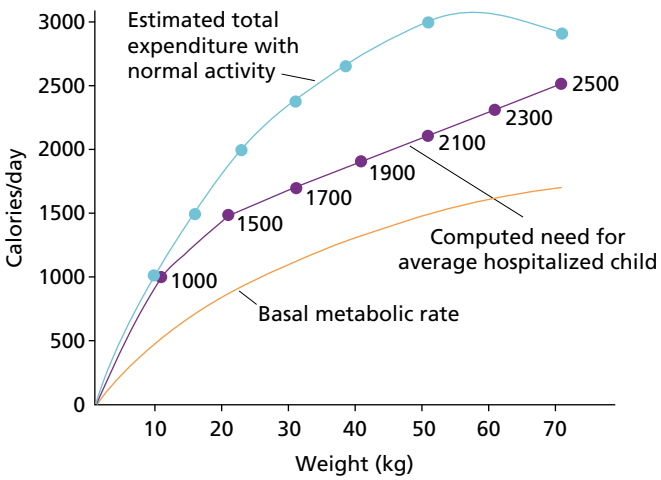

Figure 11.5 Comparison of energy expenditure in basal and ideal state. Energy expended by hospitalized patients was estimated to be approximately between that for basal and normal activity from the study by Talbot [59]. From the curve for the hospitalized patient, a 10 kg infant expends 1000 calories (requires 1000 mL/day, 100 mL/kg) and a 20 kg child, 1500 calories (requires 1500 mL/day, 100 mL/kg for 10 kg + 50 mL/kg for 10 kg). *Source*: Reproduced from Holliday and Segar [58] with permission of American Academy of Pediatrics.

Table 11.3 Hourly or daily maintenance fluid requirements of children based on bodyweight: the "4–2–1 rule"

Weight (kg)	Hourly rate	Daily volume
<10	4 mL/kg	100 mL/kg
10–20	40 mL + 2 mL/kg (for each kg between 10 and 20)	1000 mL + 50 mL/kg (for each kg between 10 and 20)
≥20	60 mL + 1 mL/kg (for each kg >20)	1500 mL + 20 mL/kg (for each kg >20)

Perioperative fluid management

Intraoperative fluid management must address fluid deficits and ongoing losses in addition to maintenance requirements. In 1975, Furman and colleagues proposed a strategy of fluid replacement whereby the preoperative deficits were calculated by multiplying the hourly rate, as dictated by the Holliday and Segar method, by the number of hours the patient was nil per os (NPO). It was then suggested that one-half of the calculated deficit be replaced in the first hour of the procedure, and one-half replaced in the subsequent 2 h [61]. This was adopted into clinical practice until 1986 when Berry proposed a simplified method of delivering a bolus of basic salt solution to otherwise healthy children over the first hour of surgery [62]. Berry concluded that children 3 years and younger should receive 25 mL/kg, whereas children 4 years and older should receive 15 mL/kg. The recommendations proposed by Furman and Berry were developed based on the assumption of a prolonged, 6–8 hr NPO time, but this has come under scrutiny with newer American Society of Anesthesiologists (ASA) NPO guidelines (Table 11.4). Current recommendations allow administration of clear liquids up to 2 h before procedures requiring anesthesia. Holliday and Segar have revised their recommendations and subsequently recommend a simpler and likely more accurate method of fluid management, which is to administer 20–40 mL/kg of a balanced salt solution during the course of the anesthetic. Postoperative fluid management should be reduced to a 2, 1, 0.5 rule: 2 mL/kg for the first 10 kg, 1 mL/kg for the next 10 kg, and 0.5 mL/kg for

Table 11.4 American Society of Anesthesiologists (ASA) NPO guidelines

Ingested material	Minimum fasting period
Clear liquids	2 h
Breast milk	4 h
Infant formula	6 h
Non-human milk	6 h
Light meal	6 h
Fried foods, fatty foods, or meat	8 or more hours

each kg above 20 kg with an isotonic fluid [63–65]. If after 12 hours the child is unable to convert to oral intake, then a standard hypotonic solution (D5 0.45% saline) is initiated at the 4–2–1 rule rate to avoid hypernatremia.

Furthermore, the idea of "third-space losses," i.e. ECF that does not equilibrate with the intravascular space and that is beyond osmotic equilibrium with the vascular space and thus non-functional, has been questioned and recent data suggest they may not exist [66]. This phenomenon was first described in 1961 by Shires and coworkers in a series of 13 adults having elective surgeries (primarily cholecystectomies). The patients were injected with ^{131}I serum albumin, ^{51}Cr-tagged red blood cells, and ^{35}S-tagged sodium sulfate to determine plasma volumes, red cell mass, and ECF volumes. Additionally, the tissue trauma associated with surgery was rated based on observed amount of necessary retraction, difficulty in exposure, and depth of anesthesia. The authors reported that the ECF volume was redistributed or sequestered into areas that no longer communicated with a functional extracellular space and that this correlated with the observed degree of surgical trauma [67]. Isotonic fluids were recommended to replace the losses from the functional extracellular space to the "third space." The Shires group had considerable impact on researchers and clinicians in the 1960s, but few other researchers have been able to replicate their findings. Several more recent studies in the adult literature have cast serious doubt on the actual existence of this "third space" [66]. These studies, using multiple blood samples and steady-state tracer kinetics, revealed that the functional fluid space is either unchanged or expanded rather than contracted after surgery [68–70].

In pediatrics, it has been proposed that, depending on the type of surgery, 1 mL/kg/h to as much as 15 mL/kg/h of additional isotonic fluids are necessary to replenish intravascular volume due to ongoing losses during surgery [71–73]. In fact, it has been stated that up to 50 mL/kg/h of replacement fluids is required for premature neonates undergoing surgery for necrotizing enterocolitis, a surgery associated with significant trauma and ischemia to bowel [74]. This ongoing fluid loss has been attributed primarily to three simultaneous physiological processes. First, anesthetic-induced relaxation of sympathetic tone produces vasodilation. Second, whole blood is lost at various rates. Third, capillary leak and surgical trauma result in extravasation of isotonic, protein-containing fluid into interstitial compartments. This third physiological process must be carefully considered because it is exacerbated by the hemodilution and increased capillary pressures caused by excessive fluid administration. In general, 1 mL of lost blood is replaced with 1 mL of colloid (5% albumin or blood) or about 1.5 mL of isotonic crystalloid such as lactated Ringer's solution (LR) [74].

Perioperative dextrose

Hypoglycemia, depending on the severity, can have devastating effects on the central nervous system, especially in neonates. Low blood glucose invokes a stress response and alters cerebral blood flow and metabolism, leading to permanent neurodevelopmental impairment if hypoglycemia goes unrecognized and untreated. In 1967, Anderson et al first described six cases of neonatal hypoglycemia and the serious clinical and pathological sequelae associated with prolonged low blood glucose [75]. Animal experiments have further demonstrated that cerebral injury is caused not only by severe prolonged hypoglycemia but also by mild hypoglycemia combined with mild hypoxia or ischemia [76]. In a 2008 study of 35 term neonates with symptomatic hypoglycemia (blood glucose level 45 mg/dL or 2.6 mmol/L), magnetic resonance imaging detected white matter abnormalities in 94%, with severe abnormalities noted in 43% of the studied population. Furthermore, at 18-month follow-up, 26 of the 35 patients studied continued to exhibit some level of impairment [77]. Hypoglycemia has also been found to be associated with an increase in morbidity and mortality in pediatric intensive care unit (PICU) patients [78].

In the last 40 years, there has been a complete re-evaluation of the place of glucose in routine intraoperative solutions. In the 1970s, research suggested that fasted children may become hypoglycemic while under anesthesia [79–82]. Administration of dextrose was deemed mandatory to avoid perioperative hypoglycemia. Unfortunately, the risk of hyperglycemia was underestimated. In 1986, Welborn et al evaluated preoperative hypoglycemia in 446 children, 1 month to 6 years old, scheduled for minor outpatient surgical procedures [83]. There were two asymptomatic children with preoperative blood glucose values of 50 mg/dL. Both of these children had fasted in excess of 17 h before presenting to the operating room. More recent studies on this topic estimate the incidence of preoperative hypoglycemia to be between 0% and 2.5% and usually associated with fast durations from 8 to 19 h, well beyond the current ASA recommended guidelines (see Table 11.4) [84].

Hyperglycemia has also been recognized as significantly detrimental for the brain. In the presence of ischemia or hypoxia, it is proposed that the impaired metabolism of excess glucose causes an accumulation of lactate, a decrease in intracellular pH, and subsequently severely compromised cellular function that may result in cell death [85]. Hyperglycemia can also induce an osmotic diuresis that may lead to dehydration and electrolyte abnormalities [74,84,86]. Furthermore, there is evidence in the pediatric literature suggesting that hyperglycemia, especially in the setting of an ischemic or hypoxic event, worsens neurological outcomes as well as morbidity and mortality statistics in the pediatric population [78,87–89].

In the 1986 study by Welborn et al, the patients were randomized to intraoperatively receive either LR or 5% dextrose in LR (D5LR). Both the LR and D5LR groups had statistically significant increases in blood glucose. However, the D5LR group had a much larger increase in blood glucose (83 ± 14 mg/dL preoperatively to 244 ± 60 mg/dL postoperatively) than the LR group (85 ± 14 mg/dL preoperatively to 111 ± 22 mg/dL postoperatively) [83].

Based on these results and those of other studies, there is a growing consensus that intraoperative dextrose should be selectively administered only in those patients at greatest risk for hypoglycemia and, in such situations, that the use of fluids with lower dextrose concentrations (e.g. 1% or 2.5%) be considered [74,84,86,90]. It should be noted that there are no IV fluids with dextrose concentrations less than 5% commercially available in the United States. The populations at highest risk of hypoglycemia include neonates, children receiving hyperalimentation, and those with endocrinopathies, in whom monitoring blood glucose levels and adjusting the rate

of infusion is also recommended [74,86,90]. Routine dextrose administration is no longer advised for otherwise healthy children receiving anesthesia.

Neonatal fluid management

Fluid needs vary according to gestational age, environmental conditions, and disease states. Assuming minimal water loss in the stool of infants not receiving oral fluids, their water needs are equal to their insensible water losses, excretion of renal solutes, and any unusual ongoing losses. Insensible water losses are indirectly related to gestational age; very immature preterm infants (<1000 g) may lose as much as 2–3 mL/kg/h, partly because of immature skin, lack of subcutaneous tissue, and a large exposed surface area [91]. Furthermore, insensible water losses are increased under radiant warmers, during phototherapy, and in febrile infants. Insensible losses are diminished when an infant is clothed, breathes humidified air, or is of advanced postnatal age. A larger premature infant (2000–2500 g) nursed in an incubator may have an insensible water loss of approximately 0.6–0.7 mL/kg/h [91].

Adequate fluid intake is essential for excretion of the urinary solute load (i.e. urea, electrolytes, phosphate). The amount varies with dietary intake and the anabolic or catabolic state of nutrition. High protein intake, formulas with a high solute load, and catabolic conditions all increase the end-products that require urinary excretion and thus increase the requirement for water. Renal solute loads may vary between 7.5 and 30 mOsm/kg. Newborn infants, especially those with very low birthweight, are also less able to concentrate urine, so they need higher fluid intake to excrete solutes.

Fluid intake in term infants is usually started at 60–70 mL/kg on day 1 and increased to 100–120 mL/kg by days 2 or 3. Smaller, more premature infants may need to start with 70–80 mL/kg on day 1 and advance gradually to 150 mL/kg/day [5]. Fluid volumes should be titrated individually, although it is unusual to exceed 150 mL/kg/day. Infants weighing <750 g in the first week of life have immature skin and a large surface area, characteristics that lead to a high rate of transepidermal fluid loss, at times requiring higher rates of intravenous fluids. Daily weights, urine output, serum urea nitrogen and sodium levels should be monitored carefully to determine water balance and fluid needs. Clinical observation and physical examination are poor indicators of the state of hydration of premature infants. Conditions that increase fluid loss, such as glycosuria, the polyuric phase of acute tubular necrosis, and diarrhea, may place additional strain on kidneys that have not yet acquired their maximal capacity to conserve water and electrolytes. The result of this may be severe dehydration. Alternatively, fluid overload may lead to edema, heart failure, patent ductus arteriosus, and bronchopulmonary dysplasia.

Due to the ongoing sodium loss secondary to the inability of the neonatal distal tubule to respond fully to aldosterone, IV fluids in the neonate must contain sodium. Given that most operations on neonates involve loss of ECF and blood, a replacement fluid with a similar electrolyte content (i.e. a balanced salt solution such as LR or Plasma-Lyte) should be used. Hypotonic solutions should not be used to replace these losses due to risk of significant hyponatremia. If a neonate presenting to the operating room is stable on a maintenance solution, it is reasonable to continue this maintenance fluid at a constant rate and add a balanced salt solution, colloid, or blood product as needed to replace operative fluid losses.

As noted earlier, appropriate glucose administration is an important issue in the fluid choice for the neonate. In most cases, maintenance fluids containing 10% glucose and 0.2 normal saline with 20 mmol/L of potassium are reasonable in the first 48 h of life. Beyond that time period, full-term infants can be changed to 5% glucose instead of 10%. Preterm infants will often require the higher glucose load for longer. Infants who have had continuous glucose infusions stopped, those who are small for gestational age, and newborns of diabetic mothers require special attention and monitoring as they have particular problems with hypoglycemia. Neonates who have been receiving hyperalimentation or supplementary glucose should continue to receive that fluid during surgery but must have their glucose levels monitored closely for hypo- or hyperglycemia.

Parenteral nutrition

Before complete enteral feeding has been established or when enteral feeding is impossible for prolonged periods, total parenteral nutrition (TPN), also called hyperalimentation, is often necessary. TPN provides fluid, calories, amino acids, fat, electrolytes, and vitamins to sustain the growth of ill infants and children. Critically ill patients often present to the operating room with hyperalimentation infusing. Infusions may be administered through a percutaneously or surgically placed indwelling central venous catheter or through a peripheral vein. The umbilical vein may also be used for up to 2 weeks. Glucose concentrations should be measured during surgery to determine if hyperglycemia is developing.

The goal of parenteral nutrition is to deliver sufficient calories from glucose, protein, and lipids to promote optimal growth. To meet nutritional needs, the infusate should contain 2.5–3.5 g/dL of synthetic amino acids and usually 10–15 g/dL of glucose (10–15% dextrose), in addition to appropriate quantities of electrolytes, trace minerals, and vitamins [92,93]. If a peripheral vein is used, it is advisable to keep the glucose concentration below 12.5 g/dL (12.5%). If a central vein is used, glucose concentrations as high as 25 g/dL (25%) may be used.

Electrolytes, trace minerals, and vitamin additives are included in amounts approximating established IV maintenance requirements. IV fat emulsion, such as Intralipid 20%, is often administered in combination with parenteral nutrition to provide calories without an appreciable osmotic load. This may decrease the need for infusions of higher glucose concentrations as well as prevent the development of essential fatty acid deficiency. Intralipid is frequently initiated at 0.5 g/kg/24 h and advanced to 3 g/kg/24 h, if triglyceride levels remain normal; 0.5 g/kg/24 h is sufficient to prevent essential fatty acid deficiency [94]. The content of each day's infusate should be determined after careful assessment of the infant's clinical and biochemical status. Slow and continuous infusion is advisable.

Neonates with >100 kcal/kg/24 h via parenteral nutrition can be expected to gain about 15 g/kg/24 h, with a positive nitrogen balance of 150–200 mg/kg/24 h, in the absence of episodes of sepsis, surgical procedures, and other severe

stress [93]. This goal can usually be achieved (and the catabolic tendency during the first week of life reversed, with subsequent weight gain) by peripheral vein infusion of 2.5–3.5 g/kg/24 h of an amino acid mixture, 10 g/dL of glucose, and 2–3 g/kg/24 h of a 20% fat emulsion [95].

Complications of IV alimentation are related to both the catheter and the metabolism of the infusate. Sepsis, the most common complication of central vein infusions, can be minimized only by meticulous catheter care and aseptic preparation of the infusate. Coagulase-negative *Staphylococcus* is the most common infecting organism [92]. Treatment includes appropriate antibiotics. If an infection persists (i.e. repeatedly positive blood culture results while the infant is receiving appropriate antibiotics), the line must be removed. Thrombosis, extravasation of fluid, and accidental dislodgment of central venous catheters also occur. Phlebitis, cutaneous sloughing, and superficial infection are the more common complications observed with peripheral infusion of hyperalimentation. Metabolic complications of parenteral nutrition include hyperglycemia, azotemia, nephrocalcinosis, hypoglycemia, hyperlipidemia, possibly hypoxemia with intravenous lipid infusions, and hyperammonemia. Metabolic bone disease and/or cholestatic jaundice and liver disease may develop in infants who require long-term parenteral nutrition and receive no enteral nutrition.

Choice of fluids

The compositions of commonly used IV solutions are presented in Table 11.5. A normal plasma osmolality is 275–290 mOsm/kg. Infusing an IV solution peripherally with a much lower osmolality can cause water to move into red blood cells, leading to hemolysis. Thus, IV fluids are generally designed to have an osmolality that is either close to 285 or greater (fluids with moderately higher osmolality do not cause problems). Normal saline (0.9% NaCl) is slightly hypertonic to plasma (308 mOsm/L) while LR solution is isotonic (273 mOsm/L) and slightly hyponatremic.

Albumin

Albumin is a natural colloid abundant in plasma and is regarded as the colloid "gold standard." Albumin is derived from pooled human plasma by the Cohn cold ethanol fractionation process: human plasma is heated to 60°C for 10 h and then sterilized by ultrafiltration, thus eliminating the risk of disease transmission [96]. Albumin has a molecular weight (MW) of approximately 69 kDa. In the United States, albumin is produced in concentrations of both 5% and 25%. A solution of 5% albumin is osmotically equivalent to an equal volume of plasma, whereas a 25% solution is osmotically equivalent to five times its plasma volume. In other words, the administration of 100 mL of 25% albumin will increase the intravascular volume up five times the amount infused while the administration of 500 mL of 5% albumin is necessary to increase the intravascular volume by a similar amount [97]. Intravascular volume expansion occurs because of fluid translocation from the interstitial compartment to the intravascular space. In subjects with increased intravascular permeability (e.g. critically ill, sepsis, trauma, and burn), this translocation of fluid between compartments may be decreased and colloids may actually leak into the interstitial space, thereby worsening edema by pulling fluid from the intravascular compartment.

Side-effects from albumin are rare. Although considered to have negligible effects on the coagulation cascade, albumin has been implicated to have weak anticoagulation effects through inhibition of platelet aggregation [98] or heparin-like effects on antithrombin III [99]. These effects are thought to be clinically insignificant if volume replacement with albumin is kept below 25% of the patient's blood volume. Allergic reactions are another possible complication of albumin administration; however, albumin is associated with significantly fewer anaphylactic reactions compared with other colloids [100].

Albumin's safety has been questioned in two separately conducted meta-analyses [101,102]. In the 2004 Saline versus Albumin Fluid Evaluation study, a 7000-patient multicenter, randomized, double-blind trial, Finfer et al noted no difference in outcomes between albumin and saline administration in adults [103]. This study showed no significant difference in mortality (726 deaths in albumin group and 729 deaths in saline group) or secondary endpoints (length of stay in the ICU or hospital, days of mechanical ventilation, and days of renal replacement therapy) between the groups. However, there seemed to be an increased mortality in a subset of patients with traumatic brain injury (TBI). A *post hoc* follow-up study was undertaken (Saline versus Albumin Fluid Evaluation–TBI study) that substantiated these findings and concluded that critically ill patients with TBI had a higher mortality rate if resuscitated acutely with albumin as opposed to saline [104].

Table 11.5 Composition of frequently used intravenous fluids [33]

Solution	Osmolality (mOsm)	pH	Na^+ (mM)	K^+ (mM)	HCO_3^- (mM equivalent)	Cl^- (mM)	Glucose (g/dL)
Plasma	275–290	7.4	140	3.6–5.1	30	100	0.07–0.11
0.9% saline	308	5	154	0	0	154	0
3% saline	1026	–	513	0	0	513	0
7.5% saline	2400	3.5–7	1250	0	0	1250	0
Ringer's lactate	273	6.5	130	4	28	109	0
Ringer's acetate	270	6	130	4	30	110	0
Plasmalyte A	294	7.4	140	5	50	98	0
D5NS	560	4	154	0	0	154	5
D5W	253	4	0	0	0	0	5
D5 0.45% NS	406	4	77	0	0	77	5
D5 0.25% NS	321	4	34	0	0	34	5

Non-protein colloids: hydroxyethyl starches

Hydroxyethyl starches (HES) are synthetic colloids that are modified natural polysaccharides. Natural polysaccharides are broken down by circulating amylases. HES solutions avoid this by substituting hydroxyethyl groups for the naturally occurring hydroxyl groups at carbon positions C-2, C-3, and C-6. This results in a more stable product, resistant to hydrolysis, with subsequent prolonged effectiveness.

HES colloids are classified by concentration, MW, molar substitution (MS, ratio of hydroxyethyl groups to glucose units), and C2:C6 ratios [105]. HES solutions expand the plasma volume with effects lasting 2–6 h, depending on the specific characteristics of the HES fluid. While the physical properties of HES promote longer times in the intravascular space compared to crystalloids, they also confer more side-effects, including hypocoagulability (decreased function of von Willebrand factor, platelets, and factor VIII), renal impairment, and pruritus [106,107]. The older high-MW, high-MS, first-generation HES solutions (e.g. HES 450/0.7) have more significant hemostatic side-effects compared with the newer low-MW, low-MS solutions (e.g. HES 130/0.4). HES solutions may worsen renal function by inducing renal tubular cell swelling and creating a hyperviscous urine [108–110].

In a prospective randomized study published in 2008, Standl et al compared third-generation 6% HES (Voluven – 6% HES 130/0.4 in 0.9% NaCl) and 5% albumin. In this study, there was no difference in perioperative hemodynamic stability, coagulation variables, blood gas, or other laboratory values in 81 pediatric patients undergoing elective non-cardiac surgery [111]. Also in 2008, a European prospective, multicenter, observational, post-authorization safety study that evaluated the safety of 6% HES for perioperative plasma replacement in children was published [112]. Some 316 children, aged 3–12 years, were infused with a mean volume of 11 ± 4.8 mL/kg of HES (130/0.42). Cardiovascular stability was maintained in all cases. There were no serious adverse drug reactions, such as anaphylaxis, renal failure, or clotting disorder. In this study, only pediatric patients with normal renal function and intact coagulation systems were investigated. Despite reassuring pediatric clinical trials, recent data from adult studies have demonstrated an increased risk for renal failure and mortality with HES as compared to crystalloid solutions in critically ill patients [113–116]. In June 2013, the US Food and Drug Administration (FDA) issued a warning against use of HES in critically ill patients. Given the 2013 US FDA warning and the risks of HES in adult patients, most pediatric anesthesia providers have moved away from their use in clinical practice.

Crystalloid versus colloid

The controversy regarding the perioperative use of crystalloid versus colloid fluid replacement remains an unresolved subject. Given a lack of pediatric studies, we continue to extrapolate from adult studies and use a combination of crystalloid and colloids to achieve the desired outcomes. In the most recent Cochrane database review of colloids versus crystalloids for fluid resuscitation in critically ill adult patients, the authors concluded that there is no evidence to support the use of colloids over crystalloids in the resuscitation of patients with burns, trauma, or after surgery, because they are significantly more expensive and not associated with improved survival [117]. A further meta-analysis analyzing the different colloid solutions available for fluid resuscitation concluded that when measuring mortality, blood administration, and the incidence of allergic reactions, there was no evidence to suggest that one colloid solution is more effective or safe than another [118].

KEY POINTS: INTRAVENOUS FLUID THERAPY

- The 1957 publication by Holliday and Segar first presented a practical method for clinicians to prescribe IV fluids. Their suggestions evolved into what is now termed the "4–2–1 rule" for maintenance fluid therapy in children
- No clear consensus exists on which intravenously administered fluid is associated with the best clinical outcomes. The use of traditional hypotonic fluids may cause complications, such as hyperglycemia and hyponatremia, in the postoperative surgical patient
- Routine dextrose administration is no longer advised for otherwise healthy patients. There is a growing consensus to selectively administer intraoperative dextrose only in those patients at greatest risk for hypoglycemia such as neonates, children receiving hyperalimentation, and those with endocrinopathies
- Neonatal fluid management requires a unique understanding of the developmental aspects of distribution of total body water and of age-related renal, hepatic, cardiorespiratory, and central nervous system physiology

Disorders of fluids and electrolytes

Dehydration

Dehydration is a commonly encountered problem in clinical pediatrics and is one of the leading causes of pediatric morbidity and mortality worldwide. Clinical history usually suggests the etiology of the dehydration. Viral gastroenteritis and/or diarrheal disease are the most common causes of pediatric dehydration. The first step in caring for the dehydrated child is to assess the degree of dehydration (Table 11.6), which dictates both the urgency of the situation and the volume of fluid needed for rehydration. Weight loss is the most reliable indicator of the degree of a child's dehydration. Due to the fact that water accounts for a higher percentage of bodyweight in infants, the degree of dehydration will be represented as a higher percentage of bodyweight lost. The infant or child with mild dehydration may have few clinical physical signs or symptoms, while the infant or child with moderate or severe dehydration typically has clear physical signs and symptoms. Intravascular space depletion is initially evident with an increased heart rate and reduced urine output. When the dehydrated infant has a decrease in blood pressure, the volume deficit is severe and vital organs may be inadequately perfused. Immediate and aggressive intravenous therapy is necessary.

Laboratory findings

Several laboratory findings are useful for evaluating the child with dehydration. In fact, serum sodium concentration

Table 11.6 Clinical manifestations of dehydration

	Mild	Moderate	Severe
Decrease in bodyweight	<5% (infant) <3% (older child or adult)	5–10% (infant) 3–6% (older child or adult)	>10% (infant) >6% (older child or adult)
Hemodynamic signs	Absent	Present	Present
Pulse	Normal	Slight increase	Tachycardia
Capillary refill	2–3 s	3–4 s	>4 s
Blood pressure	Normal	Normal	Low
Perfusion	Normal	Normal	Circulatory collapse
Skin			
Turgor	Normal	Decreased	Markedly decreased
Color	Normal	Pale	Markedly decreased
Mucous membranes	Dry	Dry	Mottled or gray, parched
Fluid loss			
Urinary output	Mild oliguria	Oliguria	Anuria
Tears	Decreased	–	Absent

determines the type of dehydration as serum sodium values vary depending on the relative loss of solute to water. Dehydration is frequently classified as isonatremic (also termed isotonic), hyponatremic, or hypernatremic. The most common clinically encountered pediatric dehydration state (~75–80%) is isonatremic dehydration (Na^+ 130–150 mEq/L) where there is an equal proportion of solute and water loss. Isonatremic dehydration is most frequently the result of secretory diarrhea. Hypernatremic dehydration (Na^+ >150 mEq/L) occurs in approximately 15% of dehydrated pediatric patients. This type of dehydration is common with viral gastroenteritis or in breastfeeding infants in whom diarrheal and insensible water losses are inadequately replaced. Hyponatremic dehydration (Na^+ <130 mEq/L) has an incidence of about 5%. Hyponatremic dehydration occurs in the child with diarrhea who is taking in large quantities of low-salt fluid, such as water or formula [119].

Metabolic acidosis may be a result of stool bicarbonate losses in children with diarrhea, secondary renal insufficiency, or lactic acidosis from shock. The anion gap is useful for differentiating between the various causes of a metabolic acidosis. Emesis or nasogastric losses usually cause a metabolic alkalosis. The serum potassium concentration may be low as a result of diarrheal losses. In children with dehydration as a result of emesis, gastric potassium losses, metabolic alkalosis, and urinary potassium losses all contribute to hypokalemia. Metabolic acidosis, which causes a shift of potassium out of cells, and renal insufficiency may lead to hyperkalemia. A combination of mechanisms may be present; thus, it may be difficult to predict the child's acid–base status or serum potassium level from the history alone.

The BUN value and serum creatinine concentration are useful in assessing the child with dehydration. Volume depletion without parenchymal renal injury may cause a disproportionate increase in the BUN with little or no change in the creatinine concentration. This condition is secondary to increased passive resorption of urea in the proximal tubule as a result of appropriate renal conservation of sodium and water. The increase in the BUN with moderate or severe dehydration may be absent or blunted in the child with poor protein intake, because urea production depends on protein degradation. The BUN may be disproportionately increased in the child with increased urea production, as occurs with a gastrointestinal bleed or with the use of glucocorticoids, which increase catabolism. A significant elevation of the creatinine concentration suggests renal insufficiency, although a small, transient increase can occur with dehydration. Acute tubular necrosis (acute kidney injury) is the most common etiology of renal insufficiency in a child with volume depletion, but occasionally the child may have previously undetected chronic renal insufficiency or an alternative explanation for the acute renal failure. Renal vein thrombosis is a well-described sequela of severe dehydration in infants; possible findings include thrombocytopenia and hematuria.

Hemoconcentration from dehydration causes increases in hematocrit, hemoglobin, and serum proteins. These values normalize with rehydration. A normal hemoglobin concentration during acute dehydration may mask an underlying anemia. A decreased albumin level in a dehydrated patient suggests a chronic disease, such as malnutrition, nephrotic syndrome, or liver disease, or an acute process, such as capillary leak.

Calculation of the fluid deficit

The fluid deficit is the total amount of body water lost expressed as the percent decrease in bodyweight. Determining the fluid deficit necessitates clinical determination of the percentage of dehydration and multiplication of this percentage by the patient's weight; a child who weighs 10 kg and is 10% dehydrated has a fluid deficit of 1 L. If the child's baseline weight is unavailable, the percentage of fluid deficit should be estimated by clinical signs and symptoms (see Table 11.6).

Approach to severe dehydration

The child with severe dehydration needs acute intervention to ensure adequate tissue perfusion. The resuscitation phase requires rapid restoration of the circulating intravascular volume and treatment of shock with an isotonic solution such as normal saline or LR. The child should be given a fluid bolus, usually 20 mL/kg, of the isotonic fluid. The child with severe dehydration may require multiple fluid boluses and may need to receive the boluses as quickly as possible. In a child with a known or probable metabolic alkalosis (i.e. the child with isolated vomiting), LR should not be used because the lactate may worsen the alkalosis.

The initial resuscitation and rehydration phase is complete when the child has an adequate intravascular volume.

Typically, the child shows clinical improvement, including a lower heart rate, normalization of blood pressure, improved perfusion, better urine output, and a more alert affect.

Once the patient has an adequate intravascular volume, further resuscitation should be based upon the etiology and type of dehydration. In isonatremic or hyponatremic dehydration, the entire fluid deficit should be corrected over 24 h; a slower approach should be taken for hypernatremic dehydration. Depending upon the etiology of the dehydration, the patient may be either hypo- or hyperkalemic. Potassium is not usually included in the IV fluids until the patient voids and normal renal function is documented via measurement of BUN and creatinine. Based upon the clinical situation, it is essential that children with significant ongoing losses receive an appropriate replacement solution.

Monitoring and adjusting therapy

Measurement of serum electrolyte levels at least daily is appropriate for any child who is receiving IV rehydration. As outlined previously, dehydrated children are at risk for sodium, potassium, and acid–base disorders. It is important to look at trends. For instance, a sodium value of 145 mEq/L is normal, but if the sodium concentration was 135 mEq/L 12 h earlier, then there is a distinct risk that the child will be hypernatremic in 12 or 24 h. The correction of both hypernatremia and hyponatremia will be discussed in detail later in the chapter. Clinicians must be proactive in monitoring electrolytes and adjusting fluid therapy accordingly.

Sodium

Sodium, the principal ECF cation and major determinant of plasma osmolality, is critical for the generation of action potentials in nervous and cardiac tissue. Abnormalities of sodium concentration are most often a reflection of an abnormal water balance rather than an increase or decrease in total body sodium. Plasma osmolality and sodium concentration are tightly regulated, both by thirst, which prompts water ingestion, and by ADH, also known as arginine vasopressin. ADH, which is released from the posterior pituitary gland in response to increased osmolality, decreased blood volume and/or decreased blood pressure, enhances water reabsorption from the tubular fluid in the kidneys.

Hyponatremia

Hyponatremia is one of the most common electrolyte disorders encountered in hospitalized patients. In fact, the condition affects approximately 25% of hospitalized children [120]. Hyponatremia, defined as a serum sodium level of less than 135 mmol/L (mEq/L), most frequently occurs as a result of excess free water in the setting of impaired free water excretion.

Hyponatremia can be the result of many different etiologies (Fig. 11.6). The first step in further evaluation of hyponatremia is to determine the patient's plasma osmolality. If the plasma osmolality is normal, pseudohyponatremia should be suspected. Pseudohyponatremia is a laboratory artifact that occurs in the presence of hyperlipidemia or hyperproteinemia when the sodium concentration is determined by an indirect method rather than by a direct ion-selective electrode. If the plasma osmolality is elevated, a hyperosmolar state should be suspected as it is frequently encountered with hyperglycemia or mannitol administration.

True hyponatremia is most often associated with a low plasma osmolality. If both the serum sodium and plasma osmolality are low, the patient's volume status and urine sodium concentration should be assessed. In patients with hyponatremia, evidence of volume overload, and a low urine sodium, congestive heart failure, cirrhosis, nephrotic syndrome or hypoalbuminemia are possible causes. Patients with acute or chronic renal failure frequently exhibit hyponatremia and hypervolemia with a variable urine sodium. In the setting

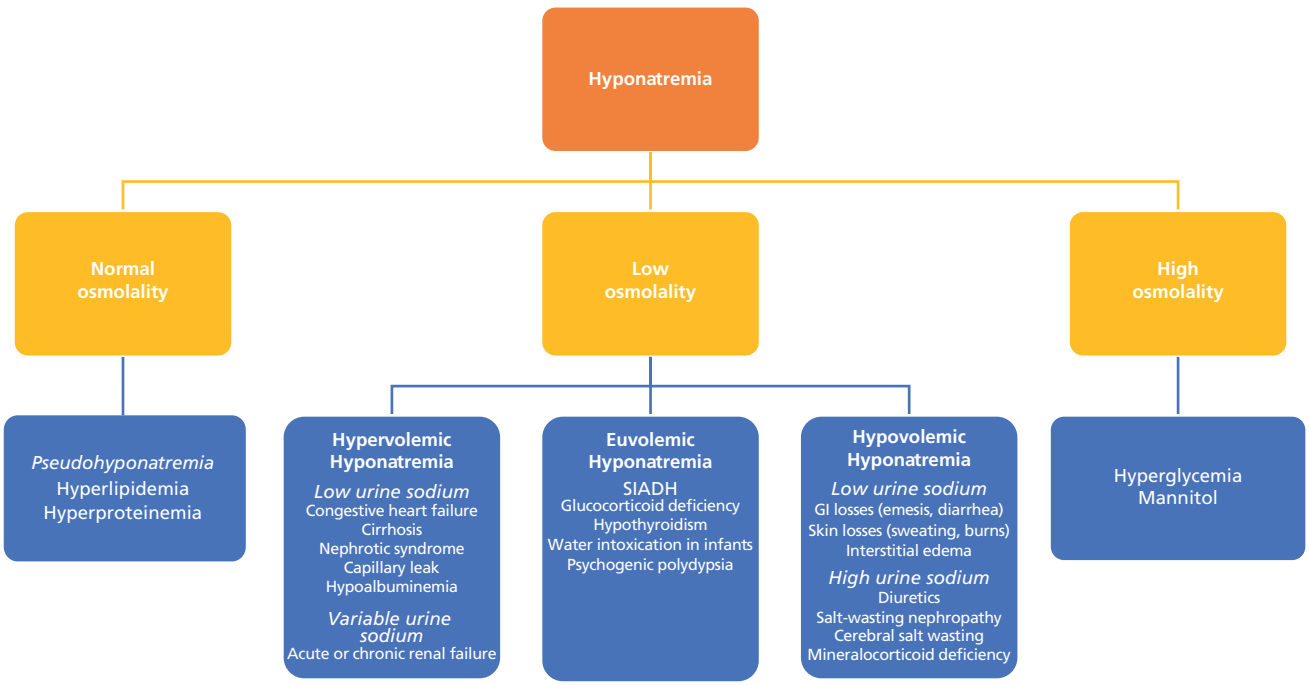

Figure 11.6 Hyponatremia. GI, gastrointestinal; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

of low plasma osmolality, hyponatremia, hypovolemia, and a low urine sodium, common etiologies include emesis, diarrhea, excessive sweating, burns, and interstitial edema. Diuretics, notably thiazide diuretics, and conditions that promote renal salt wasting lead to low plasma osmolality, hyponatremia, hypovolemia, and high urine sodium.

Euvolemic hyponatremia has several potential causes including glucocorticoid deficiency, hypothyroidism, water intoxication in infants, psychogenic polydipsia, and syndrome of inappropriate antidiuretic hormone (SIADH). In postsurgical pediatric patients, SIADH is most frequently responsible for the constellation of low plasma osmolality, hyponatremia, euvolemia, and a high urine sodium. In SIADH, ADH secretion is not inhibited by either low plasma osmolality or expanded intravascular volume. ADH-mediated retention of water leads to hyponatremia, expansion of intravascular volume, and an increase in renal sodium excretion. As mentioned previously in this chapter, inappropriate ADH release occurs in many pediatric postsurgical patient populations as a result of both hemodynamic and non-hemodynamic stimuli (see Box 11.1).

In 1983, a study of children undergoing scoliosis surgery first demonstrated that hyponatremia developed frequently in the postoperative period. Investigators in this study asserted that the phenomenon was secondary to SIADH in the setting of administration of hypotonic IV fluids [121]. Since this initial report, there has been an abundance of retrospective and prospective observational studies that have demonstrated a relatively high incidence of hyponatremia in both non-surgical and postsurgical hospitalized pediatric populations and the potentially devastating consequences of that hyponatremia [122–127]. In a prospective observational study of 81 consecutive postsurgical patients admitted to a single PICU, the incidence of hyponatremia was 21% at 12 h postoperatively and 31% at 24 h [125]. There have also been many prospective randomized controlled trials comparing hypotonic versus isotonic fluid administration in hospitalized children [128–138]. A recent meta-analysis of the available literature summarized the data of 10 randomized controlled trials comparing hypotonic and isotonic maintenance fluid therapy in 855 hospitalized children. The meta-analysis showed a significantly higher risk for developing hyponatremia with hypotonic IV fluids (relative risk (RR) 2.24, 95% confidence interval (CI) 1.52 to 3.31) and severe hyponatremia (plasma Na <130 mmol/L) (RR 5.29, 95% CI 1.74 to 16.06). There was a significantly greater decrease in sodium in children who received hypotonic IV fluids (–3.49 mmol/L versus isotonic IV fluids, 95% CI –5.63 to –1.35). Moreover, there was no significant difference between the two interventions in the risk of hypernatremia (RR 0.73, 95% CI 0.22 to 2.48) [139].

Given the current clinical evidence, hospitalized children who require IV fluid therapy should receive isotonic maintenance IV fluids or IV fluids of an appropriate composition at a rate commensurate with their ongoing volume losses. When receiving IV fluid therapy, these same patients should have both daily weights and daily electrolyte monitoring with close attention to serum sodium levels [140].

Hyponatremia produces osmotic movement of free water across cell membranes from the extracellular to the intracellular compartments, with the brain being the most significantly affected organ. Children are more prone to cerebral edema from hyponatremia than are adults. This results from differences in the ratio of intracranial capacity to brain size, cerebrospinal fluid volume, and brain water and electrolyte content. The brain of a child grows rapidly, achieving adult size by age 6 years, whereas the skull continues to grow until the age of 16 years. The volume of cerebrospinal fluid, which buffers brain expansion, is relatively smaller in children than adults. Moreover, the brain intracellular concentration of sodium is approximately 27% higher in children than adults.

Clinically, cerebral edema is the most devastating consequence of hyponatremia. In the case of mild hyponatremia, patients frequently appear anxious or agitated. As the level of hyponatremia progresses, symptoms may worsen to include headaches, vomiting, ataxia, disorientation, seizures, and even coma or death. Treatment of hyponatremia and the rate of correction of the patient's sodium should depend upon the severity of the symptoms and the chronicity of the hyponatremia. Treatment options include fluid restriction, administration of oral or IV sodium chloride, and treatment of the underlying disease (Box 11.2). Considering the risk for cerebral demyelination with rapid correction or overcorrection of severe and/or chronic hyponatremia, an increase in plasma sodium of >25 mmol/L (mEq/L) over 48 h should be avoided. In the setting of symptoms suggestive of hyponatremic encephalopathy, definitive therapy with hypertonic saline is indicated (3% NaCl, 513 mEq/L) (see Box 11.1) [141].

Hypernatremia

Hypernatremia, another frequently encountered electrolyte disorder in hospitalized children, represents a deficit of water in relation to total body sodium. Defined as a serum sodium level >145 mmol/L (mEq/L), hypernatremia is the result of either a net loss of water or a gain of hypertonic sodium (Fig. 11.7). Net water losses, in either the form of pure water or hypotonic fluids, account for the majority of cases of hypernatremia. Pure water losses occur because of insensible losses through the skin or respiratory system or as a result of nephrogenic or central diabetes insipidus. There are many potential causes of hypotonic fluid losses. In infants and children, diarrhea and/or vomiting are common etiologies because this patient population often has an inability to control their own water intake and replace ongoing losses. In the hospital setting, hypernatremia is often iatrogenic secondary to either the administration of hypertonic saline or sodium bicarbonate for the treatment of metabolic acidosis [142,143].

Box 11.2: Treatment of symptomatic hyponatremia

1. 2 mL/kg bolus of 3% NaCl over 10 min. Maximum 100 mL
2. Repeat bolus 1–2 times as needed with until symptoms improve. Goal: 5–6 mmol/L increase in serum sodium in first 1–2 h
3. Recheck serum sodium following second or third bolus or every 2 h
4. Hyponatremic encephalopathy is unlikely if no clinical improvement following an acute rise in serum sodium of 5–6 mmol/L
5. Stop further therapy with 3% NaCl boluses if either:
   a. Patient is symptom free: awake, alert, responding to commands, resolution of headache and nausea
   b. Acute rise in sodium of 10 mmol/L in first 5 h
6. Correction in first 48 h should:
   a. Not exceed 15–20 mmol/L
   b. Avoid normo- or hypernatremia

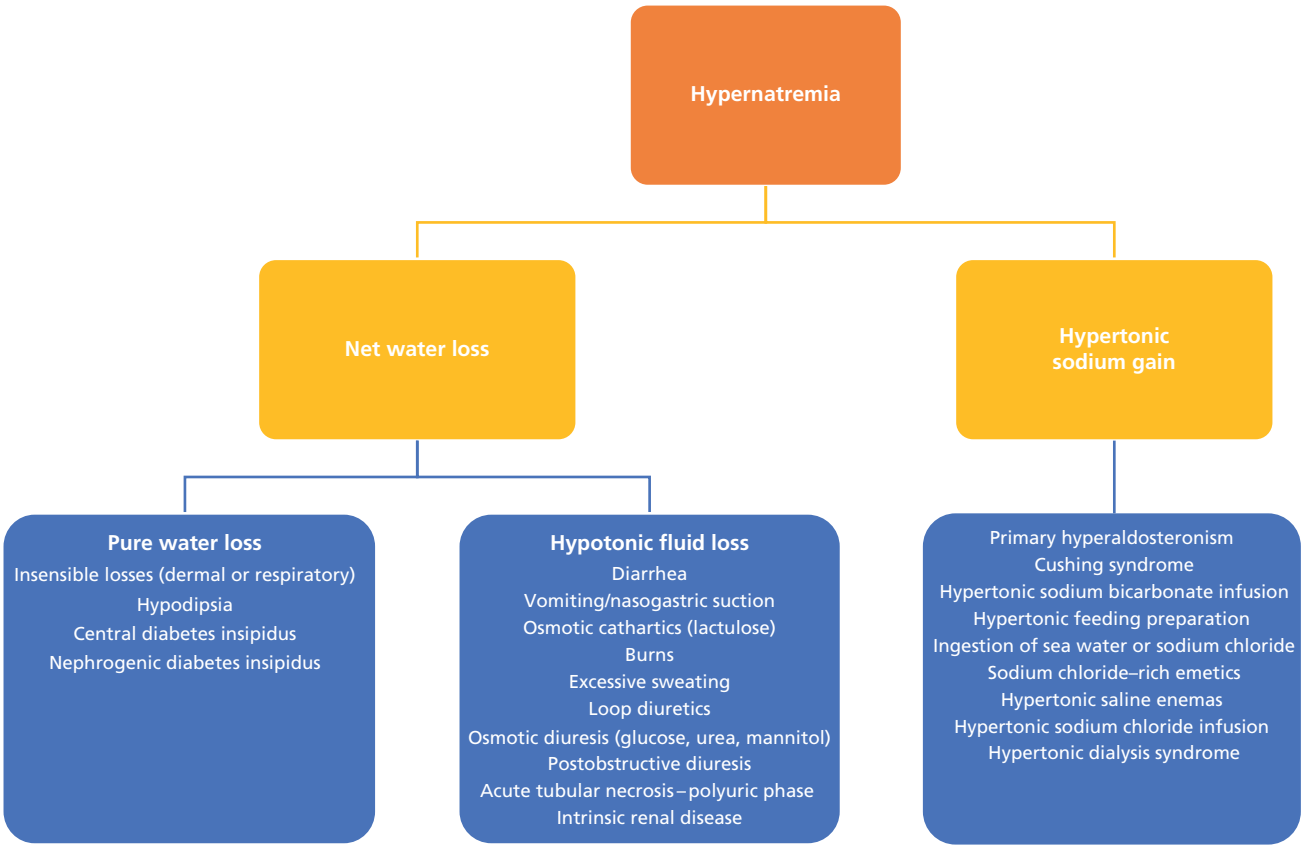

Figure 11.7 Hypernatremia.

Pure water losses that occur in the form of large volumes of dilute urine are most commonly attributable to diabetes insipidus (DI). In nephrogenic DI, there is normal ADH release and renal resistance to the water-retaining effects of ADH. In children, nephrogenic DI is more frequently inherited than acquired. Most cases of inherited nephrogenic DI occur in boys, as the disorder is an X-linked mutation of the gene for the ADH receptor. With central DI, there is a deficiency of ADH production in the hypothalamus and/or secretion from the posterior pituitary. Central DI can occur secondary to trauma, tumors, infarction, infection, or infiltrative diseases. Central DI can present in the operating room with hypernatremia, hyperosmolality, polyuria, and dehydration. The condition should be suspected in patients with the aforementioned symptoms who have suffered either an intracranial trauma or are undergoing surgery for a pituitary, hypothalamic, or optic tumor. Depending on the severity of the intraoperative central DI, these patients may require a vasopressin infusion to establish antidiuresis [144].

Clinically, cerebral hemorrhage is the most devastating consequence of hypernatremia. Severe hypernatremia, especially when associated with dehydration, induces brain shrinkage, which can cause tearing or rupture of the cerebral blood vessels and lead to cerebral hemorrhage and permanent neurological damage or death. Symptoms vary based upon both the severity of the hypernatremia and the rate at which the hypernatremia developed. Clinical manifestations in infants and children include hyperpnea, muscle weakness, restlessness, high-pitched cry, insomnia, lethargy, and even coma.

Treatment of hypernatremia and the rate of correction of the patient's sodium should depend upon the degree of associated dehydration, the severity of the symptoms, and the chronicity of the hypernatremia. In the setting of severe hypernatremic dehydration, intravascular volume should be carefully restored with isotonic IV fluids. Following re-establishment of an adequate intravascular volume, the patient's free water deficit should be calculated and the sodium level decreased by no more than 15 mmol/L per day. If hypernatremia is corrected too rapidly, cerebral edema, seizures, and death can occur [143].

Potassium

Potassium is the principal ICF cation with a normal intracellular concentration of 150 mmol/L (mEq/L) and an extracellular concentration between 3.5 and 5.5 mmol/L (mEq/L). These concentration differences are regulated by sodium–potassium adenosine triphosphate (Na^+/K^+-ATPase) pumps and lead to a transmembrane potential across the cell. Maintenance of the normal ratio of intracellular to extracellular potassium is critical to normal conductive and contractile function in the central nervous system and cardiac, skeletal, and smooth muscle cells. Total body potassium is largely dependent upon the kidneys. Potassium is freely filtered at the glomerulus and the vast majority reabsorbed before excretion in the urine. The kidneys can adjust to increased potassium ingestion by increasing excretion but cannot prevent depletion in the setting of low potassium intake. Aldosterone, the primary mineralocorticoid hormone, has an important

role in potassium homeostasis. Aldosterone primarily acts on the distal tubules of the kidneys and causes sodium and water reabsorption and potassium secretion. Disorders of potassium are typically the result of abnormal transcellular ions shifts, abnormal renal excretion, an excess or deficiency in mineralocorticoids, an exogenous or endogenous potassium load, or inadequate ingestion of potassium [145].

Hypokalemia

Hypokalemia, defined as a potassium of less than 3.5 mmol/L (mEq/L), is also commonly encountered in hospitalized children. A retrospective analysis of 512 consecutive children admitted to a single-center tertiary PICU revealed that hypokalemia affected over 40% of patients. The hypokalemia was moderate to severe (<3.0 mmol/L) in 16% of patients [146].

Hypokalemia secondary to a shift in potassium from the extracellular to intracellular fluid can occur with endogenous or exogenous β agonists, insulin, familial periodic paralysis, or barium poisoning. Alkalosis promotes hypokalemia through both potassium shifts across the cellular membrane and enhanced potassium secretion in the kidneys. Loop and thiazide diuretics, as well as acetazolamide, promote renal excretion of potassium. Children with diabetic ketoacidosis frequently have hypokalemia because of the osmotic diuresis that occurs in the setting of glycosuria. Abnormal renal losses of potassium frequently occur as a result of excess mineralocorticoids in patients with primary hyperaldosteronism, some rare forms of congenital adrenal hyperplasia and Cushing syndrome. Liddle, Barter and Gitelman syndromes also cause abnormal renal losses of potassium. Vomiting and diarrhea are the most common cause of extrarenal loses of potassium in children (Fig. 11.8).

Clinical signs and symptoms of hypokalemia are often absent or mild. With moderate to severe hypokalemia, patients may exhibit generalized weakness, lethargy, or constipation. Electrocardiographic changes include an increased P wave amplitude, prolonged PR interval, ST depression, QT prolongation, T-wave flattening or inversion, or the appearance of U waves. The risk of cardiac arrhythmias is increased in patients with heart failure or left ventricular hypertrophy. In patients with a serum potassium of less than 2.5 mmol/L, muscle necrosis can occur, and with a potassium of less than 2.0 mmol/L an ascending paralysis can occur [145].

Treatment of hypokalemia should depend upon the severity of the accompanying signs and symptoms. Whenever possible, hypokalemia should be corrected with oral supplementation. In the setting of severe symptoms (e.g. ECG changes, muscle weakness, or paralysis), IVs potassium should be administered. The rate of IV administration should not exceed 0.5–1 mEq/kg/h. IV potassium can cause pain and phlebitis when given via a peripheral vein. Potassium concentrations of 40 mEq/L or greater should be administered through central venous access.

Hyperkalemia

Hyperkalemia, defined as a potassium of greater than 5.5 mmol/L, occurs less frequently than hypokalemia in hospitalized children. The aforementioned retrospective analysis of 512 consecutive children admitted to a single-center tertiary PICU revealed that hyperkalemia affected 29% of admissions. Twelve percent of admitted PICU patients had severe hyperkalemia (K^+ >6.0 mmol/L) [146].

In children, hyperkalemia is most frequently a spurious or inaccurate measurement. Capillary sampling, blood aspiration through a small-bore needle or catheter, and a tight tourniquet can lead to hemolysis of red blood cells and release of intracellular potassium. If pseudohyperkalemia is suspected, a repeat free-flowing sample should be obtained.

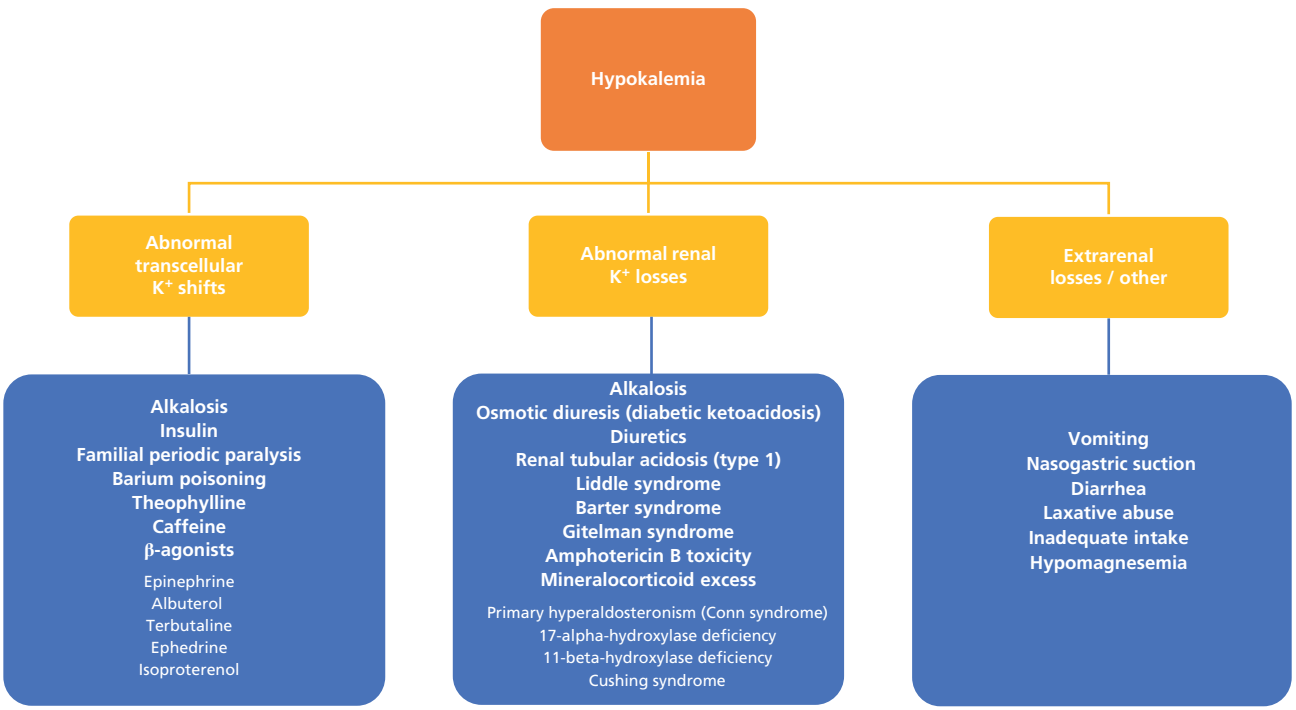

Figure 11.8 Hypokalemia.

Many clinical scenarios lead to hyperkalemia via a shift in potassium from the ICF to the ECF. Metabolic acidosis, insulin deficiency, hypertonicity, digitalis poisoning, β-blockers, succinylcholine, tumor lysis syndrome, hyperkalemic periodic paralysis, strenuous exercise, and tissue injuries from burns, trauma, or rhabdomyolysis can all cause hyperkalemia from a transcellular shift in potassium. Hyperkalemia may also occur as a consequence of acute and/or chronic renal failure. When the GFR falls below 15–30 mL/min/1.73 m^2, urinary potassium excretion is significantly impaired. Mineralocorticoid (aldosterone) deficiencies, such as Addison disease, 21-hydroxylase deficiency, or type IV renal tubular acidosis, may also cause significant hyperkalemia. A reduced effective arterial blood volume frequently leads to hyperkalemia in children via renal mechanisms. The reduced sodium delivery to the collecting ducts that occurs during hypovolemia leads to a functional impairment of urinary potassium excretion. Several medications, including spironolactone, ACE inhibitors, non-steroidal anti-inflammatory drugs, and cyclosporins, affect aldosterone and are associated with hyperkalemia. Hyperkalemia as a result of excessive intake is infrequent, especially in the setting of normal kidney function. Occasionally, it may occur following a massive blood transfusion and/or the transfusion of old banked blood (Fig. 11.9) [147].

Hyperkalemia is frequently asymptomatic in children and can go undetected until signs and symptoms of the underlying disease lead to an electrolyte evaluation. Children with potassium concentrations greater than 8 mmol/L may develop ascending muscle weakness or paralysis similar to that found in patients with Guillain–Barré syndrome. Hyperkalemia is associated with significant disturbances in cardiac conduction and, depending on the severity and the rate of development, can be associated with lethal arrhythmias. Characteristic changes seen on the ECG with increasing levels of potassium include tall, peaked T waves followed by prolongation of the PR interval, decreased or disappearing P wave, widening QRS, and amplified R wave. Finally, prior to ventricular fibrillation or asystole, there is progressive widening of the QRS complex eventually merging with the T wave to form the sine wave pattern (Fig. 11.10).

Children with muscle weakness or paralysis, ECG changes, and/or a potassium concentration >6.0–6.5 mmol/L require emergent treatment (Box 11.3). The first step in the management of hyperkalemia is to identify and remove any oral and/or parenteral sources of potassium. The next step is to stabilize the myocardium by antagonizing the effect of the extracellular potassium with either intravenous calcium chloride or calcium gluconate. Calcium exerts its effects rapidly. However, calcium's benefits may last only 30–60 min and repeat dosing may be required. Insulin in combination with glucose is indicated for symptomatic hyperkalemia. Insulin drives the extracellular potassium intracellularly while glucose prevents hypoglycemia and enhances the endogenous production of insulin. Inhaled β-adrenergic agonists and IV sodium bicarbonate should also be considered as they too promote redistribution of potassium intracellularly. Definitive therapy should be aimed at identifying the etiology of the hyperkalemia and permanently removing excess potassium from the body. Loop diuretics and enteral cation exchange resins such as sodium polystyrene sulfonate both facilitate potassium excretion through the kidneys and gut, respectively. Renal replacement therapy is indicated when conservative therapy fails.

Calcium

Calcium, a divalent cation, is the fifth most abundant element in the body and primarily stored in bone as hydroxyapatite crystal. In fact, only 1% of total body calcium is found in the

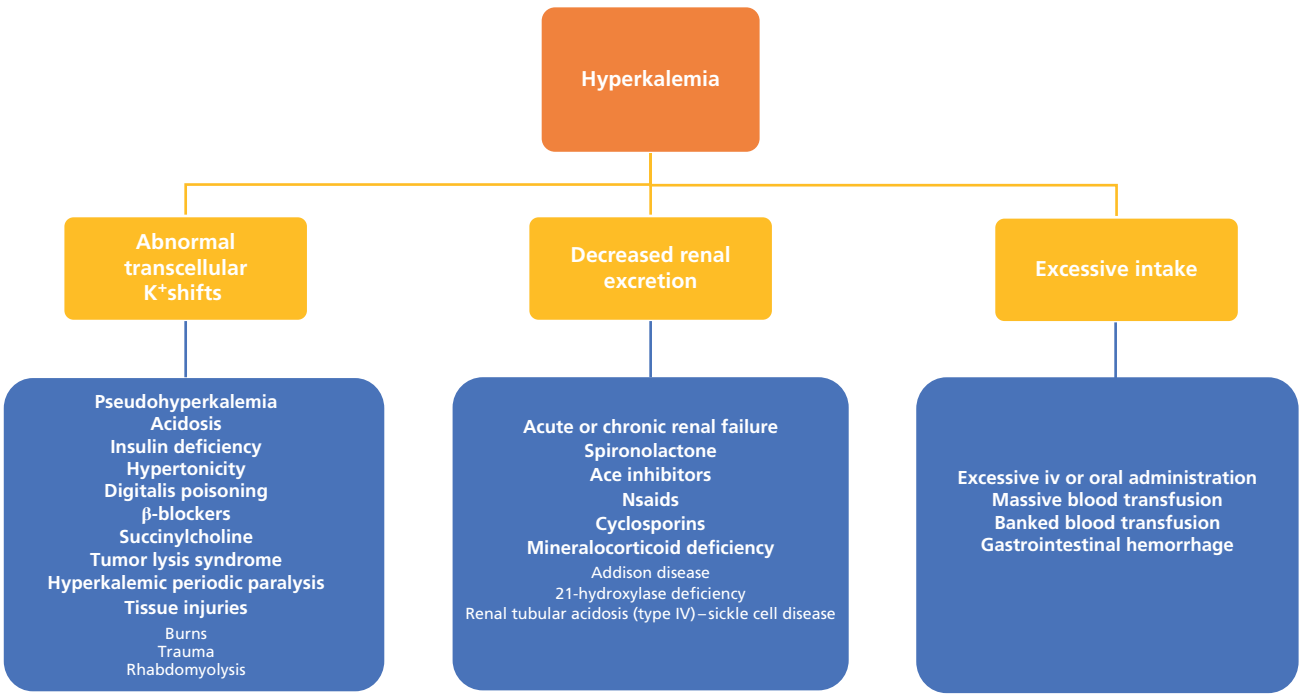

Figure 11.9 Hyperkalemia. ACE, angiotensin-converting enzyme; IV, intravenous; NSAIDs, non-steroidal anti-inflammatory drugs.

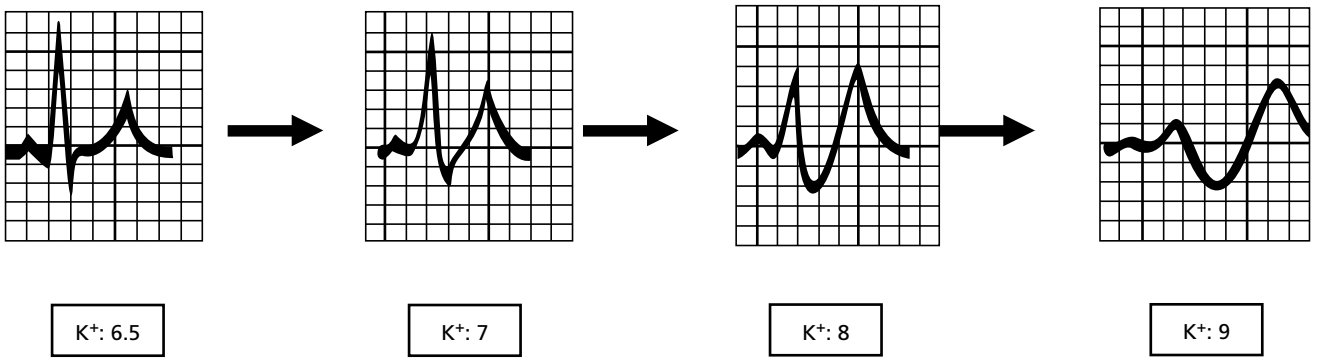

Figure 11.10 Changes in electrocardiogram with increasing hyperkalemia. *Source*: Reproduced from Masilamani and van der Voort [147] with permission of BMJ.

Box 11.3: Treatment of symptomatic hyperkalemia

1. Remove sources of oral or parenteral potassium intake
2. Administer calcium chloride (10–20 mg/kg IV) or calcium gluconate 10% (0.5 mL/kg IV) over 5–10 min
3. Administer regular insulin (0.1 unit/kg IV) and dextrose (0.5 g/kg IV) over 15–30 min
4. Consider administering sodium bicarbonate (1 mEq/kg IV) and/or inhaled albuterol
5. Consider administering furosemide (1 mg/kg IV) in patients with adequate intravascular volume and renal function
6. Consider administering sodium polystyrene sulfonate (oral or rectal)*
7. Renal replacement therapy when conservative therapy fails

*Contraindicated in neonates, postoperative patients, and patients with ileus or bowel obstruction.

ECF. Approximately 50% of extracellular calcium is circulated in the free ionized form while 40% is bound to protein (primarily albumin) and 10% complexed with anions. Only the free ionized form of calcium is biologically active. Calcium is critical to cardiac, vasomotor, and neurological function. Calcium concentrations are reported in various units including mg/dL, mmol/L, or mEq/L. Normocalcemia is 8.5–10.5 mg/dL (2.1–2.6 mmol/L or 4.2–5.2 mEq/L) for total calcium, and 4.0–5.0 mg/dL (1.0 –1.3 mmol/L or 2.0–2.6 mEq/L) for ionized calcium.

Parathyroid hormone, the primary regulator of calcium homeostasis, induces calcium release from bone, calcium reabsorption in the kidneys, and conversion of vitamin D to its most active form, 1,25-dihydroxyvitamin D (calcitriol). In turn, 1,25-dihydroxyvitamin D stimulates increased intestinal absorption of calcium. Calcitonin, a hormone released by the thyroid gland in response to rising levels of calcium, decreases calcium levels by decreasing bone resorption. However, an absence or excess of calcitonin does not result in either hypercalcemia or hypocalcemia, respectively [148].

Hypocalcemia

Hypocalcemia, defined as an ionized calcium of less than 4 mg/dL (1.0 mmol/L), is a relatively common electrolyte abnormality in hospitalized children. A prospective analysis of 145 pediatric patients admitted to a single-center PICU revealed 49% had a low total calcium and 17.9% a low ionized calcium [149].

Hypocalcemia observed in the ICU setting is often related to an acute illness or stress such as sepsis, cardiac surgery, rhabdomyolysis, pancreatitis, hepatitis, or tumor lysis. Insufficient parathyroid hormone (hypoparathyroidism) or insufficient responsiveness to parathyroid hormone (pseudohypoparathyroidism) both also lead to hypocalcemia. Hypocalcemia is common in infants with DiGeorge syndrome secondary to parathyroid aplasia or hypoplasia. Magnesium is required for both parathyroid hormone release and responsiveness. Consequently, hypomagnesemia may lead to low ionized calcium levels via indirect mechanisms. Deficiencies in vitamin D or impaired activation of vitamin D can both cause hypocalcemia. Hypocalcemia is common in neonates secondary to stress, immaturity of the parathyroid glands, and/or the administration of phosphorus-rich formula or cow's milk. Renal failure leads to hypocalcemia via numerous mechanisms including hyperphosphatemia. Elevated phosphorus levels often cause calcium phosphate precipitation and subsequent hypocalcemia. Respiratory and metabolic alkalosis promote the binding of calcium to albumin, thereby decreasing ionized calcium levels. Additionally, citrate, used to preserve blood products, chelates calcium and can rapidly decrease the free fraction of serum calcium.

The cardiovascular manifestations of hypocalcemia include hypotension, impaired cardiac contractility, and a prolonged QTc interval. A low ionized calcium is associated with neuromuscular excitability, which may present as seizures, tetany, muscle cramps, laryngeal stridor, and/or apnea in the newborn.

The most important aspect in the treatment of hypocalcemia is determination of the etiology of the electrolyte abnormality. In the critically ill child with symptomatic hypocalcemia, immediate treatment is indicated with IV calcium chloride or calcium gluconate, preferably through a large vein or central line. If hypomagnesemia is also present, IV magnesium sulfate should be administered. Long-term therapy, depending on the etiology of the hypocalcemia, may include oral calcium salts, calcitriol, and/or magnesium sulfa [148].

Hypercalcemia

Hypercalcemia, defined as an ionized calcium of greater than 5.0 mg/dL (1.3 mmol/L), is an uncommon electrolyte abnormality in hospitalized children. In pediatric patients, iatrogenic administration of calcium is a frequent cause of hypercalcemia. The other causes of hypercalcemia in children vary by age and include hyperparathyroidism, phosphate depletion, maternal hypocalcemia, malignancy,

hypervitaminosis D, immobilization, subcutaneous fat necrosis, and genetic or inborn metabolic disorders. Clinical features may be non-specific or in severe cases may include weakness, hypotonia, lethargy and stupor, and possibly seizures. Hypertension, bradycardia, and/or a shortened QT interval may also be present. Hypercalcemia can induce polyuria and dehydration. Damage to the kidneys from nephrocalcinosis may occur as well. In the symptomatic patient, the initial approach to treatment is to increase urinary excretion of calcium with loop diuretics while correcting the dehydration that commonly occurs with significant hypercalcemia. Beyond emergent management, long-term therapy, depending upon the etiology, can include parathyroidectomy, calcitonin, or bisphosphonates [150].

Magnesium

Magnesium, the second most abundant intracellular cation to potassium, is critical to cellular enzymatic activity. Specifically, it is a vital cofactor of any reaction powered by adenosine triphosphate. Magnesium also acts as a calcium channel antagonist and subsequently plays a key role in the modulation of intracellular calcium channel activities. Because less than 1% of total body magnesium is found in the extracellular space, serum magnesium levels may not accurately reflect total body concentrations of magnesium. Consequently, clinical symptoms of magnesium abnormalities often do not correlate with serum magnesium levels. The normal serum concentration of magnesium ranges between 1.8 and 2.3 mg/dL (0.75–0.95 mmol/L) [151,152].

Hypermagnesemia

Hypermagnesemia is rare in pediatric patients. The most common cause is iatrogenic administration of excessive amounts of magnesium, especially in the setting of renal failure. Symptoms include hyporeflexia, respiratory depression, somnolence, ECG changes, and even cardiac arrest. IV calcium reverses the neuromuscular and cardiotoxic effects of hypermagnesemia and should be administered in the symptomatic patient. Further treatment should be directed at identifying and removing exogenous sources of magnesium. In patients with renal failure, dialysis may be required.

Hypomagnesemia

Hypomagnesemia occurs with some frequency in PICU patients. In one retrospective analysis, the incidence of hypomagnesemia in critically ill children was 44% [153]. The main cause of hypomagnesemia is inadequate intake or supplementation. Other causes include gastrointestinal losses and renal losses. Many drugs promote renal wasting of magnesium including aminoglycosides, cisplatin, amphotericin B, loop diuretics, cyclosporine, and tacrolimus. Low magnesium levels frequently occur in patients with sepsis and burn injuries. Concurrent hypocalcemia and/or hypokalemia is also common.

Neuromuscular irritability including tetany, tremors, and/or seizures is often present with significant hypomagnesemia. Personality changes may be evident. Arrhythmias can occur, and may include premature ventricular beats, ventricular tachycardia, torsades de pointes, and ventricular fibrillation. Enteral or intravenous replacement of magnesium is indicated in symptomatic patients and/or in patients in whom losses of magnesium will be ongoing. IV magnesium should be given slowly as hypotension can occur with rapid infusion [151].

Phosphorus

Phosphorus, an intracellular ion primarily stored in bone, is essential to cell structure, cellular metabolism through the generation of ATP, regulation of subcellular processes such as cell signaling through protein phosphorylation of key enzymes, maintenance of acid–base homeostasis through urinary acid buffering, and bone mineralization. Phosphate homeostasis is maintained by regulation of intestinal uptake of dietary phosphate, renal phosphate reabsorption and excretion, and the exchange of phosphate between extracellular and bone storage pools. Normal serum concentrations of phosphorus vary by age, with the highest concentrations noted in infants. Higher concentrations observed in younger infants and children are likely related to more rapid rates of skeletal growth in the pediatric population [154].

Hyperphosphatemia

Hyperphosphatemia, while relatively uncommon in children, is most frequently a result of either renal failure or tumor lysis syndrome. The major clinical consequence of hyperphosphatemia is the associated hypocalcemia and abnormal deposition of calcium phosphate salts in soft tissues including the kidney. In severe cases, dialysis may be required.

Hypophosphatemia

Hypophosphatemia is relatively common in critically ill children with a reported rate as high as 61% during the first 10 days of a PICU stay [155]. The disorder frequently goes undiagnosed, as symptoms can be largely non-specific. The main clinical manifestations are metabolic acidosis, decreased levels of 2,3-DPG and ATP, hemolysis, leukocyte and platelet dysfunction, acute respiratory failure, arrhythmias, hypotension, seizures, and weakness. The most common causes and/or risk factors for the development of hypophosphatemia are malnutrition, refeeding, the use of diuretics, steroids, catecholamines and antacids, excessive parenteral glucose administration, diabetic ketoacidosis, sepsis, and respiratory alkalosis. Beyond identifying and addressing the cause of the hypophosphatemia, treatment is replacement with either enteral or IV phosphorus preparations. IV therapy is typically reserved for severe cases [155,156].

KEY POINTS: DISORDERS OF FLUIDS AND ELECTROLYTES

- The first step in caring for a dehydrated child is to assess the degree and cause of dehydration. The degree of dehydration dictates the urgency of the situation and the volume of fluid needed for rehydration
- Hyponatremia is common and is often caused by administration of hypotonic IV fluids. Children should generally receive isotonic maintenance IV fluids
- Hyperkalemia usually results from acute renal injury, acidosis, massive tissue trauma, or iatrogenic causes. Hypokalemia usually results from diarrhea or persistent vomiting associated with gastroenteritis

- Hypocalcemia is a relatively common electrolyte abnormality often related to an acute illness or stress such as sepsis. A low ionized calcium is associated with neuromuscular excitability, which may present as seizures, tetany, muscle cramps, laryngeal stridor, and/or apnea in the newborn
- Hypophosphatemia is relatively common in critically ill children. The main clinical manifestations are metabolic acidosis, decreased levels of 2,3-DPG and ATP, hemolysis, leukocyte and platelet dysfunction, acute respiratory failure, arrhythmias, hypotension, seizures, and weakness

Conclusion

Intravenous fluid therapy is a core component of the perioperative practice of pediatric anesthesia and an area in which pediatric anesthesiologists have a significant role in advising perioperative clinicians. It is important to recognize that IV fluids are medications that must be initiated, dosed, monitored, and discontinued just like any other pharmaceutical agent. The goal of IV fluid therapy is to preserve the extracellular volume while maintaining a normal electrolyte balance. Acutely ill patients frequently have conditions that impair normal water and electrolyte homeostasis, and choosing the appropriate volume and composition of fluid therapy requires great care and a thorough understanding of the physiology of fluid electrolyte regulation.

CASE STUDY

A 9-year-old previously healthy male, who was struck by a motor vehicle and thrown approximately 50 feet from the site of impact, presents to the Emergency Department with a complaint of abdominal pain and a urinalysis revealing frank blood. Glasgow Coma Scale score is 13 and a non-contrast head CT scan is negative for intracranial pathology. Further imaging reveals a left pubis fracture and underlying pelvic hematoma, left midfoot subluxation/dislocation, a left clavicle fracture, and a pulmonary contusion. On ICU day #1 he developed mental status changes requiring intubation and had an obvious peri-intubation aspiration event. His vital signs and ventilator settings remained stable and he was subsequently taken to the OR for repair of his left foot fracture and dislocation. His pelvic fracture is managed non-operatively through immobility in a pelvic brace. He is uneventfully extubated 4 days later after his respiratory status stabilized without any complications and is transferred to the general pediatric surgical floor. Two days later, he is again noted to have altered mental status and is taken for an urgent CT scan. He proceeds to have a full tonic-clonic seizure in the CT scanner and is readmitted to the PICU. On work-up, he is found be significantly hyponatremic with a serum sodium of 116 meq/dL. He is treated with 3% hypertonic saline and his sodium is slowly corrected over 2 days with hypertonic saline and fluid restriction. His hyponatremia was likely multifactorial, including iatrogenic administration of hypotonic intravenous fluids and SIADH secondary to his pulmonary contusion, aspiration, and pain from his multiple injuries.

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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61 Furman EB, Roman DG, Lemmer LA, et al. Specific therapy in water, electrolyte and blood-volume replacement during pediatric surgery. Anesthesiology 1975; 42(2): 187–93. This paper details a fluid replacement protocol based on preoperative deficits dictated by the Holliday and Segar method. The authors suggested replacing half of the fluid deficit volume during the first hour of surgery, followed by the other half over the next 2 h of surgery.

64 Holliday MA, Friedman AL, Segar WE, et al. Acute hospital-induced hyponatremia in children: a physiologic approach. J Pediatr 2004; 145(5): 584–7. Holliday and Segar update their classic 1957 article addressing the problems associated with applying the original formula (4 –2 – rule) to perioperative fluid management. The authors cite risks of using isotonic saline as maintenance therapy, and define a physiologically based fluid therapy protocol that avoids hyponatremia.

67 Shires T, Williams J, Brown F. Acute change in extracellular fluids associated with major surgical procedures. Ann Surg 1961; 154: 803–10. This paper details the phenomenon of extracellular fluid redistribution or sequestration into areas that no longer communicated with the functional extracellular space during surgery. The concept of third spacing of isotonic fluids is also described.

75 Anderson JM, Milner RD, Strich SJ. Effects of neonatal hypoglycaemia on the nervous system: a pathological study. J Neurol Neurosurg Psychiatry; 1967; 30(4): 295–310. This paper first described six cases of neonatal hypoglycemia and the serious clinical and pathological sequelae associated with prolonged low blood glucose.

121 Burrows FA, Shutack JG, Crone RK. Inappropriate secretion of antidiuretic hormone in a postsurgical pediatric population. Crit Care Med 1983;11(7):527–31. This study of children undergoing scoliosis surgery first demonstrated that hyponatremia developed frequently in the postoperative period and asserted that the phenomenon was secondary to SIADH in the setting of administration of hypotonic intravenous fluids.

135 Neville KA, Sandeman DJ, Rubinstein A, et al. Prevention of hyponatremia during maintenance intravenous fluid administration: a prospective randomized study of fluid type versus fluid rate. J Pediatr 2010; 156(2): 313–19. This prospective study documents that the risk for hyponatremia is associated with the type of fluid (hypotonic versus isotonic) rather than the rate of administration in the surgical pediatric patient.

CHAPTER 12
Coagulation, Bleeding, and Blood Transfusion

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Introduction

The hematological system is unique among all of the systems in the body. It is composed of multiple components, each of which engages in a very specific and unique function that is critical for life. This chapter will focus on one of those functions: coagulation. The coagulation process, maturational factors affecting coagulation in neonates and infants, tests of and defects in the coagulation system, and principles of transfusion therapy and blood conservation will be discussed.

The coagulation process

The coagulation system is a complex interplay of cellular elements and plasma proteins that functions to stop bleeding from an injured blood vessel and then to re-establish patency of that vessel. The process that stops bleeding is understood to occur in two phases. Primary hemostasis arrests bleeding by inducing vasoconstriction in the injured vessel and by causing the formation of a platelet plug. Secondary hemostasis then involves the circulating plasma coagulation factors and results in the formation of a fibrin clot at the site of blood vessel damage. While it is easy to think of these two phases as separate, distinct, and sequential, they are in fact highly coordinated, interdependent, and concurrent. In the end, the fibrinolytic system removes clot to re-establish blood flow and to allow wound healing [1].

Primary hemostasis involves the interaction of damaged blood vessel walls and platelets to form a platelet plug. Damage to blood vessel walls exposes subendothelial collagen. Platelets immediately *adhere* via their exposed glycoprotein Ib (GpIb) surface receptors to von Willebrand factor (vWF) that has bound to this collagen. Platelet *activation* then occurs with release of platelet agonists and coagulation factors from platelet storage granules and with changes in the shape and surface function of the platelets. Vasoconstriction of injured vessels results, and platelets *aggregate* as fibrinogen binds to exposed glycoprotein IIb/IIIa (GpIIb/IIIa) receptors on adjacent platelets (Fig. 12.1). With a platelet plug now formed, the phospholipid membrane of activated platelets provides the surface on which the process of secondary hemostasis occurs [2].

Secondary hemostasis involves the interaction of plasma coagulation factors to form a fibrin clot. Roman numerals are used to designate most of these factors in order to provide an international code for clear communication [3] (Table 12.1). The clotting factors exist in inactive precursor forms before being converted to active enzymes upon initiation of secondary hemostasis [4].

Initial explanations of secondary hemostasis involved "intrinsic" and "extrinsic" limbs of a cascade that converged on a "common" pathway leading to thrombin generation and subsequent fibrin formation [4,5] (Fig. 12.2). However, clinical and laboratory observations led to the recognition that the intrinsic and extrinsic coagulation pathways do not operate independently *in vivo*. Additionally, even the early descriptions of coagulation recognized the significant role of phospholipid acting as a surface catalyst for coagulation and postulated that the phospholipid might be derived from platelets during the clotting process [5]. Subsequently, a cell-based model has been proposed to explain secondary hemostasis. This model emphasizes the importance of cell surfaces as the platform upon which the events of secondary hemostasis occur [6].

The cell-based model describes three overlapping phases of secondary coagulation: *initiation* of coagulation on tissue factor (TF)-bearing cells in and around injured blood vessels, *amplification* of coagulation by thrombin generated on these

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

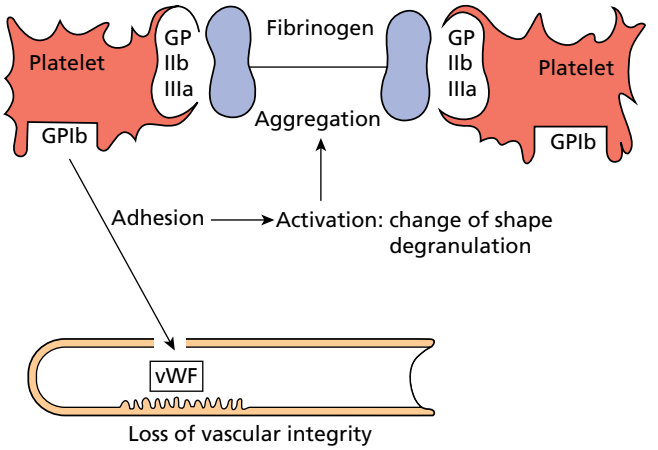


Figure 12.1 Primary hemostasis: platelet adhesion, activation, and aggregation. Gp, glycoprotein; vWF, von Willebrand factor. *Source:* Reproduced from Hardy and Desroches [239] with permission of Springer Nature.

TF-bearing cells, and *propagation* of thrombin generation on platelet surfaces. *Initiation* of coagulation occurs when TF complexes with activated factor VII (FVIIa) from plasma to catalyze the activation of FX and FIX. Involvement of FVa from platelet degranulation allows the generation of small amounts of thrombin (Fig. 12.3A) which then stimulates the *amplification* phase. This initiation phase of the cell-based coagulation model has been compared to the classically described extrinsic coagulation pathway (Fig. 12.4A).

In the *amplification* phase, the initially produced thrombin activates additional plasma coagulation factors as well as nearby platelets. The activated platelets provide the phospholipid surfaces on which large amounts of thrombin are subsequently generated in the *propagation* phase (Fig. 12.3B).

Propagation of thrombin generation occurs on the surfaces of activated platelets. FVIIIa and FIXa form a "tenase" complex which activates FX. These actions have been compared to those outlined in descriptions of the intrinsic coagulation pathway (Fig. 12.4B). FXa and FVa then form a "prothrombinase" complex which finally catalyzes the large-scale conversion of prothrombin into thrombin (Fig. 12.3C), analogous to the common coagulation pathway where the extrinsic and intrinsic pathways converge (Fig. 12.2). Unlike the small quantity of thrombin produced in the initiation phase, the quantity of this platelet-produced thrombin is sufficient to cleave fibrinogen to fibrin and to cross-link the fibrin monomers with FXIIIa to form a stable clot [6,7].

After clotting has occurred and bleeding has been stopped, activation of the fibrinolytic system allows patency of the involved blood vessel eventually to be restored so that wound healing can proceed. Both tissue plasminogen activator (tPA) and its substrate, plasminogen, bind to fibrin surfaces. Fibrin-bound tPA then converts this localized plasminogen to its active form, plasmin, which dissolves the fibrin clot to eventually re-establish blood flow through vessels [6,7].

Table 12.1 Coagulation factor numbers and synonyms

Roman numeral	Synonyms
I	Fibrinogen
II	Prothrombin
III	Thromboplastin
	Tissue factor
IV	Calcium
V	Proaccelerin
	Labile factor
VII	Proconvertin
	Stable factor
VIII	Antihemophilic factor (AHF)
	Antihemophilic globulin (AHG)
	Antihemophilic factor A
	Factor VIII:C
IX	Plasma thromboplastin component
	Antihemophilic factor B
	Christmas factor
X	Stuart factor
	Prower factor
	Stuart–Prower factor
XI	Plasma thromboplastin antecedent
	Antihemophilic factor C
XII	Hageman factor
	Contact factor
	Surface factor
	Glass factor
XIII	Fibrin stabilizing factor
	Laki–Lorand factor

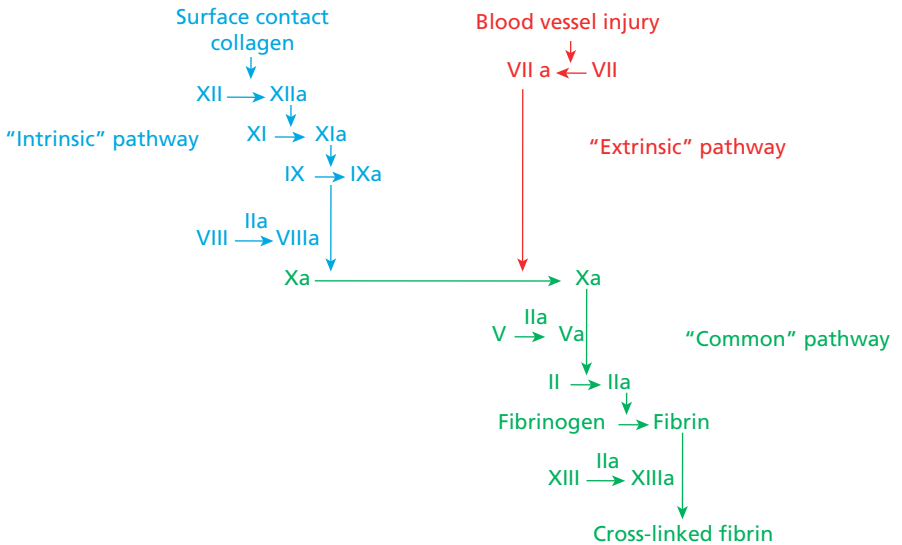


Figure 12.2 Secondary hemostasis: the coagulation cascade.

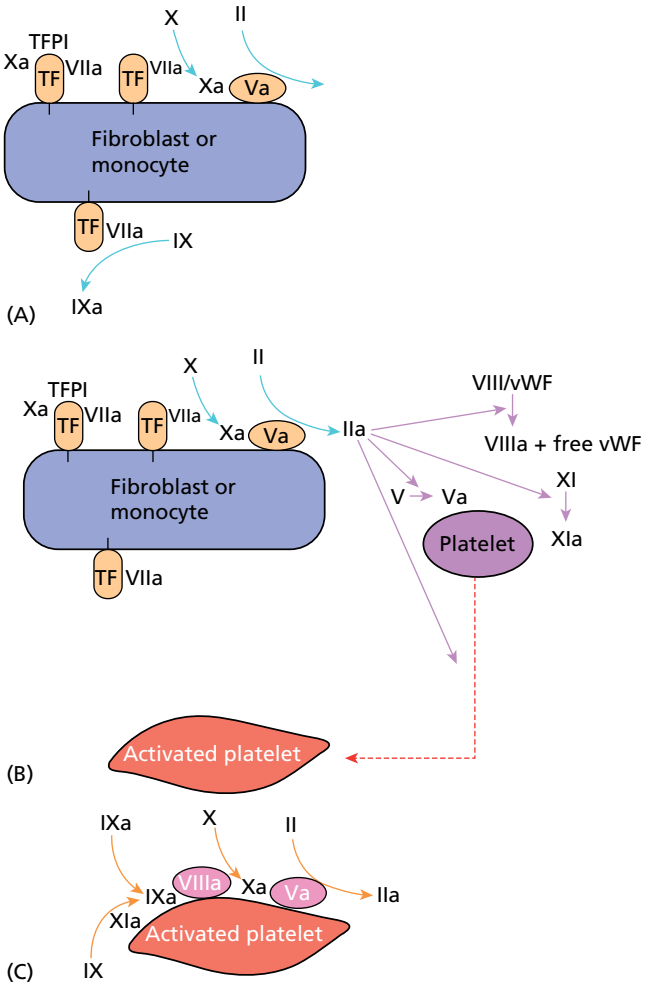


Figure 12.3 Secondary hemostasis: the cell-based model. (A) Initiation of the coagulation pathway. (B) The propagation phase. (C) FXa and FVa form the prothrombinase complex. TF, tissue factor; TFPI, tissue factor pathway inhibitor; vWF, von Willebrand factor. *Source:* Reproduced from Hoffman and Monroe [6] with permission of Elsevier.

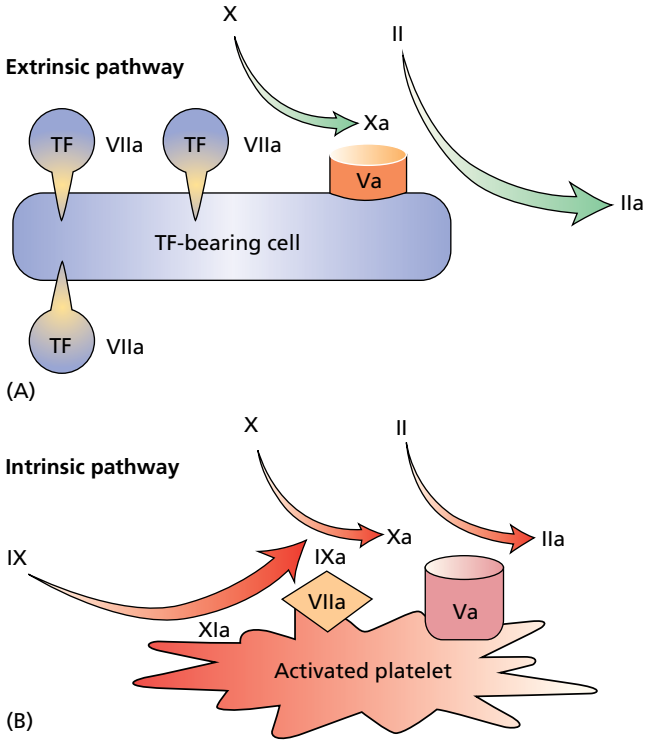


Figure 12.4 Comparison of the coagulation cascade and the cell-based model of secondary hemostasis. (A) Extrinsic pathway. (B) Intrinsic pathway. TF, tissue factor. *Source:* Reproduced from Hoffman and Monroe [6] with permission of Elsevier.

The hematological system constantly balances the ability to keep blood flowing through undamaged vessels with the ability to stop bleeding from damaged blood vessels. Under normal circumstances, the luminal surface of blood vessels is non-thrombogenic because of an intact endothelial surface and because circulating activated protein C, with its cofactor protein S, inactivates any circulating FVa and FVIIIa to attenuate thrombin generation [8]. Antithrombin (AT) neutralizes circulating FIXa, FXa, FXIa, and thrombin to prevent fibrin formation [9]. Circulating nitric oxide and prostacyclin inhibit platelet activity and release tPA to promote fibrinolysis [8]. Thus, clot formation is prevented in undamaged blood vessels while vascular damage disrupts these homeostatic mechanisms to create an environment conducive to clot formation [8]. Furthermore, when vascular damage does occur, the coagulation process is restricted only to affected vessels because the coagulation process-inducing TF is expressed only on damaged vessels and also because a host of circulating anticoagulants keep the actions of circulating activated coagulation factors in check [1,6–8]. In the end, under normal conditions, coagulation and fibrinolysis occur only where they are needed and are prevented from becoming pathological generalized problems by procoagulant and anticoagulant factors that delicately balance the system.

KEY POINTS: THE COAGULATION PROCESS

- Primary hemostasis involves the interaction of damaged blood vessel walls and platelets to form a platelet plug
- Secondary hemostasis involves the interaction of plasma coagulation factors on activated platelet surfaces to form a fibrin clot
- Fibrinolysis later reestablishes patency of involved blood vessels

Maturation of the coagulation system

Coagulation proteins, platelets, and fibrinolytic proteins do not cross the placental barrier but their synthesis by the fetus begins at approximately 11 weeks of gestational age. During the remainder of fetal development, maturation of the coagulation and fibrinolytic systems parallel each other so that a delicate hemostatic balance is maintained [10,11]. However, despite this ongoing maturation, both quantitative and qualitative deficiencies exist in these systems at birth.

Plasma levels of coagulation factors and coagulation inhibitors have been documented in detail in both healthy premature infants (30–36 weeks' gestational age) and full-term infants (>37 weeks' gestational age) from birth through 6 months of age. Plasma levels of the vitamin K-dependent coagulation factors (II, VII, IX, and X) and the contact

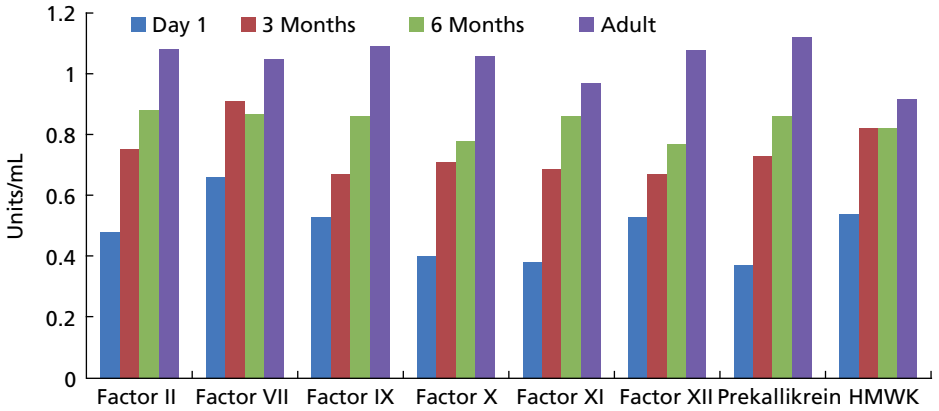


Figure 12.5 Coagulation factor levels in full-term infants and with age. HMWK, high-molecular-weight kininogen. *Source:* Adapted from Andrew et al [13].

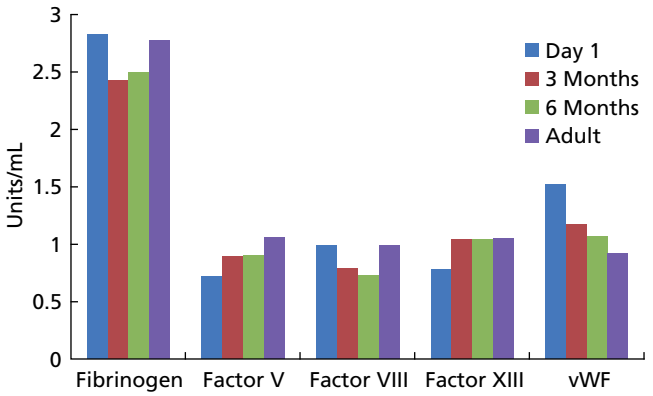


Figure 12.6 Coagulation factor levels in full-term infants. vWF, von Willebrand factor. *Source:* Adapted from Andrew et al [13].

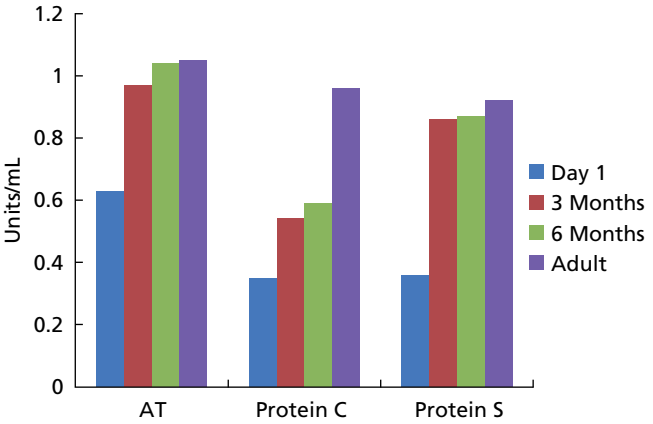


Figure 12.7 Coagulation inhibitor levels in full-term infants. AT, antithrombin. *Source:* Adapted from Andrew et al [13].

factors (XII, XI, high-molecular-weight kininogen (HMWK), and prekallikrein (PK)) are all significantly lower than adult values at 1 day of age with most rising to within adult ranges by 6 months (Fig. 12.5). This is also the situation for several coagulation inhibitors (AT, PC, and PS) and fibrinolytic factors (plasminogen and tPA) (Fig. 12.6). In contrast, levels of fibrinogen, FV, FVIII, FXIII, vWF, and platelet counts are all remarkably similar to adult values on the first day of life, as is plasminogen activator inhibitor [12–15] (Fig. 12.7).

In addition to these quantitative issues in development of the hemostatic system, qualitative issues exist. The concept of a "fetal fibrinogen" has been proposed [16,17] and evidence of impaired fibrinogen function in infants has been postulated based on thromboelastography data [18], on differences between measured activity and antigen levels of fibrinogen [19], and on differences in the microscopic structures of neonatal and adult fibrinogen [20]. Comparison of the biological activity and the plasma levels of FXII, PK, protein C, and plasminogen has suggested that these factors may also exhibit qualitative deficiencies [10,21–23] but the data are not absolute [15,19]. Finally, impairment of platelet aggregation has been documented in neonates in the first 48 h of life [24].

Coagulation tests have also been studied in infants. Activated partial thromboplastin time (aPTT) is prolonged in both term and preterm infants, maturing to adult ranges within 3–6 months. Values of prothrombin time (PT) and thrombin time (TT) are similarly prolonged at birth but reach adult ranges within several days of age [11–13,25].

Interpretation of these maturational issues of the hemostatic system is complex. There is no evidence that neonates, infants, or children have an increased risk of bleeding either spontaneously, after trauma, or during surgery compared to adults. In fact, thromboelastograms have shown intact coagulation systems even in neonates [26]. However, the alterations in coagulation factors and coagulation inhibitors in young infants result in a reduced ability to generate thrombin as well as a significant delay in thrombin generation once the coagulation system is triggered. On the other hand, deficiencies in the fibrinolytic system result in decreased plasmin generation and impairment of fibrinolysis [23,27]. Fortunately, maturation of coagulation and fibrinolysis proceeds in tandem and in accordance with gestational age, and the net effect apparently strikes the necessary balance to maintain a competent hemostatic picture. Nevertheless, while quantitative and qualitative immaturities resolve during the first year of life, normal values for plasma levels of most coagulation factors, coagulation inhibitors, and fibrinolytic proteins in young infants

must be recognized to be different from those values considered normal for adults.

KEY POINTS: MATURATION OF THE COAGULATION SYSTEM

- Quantitative deficiencies in many coagulation factor and coagulation inhibitor levels exist in early infancy
- Qualitative abnormalities may also exist in several pre- and anticoagulants
- Despite these immaturities, hemostasis seems balanced, though tenuous, in young infants

Evaluation of the coagulation system

Anesthesiologists and surgeons usually employ laboratory tests of the coagulation system to screen patients preoperatively for inherited or acquired hemorrhagic disorders or to diagnose the cause(s) and monitor the treatment of intraoperative or postoperative bleeding [28]. None of the available tests is perfect because each either reports a quantitative count with no consideration of qualitative function or is performed *in vitro* in environments that are not equivalent to *in vivo* processes. This section will describe available laboratory tests and their indications and limitations.

Evaluation of primary hemostasis

Evaluation of primary hemostasis includes quantitative and functional analysis of platelets and vWF. Platelet counts are measured by automated systems on whole blood samples. The range of normal for platelet counts is 150,000–400,000/μL. Platelet counts, however, do not assess the functional capacity of the available platelets. Bleeding time (BT) was the historical mainstay of platelet function assessment. However, because it requires making a skin cut and is very operator dependent, it has been mostly abandoned in favor of the platelet function analyzer (PFA-100, Siemens Diagnostics, Marburg, Germany). The platelet function analyzer assesses platelet adhesion to a membrane upon which either adenosine diphosphate (ADP) or epinephrine then stimulates platelet aggregation. The closure time (CT), i.e. the length of time necessary for a platelet plug to form and occlude an aperture in the membrane, is then recorded [29]. The CT is prolonged in patients with platelet counts below 50,000/μL or hematocrit below 25% and in patients with severe platelet dysfunction (Bernard–Soulier syndrome (Gp Ib receptor defect) and Glanzmann thrombasthenia (Gp IIb/IIIa receptor defect)) or severe von Willebrand disease (vWD, types 2 and 3). CT is also prolonged by aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), or Gp IIb/IIIa inhibitor use [28,30,31]. The most reliable use of the platelet function analyzer is in patients with severe bleeding where a normal CT excludes quantitative deficiencies of platelets or vWF, severe platelet function disorders, and severe vWD [30,32]. However, the platelet function analyzer has a low sensitivity as a screening test for platelet function defects thus its usefulness as a preoperative screening tool is questionable [32].

While abnormal results of PFA-100 CT indicate a problem in primary hemostasis, definitive investigation and identification of the specific problem are accomplished by sophisticated tests such as platelet aggregometry, platelet secretion assays, and platelet flow cytometry. Platelet aggregometry is considered the gold standard for global platelet function testing. Platelet secretion assays measure the release of substances from platelet granules. Platelet flow cytometry uses monoclonal antibodies to diagnose defects in platelet surface glycoproteins (Bernard–Soulier syndrome and Glanzmann thrombasthenia) [31]. Appropriate use of these tests requires extensive expertise in diagnosing hemostatic disorders, thus they should be utilized under the guidance of a hematologist.

Evaluation of secondary hemostasis

Evaluation of secondary hemostasis involves examining the steps in thrombin generation and fibrin formation. Available tests include quantitative measurements of coagulation factor levels and analyses of the interactions of these factors in the coagulation process.

Measurement of fibrinogen level is the most common quantitative test performed. Standard measurement (the Clauss method) adds exogenous thrombin to diluted platelet-poor plasma centrifuged from a whole blood sample. The fibrinogen level is deduced by plotting the time until clot formation (measured by optical density) on a calibration curve drawn from reference plasma with known fibrinogen levels [33]. Normal values for fibrinogen level range between 150 and 400 mg/dL. Viscoelastic coagulation tests, thromboelastography (TEG®) and rotational thromboelastometry (ROTEM®), are being investigated as means to measure a "functional fibrinogen" level using whole blood samples. Platelet contribution to clot strength is eliminated by blocking fibrinogen-induced platelet aggregation. The independent contribution of fibrinogen to clotting can then be measured [34]. Reference ranges are being established for these measures of fibrinogen.

The interactions of coagulation factors are commonly measured with the prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin time (TT). The PT is classically used to examine the factors involved in the "extrinsic" and common pathways of coagulation and thus is sensitive to factors VII, X, V, II (thrombin), and I (fibrinogen) (Fig. 12.8). Thromboplastin, a mixture of TF, phospholipids, and calcium, is used to initiate coagulation. The usual range for PT measurements is 10–14 s. The potency of the thromboplastin used to initiate clotting is referenced to a standard thromboplastin preparation to allow the calculation of an international normalized ratio (INR). The INR allows a more accurate comparison of PT values [33]. The PT is useful in the detection of coagulation defects due to vitamin K deficiency, intestinal malabsorption, hepatic failure, dilutional or consumptive coagulopathies, and isolated deficiencies of the factors noted above, especially factor VII. Anticoagulation with oral vitamin K antagonists (warfarin) is monitored using the PT and INR [28].

The aPTT is described as a test to evaluate the "intrinsic" and common coagulation pathways (Fig. 12.9). Only the phospholipid part of thromboplastin is used to activate factor XII, hence

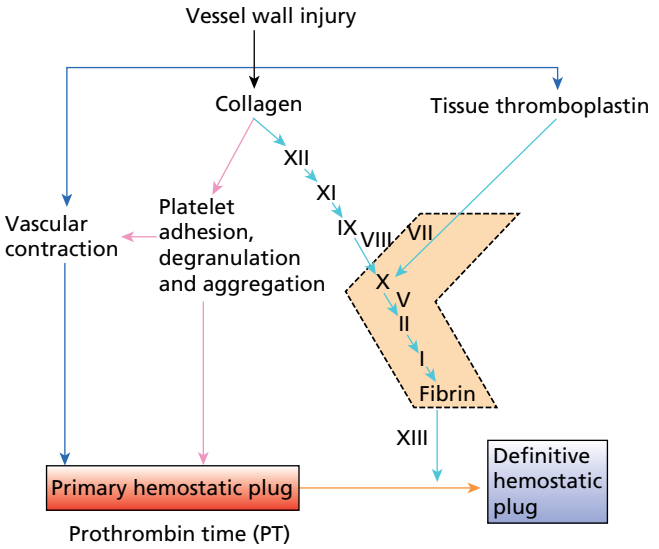


Figure 12.8 Portion of the coagulation cascade examined by the prothrombin time (PT). *Source:* Reproduced from Bleyer et al [11] with permission of Elsevier.

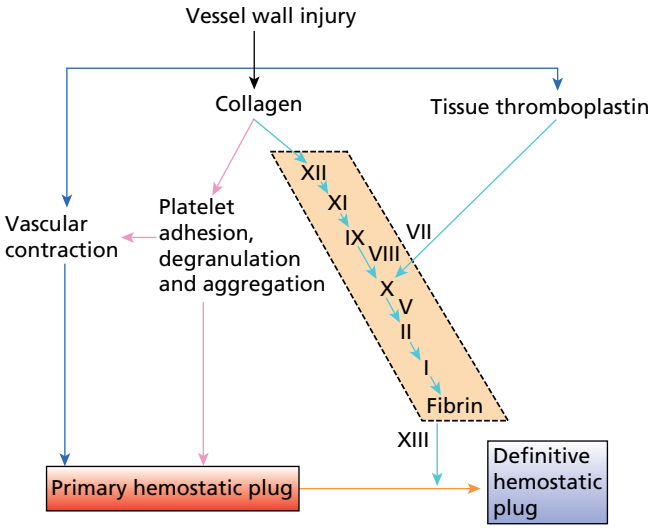


Figure 12.9 Portion of the coagulation cascade examined by the activated partial thromboplastin time (aPTT). *Source:* Reproduced from Bleyer et al [11] with permission of Elsevier.

the term "partial thromboplastin" time, and coagulation is accelerated for this test using an activator (celite, kaolin, silica, or ellagic acid), hence the term "activated" PTT. The normal range for the aPTT is typically 21–35 s. The aPTT is prolonged by deficiencies of the contact coagulation factors (XII, XI, HMWK, and PK), factors VIII and IX, and factors of the common pathway (X, V, II (thrombin), and I (fibrinogen)). It is also prolonged in the presence of heparin and lupus anticoagulants.

Lupus anticoagulants belong to the broad family of antiphospholipid antibodies and were initially thought to occur exclusively in patients with autoimmune disorders. However, they are now known to occur in up to 1% of the normal population and may appear transiently in children after viral illnesses [35,36]. Lupus anticoagulants inhibit the proper assembly of lipid-dependent coagulation complexes such as the factor VIIIa/IXa "tenase" complex and the factor Xa/Va "prothrombinase" complex. While their presence is probably the most common cause of a prolonged aPTT [37], they do not increase the risk of bleeding. In fact, their predominant clinical manifestation is the development of thrombosis secondary to their effect on platelet–endothelial interactions and their interference with protein C and protein S activity.

Initial differentiation of a prolonged aPTT may be made by using a 50:50 mixture of the plasma being tested and normal plasma. Subsequent correction of the aPTT indicates a factor deficiency whereas ongoing prolongation suggests the presence of an inhibitor such as heparin, lupus anticoagulants, or a coagulation factor-specific inhibitor [28,33].

Thrombin time (TT) is the time required for the conversion of fibrinogen to fibrin after a patient's plasma is exposed to exogenous thrombin (Fig. 12.10). The reference range for TT is typically 10–15 s. The TT is prolonged in the presence of heparin, antibodies to thrombin, hypofibrinogenemia, dysfibrinogenemia, fibrin degradation products, lupus anticoagulant, and amyloidosis [33]. In the presence of heparin, the TT can be modified to assess fibrin formation by using reptilase, a substance derived from snake venom. Reptilase, like thrombin, will stimulate the conversion of fibrinogen to fibrin but, unlike thrombin, it is not inhibited by heparin.

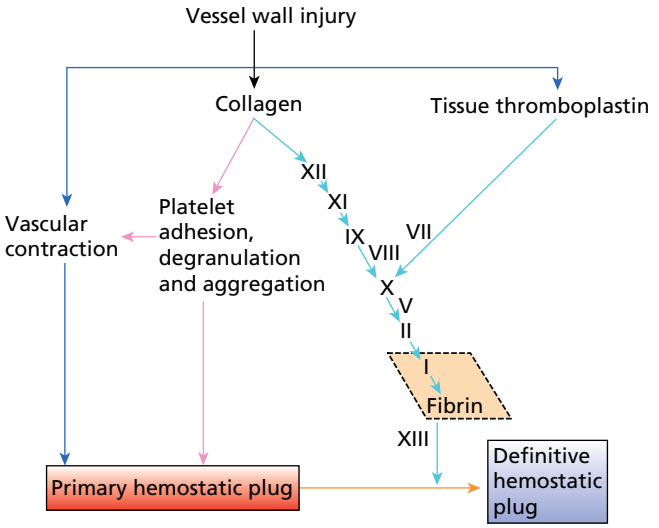
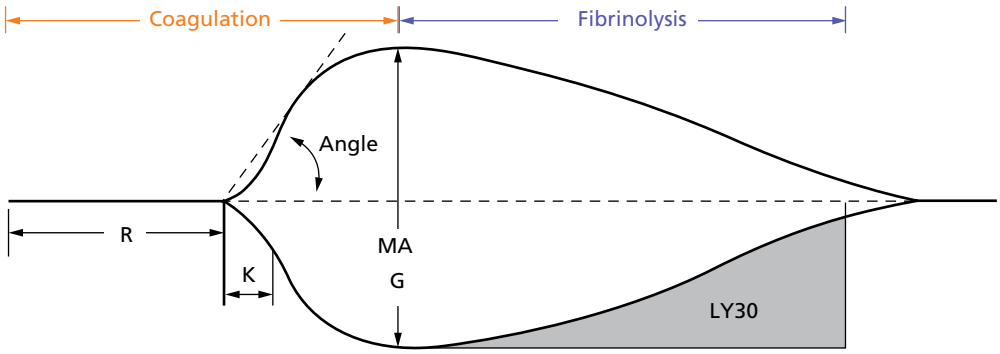


Figure 12.10 Portion of the coagulation cascade examined by the thrombin time (TT). *Source:* Reproduced from Bleyer et al [11] with permission of Elsevier.

Evaluation of fibrinolysis

The occurrence of fibrinolysis can be determined either by measuring the endproducts of fibrin degradation or by directly measuring clot lysis by viscoelastic tests [33]. When fibrinolysis occurs in response to the activation of the coagulation system, plasmin degrades the resulting fibrin clots into fibrin degradation products including D-dimers, a breakdown product composed of two of the "D" fragments of cross-linked fibrin [38]. The presence of D-dimers thus specifically indicates the breakdown of FXIII-cross-linked fibrin, as may be seen in pathological conditions such as disseminated intravascular coagulation (DIC) [39]. Assays for fibrin and fibrinogen degradation products are usually performed in reference laboratories while D-dimer assays can be performed in many hospital laboratories.



R = Reaction time to first clot formation

K = Fibrin cross-linkage, fibrinogen function

Angle = Fibrinogen function

MA (mm) = Clot strength, most reflects platelets

G = MA converted to kdynes/cm^2

LY30 = Lysis 30 minutes after MA reached

Figure 12.11 TEG® tracing. *Source:* Image used by permission of Haemonetics Corporation. TEG® and Thrombelastograph® are registered trademarks of Haemonetics Corporation in the US, other countries, or both.

The viscoelastic tests (TEG® and ROTEM®) assess hemostasis from clot formation to clot retraction and lysis as a characteristic coagulation tracing is produced in a rotating cup and pin assembly when a sample of whole blood proceeds through the clotting process [40,41] (Fig. 12.11). With the use of coagulation activators, they can provide very rapid results that can be used to immediately influence patient care [42]. These tests can identify both hypercoagulable and hypocoagulable scenarios. Additionally, any fibrinolytic activity will be dramatically displayed as the coagulation tracing produced by these tests unfolds. Viscoelastic coagulation tests have proven very useful in managing the coagulation problems associated with liver transplantation, cardiac surgical procedures, and trauma [26,43,44] and have been used to develop algorithms to guide transfusion therapy [45,46].

Use of laboratory tests

Coagulation tests typically have been used to screen patients preoperatively in an attempt to predict perioperative bleeding problems. While the rational for obtaining preoperative coagulation tests on patients with significant systemic illnesses is understandable, the rationale for routinely obtaining these tests on healthy patients who are undergoing straightforward procedures and have no history or physical signs to suggest an underlying bleeding diathesis is controversial. The main reason to obtain screening tests in this population is to detect previously undiagnosed inherited bleeding disorders such as vWD or hemophilia. However, because of the infrequent occurrence of these disorders, the routine use of coagulation tests for preoperative screening in the absence of a significant bleeding history seems unjustified from an economic standpoint [47,48]. Furthermore, the tests used for preoperative screening of patients do not provide data that reliably predict perioperative bleeding [49]. Platelet counts, for instance, are only a quantitative assessment and thus provide no information on platelet function [48]. While the CT of the PFA-100 can screen for vWD and can detect platelet function impairment due to aspirin or NSAID use, its usefulness in the perioperative setting is unproven [50]. The PT screens the "extrinsic" coagulation pathway and thus will not detect either type of hemophilia. Finally, the aPTT has not been found to predict postoperative bleeding in patients with no clinical indicators of bleeding problems [51].

The use of preoperative screening coagulation tests has been intensely scrutinized in children undergoing tonsillectomy and adenoidectomy. Approximately 2–4% of patients undergoing this surgery experience postoperative hemorrhagic complications. Results from many studies have shown no ability of the platelet count, PT, or aPTT to predict which children will bleed postoperatively [36,47,52–55]. Additionally, there are a large number of initially abnormal routine tests that return to normal on retesting thus causing unnecessary concern for parents, unnecessary delays in surgery, and increased costs [56]. Findings such as these have led some authors to state that in the absence of suspicions raised from a patient's history or physical examination, preoperative laboratory screening contributes little to patient care and should not be performed [47,56–60]. Indeed, the practice advisory published by the American Society of Anesthesiologists on preanesthesia evaluation discourages the routine use of preoperative laboratory testing in asymptomatic patients, reserving it for selected patients with pertinent findings on history or physical examination [61]. Similarly, the American Academy of Otolaryngology, Head and Neck Surgery recommends performing coagulation studies only in those patients undergoing tonsillectomy and adenoidectomy whose medical history or physical examination may indicate coagulation problems [62].

Preoperative evaluation of the coagulation system should, therefore, start with a pertinent history and physical examination. A sample of questions to ask parents and older children is outlined in Box 12.1 [47,63,64]. Pertinent findings on physical examination include petechiae, purpura, and ecchymoses with no antecedent injury [63,65]. Clinicians must always be aware, though, that the accuracy of histories and physical examinations depends on the clinician performing them and the parent and/or child answering the questions. The ability of parents and children to understand and answer medically related questions appropriately may be lacking, memories and interpretations of previous events may not be accurate, family histories may be overinterpreted, knowledge of a

Box 12.1: Questions regarding bleeding history

- Does your child have trouble with any of the following:
  - Easy bruising (larger than 2 inches)?
  - Gum bleeding with tooth brushing?
  - Frequent nose bleeds?
  - Oozing a long time from cuts or scrapes?
  - Abnormally heavy menstrual periods?
  - Bleeding into joints or muscles?
- Has your child had trouble with bleeding after:
  - Loss of teeth or dental extractions?
  - Previous surgery (including circumcision)?
  - Previous injuries?
  - When his/her umbilical cord came off?
- Is your child taking:
  - Antihistamines?
  - Aspirin?
  - Ibuprofen or other non-steroidal anti-inflammatory drugs?
  - Other over-the-counter medicines for headaches, colds, or menstrual cramps?
- Does your child take any prescribed medicines or have any chronic medical problems requiring a doctor's ongoing care?
- Has your child ever received a blood transfusion?
- Is there a family history of easy bruising or unusual bleeding after surgeries, injuries, or childbirth?
- Does anyone in your family have hemophilia, von Willebrand disease, low platelets, or any other blood disorder?

child's personal or family history by foster or adoptive parents may be deficient, ingestion of medications may be forgotten, and examinations may be incomplete [63,64]. Additionally, a negative family history may occur in up to 40% of cases of inheritable bleeding disorders because of spontaneous mutations or variable expression of the disorders in relatives. Also, young children may not have experienced an injury, undergone previous surgery, or had other experiences that would allow a bleeding problem to be revealed [63,66]. For this reason, some still advocate routine coagulation screening before tonsillectomy and adenoidectomy [54,67]. Nevertheless, the current opinion of most authorities remains that preoperative laboratory tests should only be obtained in the face of an indicative history and/or physical examination. However, one's clinical experience and judgment must be applied to the content and quality of the information obtained from the history and physical examination to make final decisions about obtaining preoperative laboratory tests.

In cases of active bleeding, quantitative assessments of platelet counts and fibrinogen levels and qualitative assessments of clotting with PT and aPTT have limitations. First, there are few agreed upon absolute values at which transfusion of blood components is indicated. Second, these tests are usually done in a central laboratory with a relatively long turnaround time. Therefore, by the time results are obtained, the clinical picture may have changed. With advances in technology, point-of-care tests have been developed and allow results to be available to the bedside clinician significantly quicker. Platelet counts, fibrinogen levels, PT, aPTT, and TT can all be obtained with this methodology but the accuracy and validation of these against conventional laboratory tests awaits confirmation [28]. The viscoelastic tests (TEG® and ROTEM®) can also provide immediate data to clinicians and have been extensively studied as aids to manage post-cardiopulmonary bypass bleeding in children [26,68]. While the use of point-of-care tests ameliorates the timeliness problem, absolute trigger values that dictate intervention are still lacking. Therefore, transfusion decisions still are heavily influenced by the clinical situation and the appearance of the operative field (and the opinions of those observing it!) while coagulation tests are used to monitor trends in the coagulation status as therapy is administered.

KEY POINTS: EVALUATION OF THE COAGULATION SYSTEM

- The indiscriminant use of screening preoperative coagulation tests may not reliably identify clinically relevant underlying coagulation abnormalities
- A pertinent history and physical exam followed by targeted coagulation tests may better identify children at risk for perioperative bleeding
- In cases of active bleeding, point-of-care tests including viscoelastic tests (TEG® and ROTEM®) may provide the most clinically useful coagulation data

Congenital hematological disorders

Congenital disorders of hemostasis can present major perioperative management challenges to anesthesiologists that extend well beyond the time when the patient is anesthetized in the operating room. Knowledge of the more common of these disorders will allow intelligent conversations with hematologists and surgeons in preparing to provide appropriate care to affected children.

von Willebrand disease

vWD is the most common inherited bleeding disorder, occurring in up to 2% of the population. The disease results from defects in the concentration, structure, or function of vWF, a large protein that plays two instrumental roles in hemostasis [69–71]. First, vWF promotes platelet adhesion and aggregation. During primary hemostasis, vWF enables platelets to adhere to injured vascular endothelium and aids in platelet aggregation through interactions with platelet GpIIbIIIa surface receptors. Second, vWF serves as a carrier protein for coagulation factor VIII, thus preventing the rapid clearance of FVIII from the circulation by activated protein C. As a result, FVIII levels and function are dependent on vWF function and activity [72]. vWF is synthesized in endothelial cells and megakaryocytes and is released from endothelial cells in response to activation of the coagulation system or to stressful stimuli such as infections, pregnancy, or physical exertion. It is also released from the α-granules of platelets upon their activation [69,73,74].

Classification of vWD is based on quantity of plasma vWF and on defects in vWF function and structure (Table 12.2).

Table 12.2 von Willebrand disease

Type	Pathology	Inheritance	Laboratory findings			
			vWF:Ag	vWF:RCo	FVIII activity	vWF multimer distribution
1	Quantitative deficiency: • Decreased amounts of otherwise normal vWF (vWF:RCo/vWF:Ag = 1.0)	Autosomal dominant	↓	↓	↓	Normal
2	Qualitative deficiency: (vWF:RCo/vWF:Ag <0.6–0.7 for 2A, 2B, and 2M)					
2A	• Failure of large vWF multimer assembly • Increased proteolysis of mutant multimers	Autosomal dominant	Normal or ↓	Normal or ↓	Normal or ↓	High and intermediate molecular weight missing
2B	• Increased binding of abnormal large vWF multimers to platelets → thrombocytopenia	Autosomal dominant	Normal or ↓	Normal or ↓	Normal or ↓	High molecular weight missing
2M	• Abnormal binding site on vWF for platelets → decreased vWF–platelet binding	Autosomal dominant	Normal or ↓	↓ or ↓↓	Normal or ↓	Normal
2N	• Abnormal binding site on vWF for FVIII → increased FVIII clearance → decreased FVIII levels	Autosomal recessive	Normal	Normal	↓ or ↓↓	Normal
3	Total deficiency: • Complete absence of vWF	Autosomal recessive	↓↓↓	↓↓↓	↓↓↓	All multimers missing
"Platelet-type" or "pseudo" vWD	Platelet abnormality: • Abnormal platelets with enhanced binding to vWF → thrombocytopenia	Autosomal dominant	Normal or ↓	↓↓	Normal or ↓	High molecular weight often missing

Ag, antigen; RCo, ristocetin cofactor assay; vWD, von Willebrand disease; vWF, von Willebrand factor.

Three major types of vWD are generally identified: partial quantitative deficiency (type 1), qualitative deficiency (type 2), and total deficiency (type 3). Type 1 is characterized by decreased amounts of normal vWF and accounts for 70–80% of patients with vWD. Type 2 is characterized by various qualitative defects in vWF and is further divided into four subtypes: 2A, 2B, 2M, and 2N. Type 3 is characterized by a complete absence of vWF and very low levels of FVIII and is the most severe form. Additionally, a "platelet-type" or "pseudo" vWD has been described where abnormal platelets demonstrate an enhanced affinity for normal vWF. Finally, an "acquired" von Willebrand syndrome has been described that is characterized by low plasma vWF levels secondary to autoantibodies against vWF, adsorption of vWF by malignant cell clones, or loss of high-molecular-weight vWF multimers under conditions of high shear stress. Possible etiologies include autoimmune disorders (such as systemic lupus erythematosus), lymphoproliferative disorders, myeloproliferative disorders, Wilms' tumor, and conditions such as congenital heart defects, aortic stenosis, bacterial endocarditis, and atherosclerotic lesions [69,75].

Clinical presentation

Clinical manifestations of types 1 and most variants of type 2 vWD are typically relatively mild and usually consist of mucocutaneous bleeding: epistaxis, gingival bleeding, gastrointestinal bleeding, menorrhagia, excessive postpartum bleeding, cutaneous bleeding, and easy bruising. These patients may have excessive bleeding after dental extractions, tonsillectomy and adenoidectomy, minor surgeries, or minor traumas. Types 2N and 3 vWD may have severe bleeding, such as the hemarthroses and intracranial bleeding seen with hemophilia patients, since these types also are associated with low FVIII levels.

Diagnosis

The diagnosis of vWD is based on a personal history of mucocutaneous bleeding, a family history of vWD, and/or coagulation tests consistent with vWD [76–78]. Screening tests for vWD may include aPTT, BT, and platelet function assay, but these tests lack sensitivity and specificity for a definitive diagnosis. Instead, assays that measure vWF quantity, function, and structure are used for both diagnosis and management (see Table 12.2). The most common tests include vWF antigen (vWF:Ag) to quantify vWF levels, vWF ristocetin cofactor assay (vWF:RCo) to assess vWF function, and FVIII assay (FVIII:C) to assess FVIII function in plasma. When interpreting vWF levels, it is important to remember that people with type O blood have mean vWF levels that are about 25% less than people with other blood types. On the other hand, inflammation and stress (i.e. during blood draws in children) can cause a falsely elevated vWF level, so repeated testing may be necessary to establish a suspected diagnosis of vWD when initial tests are normal. Measurement of FVIII activity levels is useful in establishing the diagnosis of types 2N and 3 vWD since FVIII is unbound and thus rapidly cleared in these patients. Varying degrees of thrombocytopenia due to spontaneous *in vivo* binding and consumption of vWF and platelets are seen in patients with type 2B or "platelet type" vWD [73,76,79].

Management

The goals of treatment of vWD are to restore the normal platelet adhesion of primary hemostasis and to increase abnormally low levels of FVIII. For minor surgery or tooth

extraction, levels of 40–50% of vWF:RCO and FVIII:C are considered sufficient. For patients requiring major surgery or with life-threatening hemorrhage, levels of 80–100% are desired. Postoperatively, levels greater than 50% for at least 3 days for vWF:RCo and for 5–7 days for FVIII:C are sought [77].

1-Deamino-8-D-arginine vasopressin (DDAVP, desmopressin), a synthetic vasopressin analog, releases vWF from endothelial cells and platelets and increases plasma levels of vWF and FVIII. It is effective in treating patients with type 1 vWD. It will also restore plasma levels of FVIII and vWF in many patients with type 2 vWD but the vWF will still be qualitatively deficient so primary hemostasis may continue to be abnormal. DDAVP is contraindicated in type 2B and platelet-type vWD since the release of vWF will exacerbate the thrombocytopenia common to these conditions. A trial dose of DDAVP with measurement of the subsequent vWF:RCo response is recommended in order to guide its use before a child with vWD encounters a hemostatic challenge. Replacement of vWF and FVIII will be required in patients with type 3 vWD and in those with type 2 vWD who do not respond to DDAVP [69,72,74,79].

Preoperative evaluation

Patients with a known personal or family history of vWD should undergo preoperative consultation with a hematologist at least 1 month prior to any scheduled surgery to allow time for appropriate evaluation, testing, and treatment planning. The type of vWD and the extent of surgery will determine the appropriate resources that should be available prior to the beginning of surgery.

Intraoperative management

The goal of perioperative treatment is to achieve therapeutic levels of vWF and FVIII to allow for adequate hemostasis. As noted, DDAVP-stimulated release of vWF from endothelial cells and platelets can adequately raise vWF levels for many patients with type 1 disease in anticipation of surgery. Repeated use may lead to tachyphylaxis, however, thus requiring additional intervention [69].

For patients in whom DDAVP is either contraindicated (type 2B, platelet type) or ineffective (types 2, 3 vWD, major surgery), replacement of vWF and FVIII may be required perioperatively. Options for these patients include treatment with a commercially available factor concentrate or cryoprecipitate, which contains both vWF and FVIII. Concentrates approved by the US Food and Drug Administration (FDA) include Humate-P® (human derived vWF; CSL Behring, Marburg, Germany), Wilate® (human derived vWF/FVIII complex; Octapharma USA, NJ, USA), and VONVENDI® (recombinant vWF; Shire Pharmaceutical Holdings Ireland Limited, Baxalta Incorporated, Dublin, Ireland) [72].

In patients with oral or mucosal bleeding, antifibrinolytic treatment (e.g. tranexamic acid and ε-aminocaproic acid) is an important adjuvant therapy to prevent clot lysis after hemostasis has been achieved. Antifibrinolytics are typically given for 3–7 days following the surgical procedure. If a patient continues to bleed despite adequate vWF and FVIII replacement therapy, platelet transfusions may be required. Consideration should always be given to careful surgical hemostasis, which may require topical agents such as bovine thrombin or fibrin sealant or local pressure [74,77].

Postoperative management

As patients with vWF are at increased risk for bleeding after surgical procedures, the severity of disease and hemostatic challenge should be considered when planning for postoperative monitoring and discharge. These patients may require admission or close follow-up postoperatively for possible rebleeding, electrolyte abnormalities, and volume overload after DDAVP treatment, antifibrinolytic treatment, or continued factor replacement and monitoring.

KEY POINTS: VON WILLEBRAND DISEASE

- The most common inherited bleeding disorder
- Results from defects in the concentration (types 1 and 3) or structure and function (types 2A, 2B, 2M, and 2N) of vWF
- Most variants present with mucocutaneous bleeding
- Definitive diagnosis is made with assays of vWF quantity (vWF:Ag) and function (vWF:RCo) and with assays of FVIII activity
- Management for most variants includes the use of DDAVP and/or replacement of vWF and FVIII

Hemophilia

Hemophilia is an X-linked congenital bleeding disorder caused by a deficiency of FVIII (hemophilia A) or FIX (hemophilia B or Christmas disease) [80,81]. Low levels of FVIII or IX activity prevent adequate formation of the FVIIIa/FIXa "tenase" complex on the surface of activated platelets during the coagulation process. Thus, the activation of FX and subsequent thrombin generation are blunted, resulting in defective clot formation and bleeding. Hemophilia A is more common than hemophilia B, comprising 80–85% of all cases. As an X-linked recessive trait, hemophilia generally affects males on the maternal side. However, approximately a third of patients with hemophilia have negative family histories and appear to be affected by *de novo* mutations [82–85].

Clinical presentation

Patients with hemophilia suffer from bleeding manifestations that range from prolonged oozing after minor insults to life-threatening hemorrhage after trauma or major surgery, depending on the severity of the clotting factor deficiency. In patients with mild to moderate disease, bleeding may only manifest after surgery or trauma. In contrast, those with severe disease are usually diagnosed before 2 years of age due to bleeding associated with the usual activities of life. In neonates, bleeding may occur after venipunctures, heel sticks, injections, or circumcision. Boys born to mothers known to be carriers of hemophilia thus should not be circumcised until it has been determined that they do not have the disease. Toddlers and young children may have excessive bruising associated with regular activity, mouth bleeding after tooth loss, and even muscle hematomas and joint hemorrhages. Intracranial hemorrhage is the leading cause of death related to bleeding in patients with severe hemophilia.

Another common manifestation of severe hemophilia is non-traumatic (spontaneous) intra-articular bleeding. The most frequent sites of bleeding are knees, ankles, and elbows.

Often recurrent bleeds occur in the same joint, resulting in inflammation of the synovial tissue with progressive joint damage and arthropathy. When recurrent bleeding has occurred at least four times in 6 months or 20 total times, the joint is described as a "target joint." Chronic joint pain and dysfunction may ultimately necessitate arthroscopic intervention or joint replacement. Chronic joint disease is the major cause of disability for patients with severe hemophilia [84–89].

Diagnosis

While patients usually have a family history or clinical history of easy bruising or bleeding, the diagnosis of hemophilia is made by measurement of low activity levels of FVIII or FIX with normal, functional vWF. Coagulation screening tests typically demonstrate a prolonged aPTT with a normal PT, but these tests are not consistent, sensitive, or specific enough to be used as diagnostic tools. Results of factor assays are expressed as "% activity" with 1 unit of factor per mL of plasma being equivalent to 1% activity. In families with a history of hemophilia, newborns can be diagnosed by testing plasma from cord blood, and fetal diagnosis can even be made as early as 20 weeks' gestation. Classification of both types of hemophilia is based on levels of FVIII or FIX activity and is described as severe (levels <1%), moderate (levels 1–5%), or mild (levels >5–40%). Severe hemophiliacs are usually diagnosed before 2 years of age, while those with moderate or mild forms are diagnosed later in life, usually after a hemostatic challenge [82,83,85].

Management

Management of hemophilia strives to increase the plasma concentration of the deficient factor sufficiently to control traumatic bleeding, provide hemostatic coverage for planned invasive procedures, and/or prevent spontaneous bleeding episodes [90]. In cases of mild hemophilia, where life-threatening and spontaneous bleeding are rare, administration of DDAVP may release enough vWF and FVIII from endogenous stores to overcome the mild factor deficiency [74,91]. For patients with moderate to severe hemophilia A or with hemophilia B, treatment focuses on prophylactic or "on-demand" factor replacement with recombinant or plasma-derived FVIII or FIX [84]. Prophylactic therapy may be given one to four times per week to maintain clotting factor activity level >1% to prevent bleeding. In contrast, "on-demand" therapy is used to treat acute bleeding episodes. The dose and frequency of "on-demand" therapy depend on the location and the severity of the bleeding. A minimum level of 40% factor activity should be targeted for minor oral, nasal, or urinary tract bleeding and should be maintained for several days. For bleeding in more critical anatomical areas such as the brain, retropharynx, or target joints and for severe bleeding in the gastrointestinal tract or muscle, levels of 80–100% should be achieved and then maintained for 3–14 days (depending on the severity of bleeding) [82,92,93].

Historically, treatment for hemophilia involved direct blood transfusions in the nineteenth century, which progressed to fresh frozen plasma (FFP) and cryoprecipitate by the 1950s to 1960s. By the 1990s, plasma-derived and recombinant FVIII and FIX had become the mainstay of treatment. When available, recombinant factors are the treatment of choice as they reduce the risk of transfusion-related infections. Unfortunately, most products have a short half-life (8–12 h for FVIII and 18–24 h for FIX) and thus patients require frequent transfusions [85]. Additionally, up to 30% of patients develop neutralizing IgG inhibitor alloantibodies to FVIII or FIX, thus rendering replacement therapy with plasma-derived or recombinant products ineffective [83,93]. Elimination of these antibodies by immune tolerance induction therapy, where large and frequent (usually daily) doses of FVIII or FIX are administered with or without immunosuppressants, is successful in approximately 70% of these patients [94]. Bleeding in the setting of high-titer inhibitors typically requires treatment with recombinant FVIIa or **f**actor eight **i**nhibitor **b**ypassing **a**gent (FEIBA), an activated prothrombin complex concentrate (APCC) containing factors II, VII, IX, and X [95]. Recombinant FVIIa and APCC can also be used as prophylactic agents to prevent spontaneous bleeding or to provide perioperative hemostatic coverage in hemophiliacs with inhibitors. "Bypassing" agents, however, are not a panacea. They do not normalize thrombin generation, the hemostatic response to them is less predictable than to factor concentrates, they are more costly and more difficult to monitor, and they carry a thrombotic potential [82,83,96].

Preoperative evaluation

Surgery for hemophilia patients requires advanced planning and coordination. A multidisciplinary team (surgeon, hematologist, anesthesiologist, blood bank physician, pharmacist, and laboratory personnel) is important to ensure appropriate resources are available to care for a patient with severe hemophilia [97]. Elective surgery should be scheduled early in the week and early in the day to allow for adequate personnel support in the blood bank and laboratory both intraoperatively and during the necessary postoperative healing time.

Preoperative laboratory studies include: (1) factor assays to measure factor activity; (2) inhibitor screening and inhibitor assays; and (3) type and cross for blood products. A laboratory equipped to measure clotting factor levels and inhibitor testing is required for optimal care. The pharmacy and blood bank should be notified to ensure that adequate quantities of factor concentrates and blood products are available to maintain the necessary factor levels during the entire perioperative period.

Intraoperative management

The expert help of a hematologist will be crucial in providing the best perioperative care to children with hemophilia who are scheduled for surgery. For minor surgeries, increasing factor activity levels to >30% is usually adequate. For more invasive procedures, levels greater than 50% are necessary. In the setting of life-threatening hemorrhage or surgical procedures that will result in significant blood loss, factor activity should be 80–100%. Therefore, adequate factor concentrates and blood products (red blood cells, cryoprecipitate, FFP, platelets) should be in the operating room or readily available. Laboratory personnel should be available to run factor activity assays as needed. In addition to replacing clotting factors, other measures that can reduce intraoperative blood loss include careful attention to surgical hemostasis (i.e. pressure, thrombin gel foam) and antifibrinolytics (i.e. tranexamic acid, aminocaproic acid) to prevent clot lysis [84,85,87,89].

Postoperative management

As hemophiliacs have prolonged wound healing and may have delayed or recurrent bleeding postoperatively, patients should be monitored closely for bleeding in the postoperative period. Depending on the disease severity, surgical procedure, and patient's comfort with their disease, this may be done as an inpatient or outpatient. A hematologist should be consulted to monitor factor activity levels and make recommendations regarding factor replacement requirements and duration to prevent recurrent bleeding.

KEY POINTS: HEMOPHILIA

- An X-linked recessive trait: hemophilia A is a deficiency of FVIII; hemophilia B is a deficiency of FIX
- Hemophilia is classified as mild, moderate, or severe depending on residual factor activity
- Severe disease leads to spontaneous bleeding, most frequently in joints
- Diagnosis is made by measurement of FVIII or FIX levels with normal vWF levels and function
- Management includes prophylactic or "on-demand" factor replacement with recombinant or plasma-derived FVIII or FIX or the use of recombinant FVIIa or activated prothrombin complex concentrates

Thrombophilias

Thrombosis and thromboembolism are fortunately uncommon in children, with a reported incidence of 0.07–0.14 per 10,000 children [98,99]. Predisposing clinical risk factors include indwelling central venous lines, immobility, malignancy, systemic infections, cardiac disease, nephrotic syndrome, obesity, smoking, pregnancy, and the use of estrogen-containing oral contraceptives. Medical advances that have increased the occurrence and the duration of these clinical factors are increasing the risk of occurrence of thrombotic problems. The presence of congenital prothrombotic disorders (thrombophilias) can also increase this risk [99–105].

Inherited thrombophilias include deficiencies of antithrombin (AT), protein C (PC), or protein S (PS) and mutations resulting in production of FV Leiden (FVL) and prothrombin G20210A, and reductions in methylenetetrahydrofolate reductase (MTHFR) activity. Deficiency of AT leads to reduced inhibition of thrombin, FXa, FIXa, FXIa, and FXIIa while deficiencies of PC or PS prevent the inactivation of FVa and FVIIIa. FVL is a mutant FV that is resistant to inactivation by PC. The prothrombin G20210A mutation leads to an increased production of prothrombin. MTHFR gene mutations lead to elevated blood levels of homocysteine which can induce endothelial cell injury and dysfunction. All of these potentially allow the development of a hypercoagulable state. Deficiencies of AT, PC, and PS are the least common of these but carry the highest risk for thrombosis development [96,100,101,103,104,106–112].

The presence of "lupus anticoagulants" may also pose a risk factor for thrombosis. "Lupus anticoagulant" is a term applied to antibodies produced against phospholipids in cell membranes and mitochondria or against antigens that then bind to phospholipid. Lupus anticoagulants may occur in patients with autoimmune disorders or transiently with malignancies or viral infections. As previously noted, they cause a prolonged aPTT by preventing the proper assembly of lipid-dependent coagulant complexes such as the FVIIIa/FIXa "tenase" complex and the FXa/FVa "prothrombinase" complex. More importantly, lupus anticoagulants alter platelet–endothelial interactions and inhibit the PC/PS system thus predisposing patients to thrombosis [96,109,113–115].

Clinical presentation

Neonates and adolescents are the children most at risk for thrombotic problems. Neonatal issues usually center around indwelling central catheters and are more common in the upper venous system. Adolescents are more likely to have concurrent medical risk factors or be taking estrogen-containing oral contraceptives or abusing tobacco. Additionally, affected adolescents are more likely to have an inherited thrombophilia (21% versus 6% in neonates). Their thromboses more likely involve the lower venous system [99,101,103]. PC deficiencies are more often seen in children less than 2 years old whereas AT and PS deficiencies are found more in school-aged children [105]. FVL and MTHFR mutations have been linked to recurrent pregnancy losses due to abnormal clotting in small placental vessels [116]. The vast majority (85%) of thromboses in children develop during a hospitalization [99].

About two-thirds of thrombotic episodes in children are symptomatic. Clinical manifestations depend on the location of the thrombus or embolus. Headache, vomiting, and seizures can occur with intracranial episodes, chest pain, and tachypnea with pulmonary emboli, hematuria with renal thromboses, and superior vena cava (SVC) syndrome and chylothoraces with SVC obstruction [99].

Diagnosis

Diagnostic tools include ultrasonography, including echocardiography, where the diagnosis may be incidentally made while evaluating cardiac issues. CT angiography and ventilation–perfusion scans are also useful tools [99,102].

Management

Avoidance of thrombosis development obviously is the goal and should center on minimizing clinical risk factors and promoting healthy lifestyle choices. Specific therapies may be helpful in identified inherited factor deficiencies. Recombinant AT concentrate is available for AT-deficient patients. FFP may replace AT, PC, and PS. A PC concentrate is also available.

A difficult question in dealing with thrombophilias is, "Who should be screened?". Interpretation of thrombophilia screening tests requires expert insight. Indiscriminant use of these tests is discouraged, but the infrequency of these abnormalities makes controlled trials to determine who should be screened difficult. Test results may be useful in determining ongoing management and in advising asymptomatic relatives. General guidelines based mostly on expert opinions suggest screening individuals who present with thrombotic events unprovoked by concurrent clinical risk factors (especially at early ages) and those with recurrent thromboses or strong family histories of thromboses. Long-term anticoagulation is often advised in patients with "high risk" thrombophilias, i.e. those with AT, PC, or PS deficiencies, those homozygous for FVL, and those with multiple coexisting defects [101,117,118].

Anesthetic implications

The anesthetic implications of thrombophilias are mainly those of awareness of their existence, pathophysiological mechanisms, and potential for long-term anticoagulant use. Heparin may be ineffective until adequate AT levels are restored in deficient patients. Nitrous oxide should be avoided in patients with MHTFR mutations as it interferes with vitamin B12/homocysteine metabolism, thus further increasing plasma homocysteine levels [119]. The advice of an experienced hematologist is invaluable in preparing a perioperative plan for this group of patients.

KEY POINTS: THROMBOPHILIAS

- Predisposing clinical risk factors are the most common contributors to thrombosis in children
- Neonates and adolescents are most at risk
- Congenital prothrombotic disorders (thrombophilias) increase this risk
- Screening is advised in cases of unprovoked thrombosis or strong family histories

Sickle cell disease

Sickle cell disease (SCD) is a genetic disorder of hemoglobin and is the most common inherited red blood cell disorder [120]. Hemoglobin molecules are composed of two pairs of globin chains, each possessing an Fe^{2+}-containing heme group. Hemoglobin A is composed of two α and two β chains and accounts for 95% of normal adult hemoglobin. Hemoglobin S (HbS) contains abnormal β chains as a result of a single nucleotide substitution of valine for glutamic acid in the sixth position of the β chain. Populations and descendants from sub-Saharan Africa, the Middle East, Southeast Asia, the Mediterranean, and parts of South and Central America have the highest prevalence of HbS. In developed countries, neonatal diagnosis, vaccinations, penicillin prophylaxis, disease-modifying medications (i.e. hydroxyurea), and blood transfusion allow people with SCD to survive into their fifth or sixth decades, but 50–90% of those born in developing nations die before age 5 [121,122].

The genes coding for the β chains of hemoglobin are codominant so a person who is heterozygous for normal and sickle β chains produces both HbA and HbS. This predominantly benign carrier state is termed sickle cell trait (SCT). SCT is considered to have persisted in some populations because it offers protection from the fatal complications of *Plasmodium falciparum* malaria. Homozygotes for the sickle β chain produce only HbS. Unlike SCT, this condition (HbSS disease) may be associated with significant clinical manifestations [123–125]. The term SCD includes HbSS disease as well as conditions with a combination of HbS and HbC (lysine substituted for glutamic acid in the sixth position of the β chain) and those with a combination of HbS and a hemoglobin molecule with decreased (β^+ thalassemia) or absent (β^0 thalassemia) β chains. Of these genotypes, HbSS and HbS/β^0 disease produce the most severe clinical manifestations while the symptoms of HbSC disease are more moderate and those of HbS/β^+ disease are mild [121,125–127].

The instability of HbS results in the polymerization, accelerated denaturation, and breakdown of the hemoglobin molecule, leading to red blood cell (RBC) membrane damage and RBC rigidity. During periods of low oxygen, the erythrocyte becomes stiff and "sickle shaped," preventing easy passage through capillary beds. These deformed RBCs block blood flow to organs and tissues, resulting in a vaso-occlusive event, end-organ damage, and severe pain for the patient. Due to the instability of the HbS molecule, sickle RBCs also have a shorter life span (10–12 days) than normal RBCs (120 days) resulting in hemolytic anemia. The chronic intravascular hemolysis is associated with increased chronic vascular inflammation, pulmonary hypertension, and ischemic strokes [121,125,126,128]. Surgical interventions are common in SCD patients, and the seriousness of the pathology associated with SCD necessitates a multidisciplinary approach to plan appropriate perioperative management.

Clinical presentation

Intermittent painful vaso-occlusive crises are the clinical hallmark of SCD. Infection and surgical stress as well as physical exertion and emotional stress can trigger these "sickle cell crises" [127,129]. However, more than half of all events do not have an obvious cause. In young children, the initial manifestation of the disease is often dactylitis, a painful swelling of the hands and feet. The most severe complications in SCD are vaso-occlusive pain crises, acute chest syndrome (ACS), ischemic stroke, and splenic sequestration. However, the disease affects all organ systems, resulting in a variety of long-term morbidities (Table 12.3).

ACS is the leading cause of death in patients with SCD. ACS is defined as a new pulmonary infiltrate in combination with fever, chest pain, or respiratory symptoms. Etiologies include infections and fat emboli from necrotic bone marrow. Treatment includes the administration of a broad-spectrum antibiotic, the use of incentive spirometry, bronchodilators, and supplemental oxygen if hypoxia is present, the restoration and maintenance of adequate hydration, and the appropriate management of pain. If there is no improvement from the initial interventions, then exchange transfusion should be implemented. Repeated episodes of ACS often lead to chronic lung injury and pulmonary hypertension. Asthma and pulmonary emboli are additional issues that accompany SCD [126,127,130,131].

Neurological complications, including transient ischemic attacks and strokes, are common with HbSS disease. In instances of ischemic cerebral infarctions, emergent exchange transfusion to reduce the level of circulating HbS to less than 30% may be undertaken upon presentation. Chronic transfusion regimens are then useful to prevent recurrences [128,131].

Splenic sequestration or aplastic crises may cause acute exacerbations of compensated chronic anemia. Splenic sequestration may occur in children under 4 years of age in association with a viral illness and may lead to severe anemia, hypovolemia, and even shock. Management often requires aggressive volume resuscitation, emergent transfusion, inotropic support, and urgent splenectomy. Splenic involution usually occurs by 5 years of age, thus eliminating this problem beyond that age. Aplastic crises are usually the result of a parvovirus B19-mediated temporary suppression of bone marrow function and may also result in the need for RBC transfusion [125–127,130,132].

Table 12.3 Organ system involvement in sickle cell disease

System	Clinical manifestations	Treatment
Neurological	TIA, ischemic stroke	Emergent exchange transfusion (decrease HbS to <30%); hydration
Pulmonary	ACS, PHTN, pulmonary infarction, asthma, RAD	Acute: broad-spectrum antibiotics, supplemental O2, bronchodilators, hydration, pain management, exchange transfusion Chronic: diuretic, pulmonary vasodilator
Cardiac	Vaso-occlusion of coronary arteries, cardiac autonomic dysfunction, right heart dysfunction	Supplemental O_2, inotropic support as necessary
Genitourinary	Priapism, papillary necrosis, renal failure, nocturnal enuresis	Priapism: hydration, pain control, injection of α-agonists Other: dialysis, renal transplant
Skeletal	Avascular necrosis, septic arthritis, osteomyelitis, osteoporosis, vertebral collapse	Acute: antibiotics, pain management Chronic: pain management, physical therapy, osteotomy, joint replacement
Hematological	Hemolytic anemia, acute aplastic anemia, splenomegaly or splenic sequestration, iron overload	Emergent transfusion, splenectomy, chelation therapy
Gastrointestinal	Acute/chronic cholecystitis, gallstones, hepatomegaly	Cholecystectomy
Other complications	Retinopathy, chronic pain, leg ulcers	Pain management consultation, ophthalmological consultation

ACS, acute chest syndrome; PHTN, pulmonary hypertension; RAD, reactive airway disease; TIA, transient ischemic attack.

Long-term morbidities from vaso-occlusive crises include avascular necrosis of the femoral and humeral heads, osteomyelitis, osteopenia, retinopathy, and cholelithiasis/cholecystitis. Renal and genitourinary problems range from nocturnal enuresis to priapism to renal failure requiring dialysis. These patients should be followed by a team that specializes in managing treatment for acute and chronic manifestations of SCD [126,127,133].

Diagnosis

Hemoglobinopathies can be diagnosed by hemoglobin electrophoresis or high-performance liquid chromatography. Patients with SCT as well as those with SCD will show positive results from sickle hemoglobin solubility testing (Sickledex). Currently, newborns in the United States are screened by this method shortly after birth. This early identification of affected children in combination with the use of prophylactic penicillin and vaccinations has increased the survival rates of patients with HbSS disease to 93.9% at 18 years. Older patients from regions where HbS occurs frequently should be tested if there is concern based on clinical presentation [121,126,130,134].

Management

Current treatment strategies are aimed at reducing acute crises, decreasing long-term complications, and improving survival. The only FDA- approved drug for SCD is hydroxyurea, which has significantly decreased acute crises and improved mortality rates in adults and children with SCD. Hydroxyurea augments the release of nitric oxide thus promoting vasodilation, attenuating pulmonary hypertension, and inhibiting platelet aggregation. It also induces the production of fetal hemoglobin (HbF). HbF inhibits the polymerization of HbS and thus helps to reduce sickling of RBCs. For some patients, stem cell transplantation is an option that, if successful, essentially restores normal production of erythrocytes and prevents further morbidity. Additionally, gene therapy may be on the horizon for some cases [120,122,126,129].

Chronic RBC transfusions are a mainstay of maintenance therapy. SCD patients are usually anemic, so transfusions treat anemia and increase the concentration of HbA while suppressing endogenous production of new RBCs containing HbS. RBCs chosen for transfusion should be sickle negative and negative for all antigens against which the patient has pre-existing antibodies. Phenotypic matching of RBCs for C, E, and Kell antigens has been shown to decrease rates of RBC alloimmunization and ultimately to decrease rates of hemolytic transfusion reactions in patients with SCD [135]. Thus, RBCs chosen for transfusion should also ideally be phenotypically matched for these antigens. However, transfusing non-phenotypically matched RBCs (or RBCs from donors whose sickle status is not known) is acceptable in urgent situations.

Treatments for an acute sickle cell crisis include oxygen supplementation for hypoxemia, aggressive hydration, correction of acidosis, administration of antibiotics, promotion of normothermia and good perfusion, adequate pain control, and possible transfusion (simple or exchange to decrease concentration of HbS). Pain control in SCD can be difficult but includes treatment with acetaminophen, NSAIDs, narcotics, and possibly regional anesthetic techniques. Guidelines for pain management in children with SCD are available from the American Pain Society [136].

Preoperative evaluation

The complications from SCD mean that patients often require a variety of surgical interventions. Cholecystectomy is the most frequently performed procedure because of gallstone formation in the face of persistent hemolysis [127]. Splenectomy and orthopedic, neurosurgical, cardiac, and obstetric procedures are also commonly undertaken. Preoperative evaluation should include a multidisciplinary team (surgeon, anesthesiologist, and the primary physician managing the SCD) to aid in the prevention and management of perioperative complications.

Co-morbidities and the severity of the patient's SCD should be established during a thorough history and physical examination (Box 12.2). Important preoperative studies will be

Box 12.2: Preoperative evaluation of patients with sickle cell disease

- When was the last acute sickle cell crisis?
- How frequently does the patient have crises?
- Is there a specific trigger for acute crisis?
- What is their current treatment for SCD (i.e. hydroxyurea, chronic blood transfusions)?
- When was their last blood transfusion?
- What is their pain regimen during a crisis?
- Who is the primary physician who manages their SCD?

determined by the severity of an individual patient's disease and may include hematocrit, hemoglobin, blood urea nitrogen (BUN), creatinine, chest X-ray, and possibly electrocardiogram or echocardiogram if there is concern for pulmonary hypertension [127]. SCD patients should be scheduled early in the day to avoid prolonged nil per os (NPO) times, as hypovolemia and dehydration may precipitate a crisis. Surgery for superficial procedures on patients with stable disease may be scheduled on an outpatient basis but requires thoughtful consideration.

Prophylactic preoperative RBC transfusions have been shown to decrease the incidence of perioperative complications by diluting the abnormal RBCs with normal ones. Aggressive transfusion regimens aim to decrease the HbS concentration to less than 30% while conservative regimens aim to increase the hemoglobin level to 10 g/dL without concern for HbS concentrations. The conservative regimen has been found to be as effective as the aggressive approach in preventing perioperative SCD-associated complications while significantly reducing transfusion-associated risks [137]. Preoperative transfusion may be foregone in children undergoing minor superficial elective surgical procedures but is important prior to major surgical procedures (including thoracotomies, laparotomies, orthopedic procedures, and tonsillectomies and adenoidectomies) [138,139].

Intraoperative management

Intraoperative anesthetic management includes exercising caution about adequate oxygenation, hydration, thermoregulation, and acid–base balance. Postoperative pain control is often a challenge for these patients. Therefore a multimodel approach, including regional anesthetic techniques, may be useful both intraoperatively and postoperatively for pain control [127].

Orthopedic and cardiac surgery presents several challenges for SCD patients. The use of tourniquets for orthopedic procedures is controversial [140,141], but their uncomplicated use has been documented in patients after preoperative exchange transfusions [142]. Similarly, cardiac surgery involving cardiopulmonary bypass (CPB) has been safely conducted after performing preoperative and intraoperative exchange transfusions [143,144]. No consensus exists on the appropriate body temperature to be maintained during CPB or on the use of cold cardioplegia, but the maintenance of normothermia seems intuitive.

Postoperative management

No evidence exists to support the prolonged postoperative administration of supplemental oxygen in the absence of hypoxemia. However, pulse oximetry should be monitored and oxygen therapy should be used to maintain normal oxygen saturations. Aggressive pulmonary toilet and early ambulation postoperatively may limit pulmonary complications. Adequate postoperative pain management is critical. As mentioned above, the use of acetaminophen, NSAIDs, narcotics and regional anesthesia may provide good postoperative pain control. Consultation with pain management specialists may be needed in more complex patients.

KEY POINTS: SICKLE CELL DISEASE

- The most common inherited red blood cell disorder
- Intermittent painful vaso-occlusive crises ("sickle cell crises") are the clinical hallmark
- Acute chest syndrome is the leading cause of death
- Cholecystectomy is the most frequently performed surgery in these patients
- Prophylactic preoperative red blood cell transfusions to a hemoglobin of 10 g/dL (conservative) or to a hemoglobin S level <30% (aggressive) may be used before more invasive surgeries

Transfusion therapy

Transfusion medicine has played a major role in propelling medical and surgical advances that have benefitted the pediatric patient population. This section will describe the basic principles of transfusion therapy, the blood products available for transfusion, the logistics of transfusion, the indications and triggers for administering blood products, and the potential adverse effects that can accompany transfusion of these products. It is important to realize that most medical centers have a Blood Bank Medical Director or Transfusion Specialist available for consultation on these topics.

Principles of transfusion therapy

ABO blood group system

Blood is classified into groups based on the presence or absence of specific inherited RBC surface antigens. The International Society of Blood Transfusion recognizes 30 major blood group systems, the most important of which is the ABO system. The ABO system defines an individual's "blood type" by the presence or absence of A and/or B antigens on RBC surfaces. The homozygous presence of alleles coding for the A or B antigen produces group A or group B. Additionally, the heterozygous presence of one of these alleles in combination with the O allele, which codes for no antigen production, also produces group A or B. The heterozygous presence of both A and B alleles produces both antigens and yields group AB. Finally, the homozygous presence of O alleles produces no antigen and thus group O (Table 12.4). Ethnic and racial differences exist in the distribution of ABO blood groups across the world. In the United States, approximately 44% of the population has type O, 42% has type A, 10% has type B, and 4% has type AB blood.

Individuals naturally develop antibodies against the ABO antigen(s) not present on their own RBCs during the first year

Table 12.4 ABO blood group system

ABO type				
	A	**B**	**O**	**AB**
Allele combinations	AA AO	BB BO	OO	AB
ABO antigen present	A	B	None	A and B
ABO antibody present	Anti-B	Anti-A	Anti-A Anti-B	None

Table 12.5 ABO compatibility

Recipient ABO type				
	A	**B**	**O**	**AB**
Compatible donor RBCs (contain antigens)	A O	B O	O	A B AB O
Compatible donor plasma-containing products (contain antibodies)	A AB	B AB	O A B AB	AB

of life. This occurs even without exposure to blood transfusions, probably in response to exposure to antigens from bacteria, viruses, or plants that are structurally very similar to the ABO antigens. Thus, those with type A blood develop anti-B antibodies (IgM type), those with type B blood develop anti-A (IgM type), those with type O blood develop both anti-A and anti-B (IgM and IgG types), and those with type AB blood develop no anti-ABO antibodies (see Table 12.4). IgG-type anti-A and anti-B antibodies in type O mothers can cross the placenta and cause hemolysis in children with A or B antigens on their RBCs.

Rh blood group system

The Rh blood group system is second in importance after the ABO group. An RBC antigen in the Rhesus macaque monkey, designated as "Rh factor," was reported in 1940 after the finding that the serum of rabbits immunized with RBCs from this monkey agglutinated about 85% of human RBCs. A serologically similar antigen, termed a D antigen, was subsequently identified on these human RBCs. Consequently, people whose RBCs have this D antigen are referred to as being "Rh positive" whereas those whose RBCs do not carry this antigen are designated as "Rh negative." As noted, approximately 85% of the US population is Rh positive.

In contrast to the ABO blood group system, anti-Rh antibodies only develop in Rh-negative individuals after exposure to Rh-positive blood by a blood transfusion or by placental exposure during pregnancy. Once anti-Rh antibodies have developed, repeat exposure to Rh-positive RBCs can result in hemolysis. Since anti-Rh antibodies are of the IgG class, they can cross the placenta. This can be of grave importance to sensitized Rh-negative mothers carrying an Rh-positive child. These mothers may have been sensitized by the feto-maternal transfer of Rh-positive RBCs during a previous pregnancy with an Rh-positive child. Transplacental transfer of the sensitized mother's IgG anti-Rh antibodies to her second Rh-positive child can lead to hemolytic disease of the newborn (erythroblastosis fetalis) as the unborn child's Rh-positive RBCs are hemolyzed.

Transfusion compatibility between recipients and donors

The presence of RBC surface antigens and circulating plasma antibodies to these antigens mandates immunological compatibility between recipients and donors of blood products. Since whole blood (WB) contains both ABO antigens and antibodies, it can be transfused only to ABO-identical recipients. Packed RBCs (PRBCs) contain antigens expressed on the surfaces of the RBCs with minimal amounts of antibody-containing plasma, so donors and recipients do not have to be ABO identical. However, patients can only receive PRBCs whose ABO surface antigens will not react with the patient's circulating anti-ABO antibodies. For example, type O patients with no A or B antigens on their RBC surfaces but with anti-A and anti-B antibodies in their plasma may receive only type O RBCs (no antigens). In contrast, type AB patients with both A and B antigens on their RBC surfaces but with no antibodies in their plasma may receive A, B, AB, or O RBCs (Table 12.5). Thus, when transfusing PRBCs, type O individuals are universal donors whereas type AB patients are universal recipients.

Conversely, plasma-containing products (including FFP and platelets), which contain negligible RBCs, contain anti-ABO antibodies so patients can only receive plasma-containing products whose anti-ABO antibodies will not react with the patient's ABO surface antigens. Type AB patients may receive only type AB plasma and platelets because the plasma from any other blood type will contain antibodies to the A or B antigens present on their RBCs. In contrast, type O patients may receive plasma-containing products from A, B, AB, or O donors since these patients have no RBC antigens (see Table 12.5). Therefore, when transfusing plasma-containing products, type AB individuals are universal donors whereas type O patients are universal recipients.

Rh antigen status must also be considered when transfusing blood products. Rh-positive individuals may receive PRBCs from either Rh-positive or Rh-negative donors and plasma-containing products from donors without anti-Rh antibodies (either Rh-positive or previously untransfused Rh-negative donors).

Rh-negative individuals preferentially should receive Rh-negative PRBCs since exposure to Rh-positive RBCs invokes the production of anti-Rh antibodies in 30–80% of these recipients. This matching is especially important if these recipients will be receiving further PRBCs in the future or are females who may bear children in the future. Although platelets contain ABO antigens, they do not contain Rh antigens. However, RBCs contaminate all platelet preparations to some extent. Thus, Rh-negative patients should preferentially receive Rh-negative platelets. If transfusion of Rh-positive platelets to Rh-negative recipients is necessary, Rho(D) immune globulin can be given within 72 h to the high-risk populations previously identified to prevent the development of anti-Rh antibodies that may be induced by contaminating RBCs. Since FFP is an acellular product, Rh-negative individuals can receive plasma from either Rh-positive or Rh-negative donors.

Available blood products

Collection techniques

A variety of blood products are available for transfusion (Table 12.6) and can be collected via two processes. Whole blood (WB) can be collected from a single donor as a 450–500 mL aliquot. While being collected, the blood is mixed with 70 mL of an anticoagulant/preservative solution. Basic "CPD" solutions contain citrate for anticoagulation, phosphate to buffer the acidosis that develops during storage, and dextrose to serve as a source of energy for the RBCs. These CPD anticoagulant/preservative solutions allow RBC-containing products to be stored for 21 days when kept at 1–6°C. The addition of adenine to the solution (CPDA-1) supports the synthesis of ATP by the RBCs and prolongs the shelf-life to 35 days. Newer adenine–saline additive solutions, such AS-1 (Adsol), AS-3 (Nutricel), and AS-5 (Optisol), add various additional amounts of phosphate, dextrose, adenine, mannitol, and saline and further extend the shelf-life to 42 days [145–147].

Most units of WB are subsequently separated into various components. This practice allows several patients to benefit from one blood donation, optimal storage of the different components, and focused administration of specifically indicated components. Centrifugation of one unit of WB ultimately can provide one unit each of PRBCs, plasma, and platelets. In the majority of centers in North America, a unit of WB is separated initially into PRBCs and platelet-rich plasma. The platelet-rich plasma is then further separated into plasma and platelets. Cryoprecipitate and other human-derived products including albumin and fibrin glue can subsequently be obtained from plasma.

Alternatively, individual components can be specifically collected from a donor by apheresis. In this process, blood from the donor is drawn into an external circuit and a specific component is separated by centrifugation based on its specific gravity and removed from the whole blood while the remaining components are returned to the donor. This process can be used to collect RBCs, platelets, plasma, or granulocytes. Its use can minimize donor exposures for blood product recipients by providing larger quantities of a desired component from one donor than WB separation techniques can provide [145].

Whole blood

WB is obtained from donors with a hematocrit of at least 38% [146] and is used not only to support hemoglobin levels but also to provide coagulation factors [148]. The ability of WB to raise hemoglobin levels, however, is limited by the hemoglobin level of the donor. Its use may be advantageous in neonatal exchange transfusions and in controlling bleeding after complex cardiac surgeries requiring CPB in children less than 2 years old and after massive blood loss and transfusion [145,149]. However, only relatively "fresh" WB (i.e. less than 24–48 h old) is useful in correcting coagulopathic bleeding. During storage at 1–6°C, the activities of the temperature-sensitive labile coagulation factors, V and VIII, progressively diminish in WB [145]. Additionally, storage at this temperature rapidly and dramatically alters platelet survival. After 3 h of storage at 4°C, platelet viability drops to 62%, then to 12% after 24 h, and to 2% after 48 h [150]. However, the logistics of timely acquiring, testing, and transporting WB so that it is available for use at many facilities within 24–48 h of its collection pose major barriers to its regular availability. Because of these practical considerations as well as the previously mentioned benefits of separating WB into components, WB is rarely used today.

Packed red blood cells

PRBCs are the component most commonly used to raise hemoglobin levels and thus increase the oxygen-carrying capacity of blood. They can be prepared by separation from WB or by apheresis. Like WB, PRBCs are stored at 1–6°C in an anticoagulant/preservative solution. If CPDA-1 is the solution used, the hematocrit of the unit of PRBCs is 65–80%, the volume is approximately 250 mL, and the shelf-life is 35 days. If one of the additive solutions (AS-1, AS-3, or AS-5) is used, the volume of the unit is increased to approximately 350 mL, the hematocrit is decreased to 55–65%, and the shelf-life is extended to 42 days [145,146,148]. PRBCs can be further processed by freezing, washing, irradiation, or leukocyte reduction as necessitated by the recipient's condition and previous tolerance of transfusions.

Table 12.6 Available blood products

	Storage	Shelf- life	Special preparations (reasons)
Whole blood	1–6°C	21–35 days*	
Packed red blood cells	1–6°C	21–42 days*	Leukocyte reduction** (febrile HTRs, alloimmunization, CMV reduction, TRIM) Irradiation (immunocompromised, neonates, blood relatives, TAGVHD) Washing (removes potassium)
Frozen packed red blood cells	≤–65°C	10 years	Thawing Washing (removes glycerol and potassium)
Fresh frozen plasma	≤–18°C (within 8 h of collection)	1 year	Thawing
Plasma frozen within 24 hours	≤–18°C (after 8 but within 24 h of collection)	1 year	Thawing
Cryoprecipitate	≤–18°C	1 year	Thawing
Platelets	20–24°C	5 days	Leukocyte reduction** (as with PRBCs) Irradiation (as with PRBCs)

* Depending on storage solution used.

** Typically performed at collection before storage CMV, cytomegalovirus; HTRs, hemolytic transfusion reactions; PRBCs, packed red blood cells; TAGVHD, transfusion-associated graft versus host disease; TRIM, transfusion-related immunomodulation.

PRBCs with unique phenotypes or RBCs collected for autologous use that need to be stored for more than 42 days can be frozen for up to 10 years at -65°C or lower after adding glycerol as a cryoprotective agent. After these frozen PRBCs have been thawed for transfusion, they must be transfused or frozen again within 24 h. The glycerol is removed by washing the RBCs with progressively lower concentrations of sodium chloride-containing solutions. Unfortunately, this process may cause cell volume loss, resulting in a product with a lower baseline hematocrit. Washing RBC units removes plasma proteins, inflammatory mediators such as cytokines, and other plasma contaminants. Washed RBCs are indicated to prevent severe recurrent allergic reactions caused by foreign plasma proteins, to remove excess potassium from older units of PRBCs or from those that have been irradiated, and to remove plasma IgA prior to transfusion to IgA-deficient patients who have developed anti-IgA antibodies. After washing, PRBC units must be used within 24 h if stored at 1– 6°C or within 4 h if stored at 20–24°C since the hermetic seal of the unit will have been broken [146].

Irradiation of PRBCs (or WB) with γ-irradiation using a cesium (^{137}Cs) source or with X-rays using a linear accelerator is performed to inactivate viable lymphocytes, thus preventing transfusion-associated graft versus host disease. Irradiation is indicated when PRBC (or WB) recipients are immunocompromised, are first- or second-degree blood relatives of the donor, or are neonates. The shelf-life of PRBCs after irradiation is reduced to 28 days if the anticoagulant/preservative-dictated shelf-life still exceeds 28 days at the time of irradiation. Potassium and free hemoglobin leak from the RBCs into plasma after irradiation so washing of irradiated PRBCs may be considered when there is an extended length of time between irradiation and transfusion [145–147].

Leukocyte reduction of PRBCs is performed to decrease the incidence of febrile non-hemolytic transfusion reactions, to decrease the incidence of alloimmunization of recipients to HLA antigens, to reduce the risk of transmission of cytomegalovirus (CMV) and other infectious diseases transmitted by white blood cells (WBCs), and possibly to reduce the effects of transfusion-related immunomodulation. Leukocyte reduction is typically performed before storage at the time of collection of the blood but can be performed post storage in the laboratory or at the bedside. Poststorage leukocyte reduction has been reported to cause unexpected severe hypotension in some recipients (especially those taking angiotensin-converting enzyme (ACE) inhibitors) due to bradykinin activation. Additionally, inflammatory mediators released by leukocytes during storage are not removed by poststorage leukoreduction. Given these considerations, more than 80% of RBCs transfused in the United States are leukoreduced before storage, with leukoreduction filters removing more than 99% of leukocytes [145,146,151].

Plasma

Plasma is prepared by separation from the platelet-rich plasma component of WB or by apheresis. The volume of a unit of plasma derived from WB is 170–250 mL whereas a unit obtained by apheresis measures up to 500 mL. To be labeled as "fresh frozen plasma" (FFP), the plasma has to be stored at -18°C or colder within 8 h of collection. This prevents the inactivation of the temperature-sensitive "labile" coagulation factors, V and VIII, and allows a shelf-life of 1 year. If plasma is not frozen within 8 h of collection, the activity of factors V and VIII will diminish, but the plasma can still be frozen at or below -18°C within 24 h, labeled "plasma frozen within 24 hours," and stored for up to 1 year. By definition, each mL of FFP contains 1 international unit (IU) of each coagulation factor. FFP also contains 2–4 mg of fibrinogen per mL. No cryoprotectant is included in the unit and, therefore, the majority of leukocytes are killed or rendered non-functional. As a consequence, irradiation to prevent transfusion-associated graft versus host reaction and leukocyte reduction to prevent CMV infection are not necessary for FFP. Prior to administration, FFP is thawed in a waterbath at 30–37°C for approximately 20–30 min. The unit should then be infused immediately or it may be stored at 1–6°C and transfused within 24 h. If it is not used within this 24 h window, it can be stored for an additional 4 days at 1–6°C but it must be relabeled as "thawed plasma" and it will have diminished, although still hemostatic, levels of factors V and VIII [145,146,152].

Cryoprecipitate

Cryoprecipitated antihemophilic factor, or "cryoprecipitate," is the cold-insoluble white precipitate that forms when a unit of FFP is thawed only to 1–6°C. Once prepared from FFP, cryoprecipitate must be refrozen at -18°C or colder within 1 h and then has a shelf-life of 1 year. Each unit of cryoprecipitate contains concentrated amounts of fibrinogen (150–250 mg), FVIII (80–150 IU), vWF (40–70% of original plasma concentration), FXIII (30% of original plasma concentration), and fibronectin (30–60 mg) in approximately 5–15 mL of plasma. The plasma remaining after extraction of cryoprecipitate is relabeled as "cryoprecipitate reduced plasma." Since this plasma is deficient in the previously mentioned coagulation factors, it should not be used as a substitute for FFP.

Once thawed in preparation for transfusion, cryoprecipitate must be administered within 6 h to prevent loss of FVIII activity. If several cryoprecipitate units are pooled, transfusion must take place within 4 h to minimize risks from potential contamination. Since cryoprecipitate, like FFP, is stored at temperatures below –18°C, irradiation and/or leukocyte reduction are not necessary before cryoprecipitate transfusions. Additionally, since cryoprecipitate contains no RBCs and only small amounts of plasma (thus, minimal amounts of anti-ABO antibodies), ABO and Rh compatibility are not required before its use in adults [145,146,152,153]. However, the small amount of plasma in cryoprecipitate units may be significant relative to the blood volume of infants and young children, so pediatric centers often administer cryoprecipitate whose plasma is ABO compatible with the recipient.

Platelets

Platelets are prepared by separation from the platelet-rich plasma component or the buffy coat layer of WB or by apheresis. Platelet units prepared from WB are termed "random donor platelets" and contain a minimum of 5×10^{10} platelets in 50–70 mL of plasma. Platelet units obtained by apheresis are designated as "single donor platelets" and contain at least 3.5×10^{11} platelets in 200–400 mL of plasma. One single donor apheresis platelet unit is equivalent to 6–8 units of random donor platelets. Apheresis platelet units have become the primary source of platelets for transfusion in the United States

since their use minimizes donor exposures to recipients. Platelet units are stored at 20–24°C with continuous gentle agitation to prevent aggregation. Because of the risk of bacterial contamination at this temperature, platelet units in the United States currently have a shelf-life of only 5 days. Since platelet units are not subjected to the extremely cold temperatures at which plasma and cryoprecipitate are stored, they (like WB and PRBCs) must be irradiated to kill viable lymphocytes in clinical situations where transfusion-associated graft versus host disease is a concern and must be leukocyte reduced when transmission of CMV is a risk [145,146].

In adult centers, type compatibility may not be required between recipients and donors of platelet units for small-volume transfusions. However, platelets express multiple surface antigens, including ABO and platelet-specific antigens, so ABO-identical platelets may be needed if survival of ABO-incompatible platelets is decreased. With the significant amount of plasma contained in platelet units, though, compatibility between donor plasma and recipient ABO type is necessary in infants and children. Additionally, since a small amount of RBCs remain in both random and single donor platelets, Rh-negative patients preferentially should be transfused with platelets from Rh-negative donors to prevent Rh alloimmunization, especially in females or in patients who may receive future transfusions [145,154].

Factor concentrates

Several factor concentrates were developed for clinical use in specific diseases, such as hemophilia. However, as clinicians seek alternatives to allogenic blood products to aid in perioperative hemostasis, the off-label use of factor concentrates such as fibrinogen concentrate (FC), recombinant activated FVII (rFVIIa), and prothrombin complex concentrates (PCC) is increasing. Proponents of these alternative procoagulant adjuncts emphasize the benefits of small-volume infusions, immediate availability (they do not require thawing or cross-matching), decreased infectious and immune risks, and cost-effectiveness. However, few studies have evaluated the safety and efficacy of these products. Therefore, it is important to consider thrombotic risk when using these adjuncts in perioperative hemostasis management.

rFVIIa (rFVIIa; NovoSeven ®, RT, Novo Nordisk, Bagsvaerd, Denmark), synthesized from hamster cells, was developed specifically for hemophiliacs who developed inhibitors against exogenous FVIII or FIX. rFVIIa works by both TF-dependent and independent mechanisms to activate FXa on platelet surfaces. These complexes catalyze a large thrombin burst, which promotes fibrin generation and thus dense clot formation [155,156]. Although rFVIIa was FDA approved for hemophilia A and B patients with inhibitors against FVIII and FIX, this medication has been used off-label in adults and pediatric patients as a rescue for massive bleeding associated with trauma, intracranial hemorrhage, liver transplantation, and cardiac surgery [157–161]. Despite demonstrating some efficacy in reducing transfusion, it has been associated with increased thromboembolic complications and mortality in some studies [162–166].

There are several commercially available PCCs that have been FDA approved for various uses. These are lyophilized products from human plasma that contain all the factors to promote coagulation [167]. Each PCC has a different composition and function, but most include the vitamin K dependent factors (FII, FVII, FIX, FX), while some also contain PC, PS, antithrombin, and heparin. Three-factor PCCs contain low levels of inactivated FVII and therapeutic levels of FII, FIX, and FX. In contrast, four-factor PCCs contain therapeutic levels of all the vitamin K dependent factors. PCCs are most commonly used for replacement in patients with congenital or acquired factor deficiencies or reversal of anticoagulants, such as warfarin [168]. As with rFVIIa, the "off-label" use of PCCs to manage bleeding associated with trauma and post-bypass bleeding is increasing. There are some reports of increased thrombotic complications, but so far there are no studies examining the appropriate dose, dosing regimen, thrombotic complications, or mortality associated with off-label use.

Fibrinogen concentrate (RiaSTAP, CSL Behring, Marburg, Germany) is purified fibrinogen derived from adult plasma. It is FDA approved for patients with congenital hypofibrinogenemia, but is being used as a fibrinogen replacement instead of cryoprecipitate or FFP. Of note, FC does not contain other factors (vWF, FVIII, and FXIII) found in cryoprecipitate [168,169].

Logistics of transfusion

Typing, screening, and cross-matching

Preparation for transfusion begins with determining the blood type and Rh status of the intended recipient and the prospective donor unit. ABO group is defined using forward and reverse typing. Forward typing confirms the presence of certain antigens on the recipient's RBCs while reverse typing tests for the presence of naturally occurring antibodies in the recipient's plasma to A and B antigens not present on the recipient's RBCs. Therefore, blood group is defined by identifying the ABO antigen(s) and anti-ABO antibody(ies) present. Neonates typically do not develop anti-ABO antibodies until 4–6 months of age; therefore, forward typing is primarily utilized to determine their blood type. Rh status is defined by testing RBCs for the presence of the D antigen using anti-D-containing reagent.

The plasma of the intended recipient is then screened for the presence of unexpected antibodies to antigens of any of the other blood group systems that can be present on RBC surfaces. This is accomplished by incubating the recipient's plasma with screening RBC panels composed of three or four group O RBCs selected in such a way that most common non-ABO antigens capable of inducing the production of significant antibodies that could cause hemolysis are represented on at least one screening cell. Antihuman globulin is then added to agglutinate any RBCs to which an antibody has attached (indirect Coombs test). If an antibody is detected, the screen is considered positive and further investigation must be undertaken to identify the specific antibody present. Antibody screening must be repeated if RBCs are ordered and 3 days have elapsed since the last antibody screen or if the patient was discharged from the facility in the 3 days since obtaining the initial screen. An exception is in neonates where, due to the immaturity of their immune systems, an initial negative screen does not have to be repeated during the same hospitalization until after 4 months of age [145].

Cross-matching of recipient plasma and donor RBCs is the next step prior to PRBC transfusions. If the recipient has a negative antibody screen, only ABO compatibility between the recipient and the donor RBCs must be verified. This can be done with an immediate spin cross-match to provide serological verification (mixing the recipient's plasma with the donor's RBCs to ensure there is no agglutination or hemolysis) or with an electronic cross-match that uses a series of computer algorithms to select a suitable PRBC unit that is in stock in the blood bank. Either of these cross-matching techniques can be used to have PRBCs ready for transfusion in 5–10 min for recipients with negative antibody screens. However, if the recipient has a positive antibody screen, a more detailed serological cross-match, called an antihuman globulin (AHG) or "full Coombs" cross-match, must be performed to verify compatibility of the recipient's plasma against clinically significant non-ABO antigens that may be present on donor RBC surfaces. This process requires up to 45 min to perform, although identifying the recipient antibody and finding compatible donor RBCs may take considerably longer.

In contrast to PRBCs, cross-matching is not necessary prior to plasma, cryoprecipitate, or platelet transfusions. For each of these products, units whose plasma is ABO-compatible with the recipient's RBCs are administered. FFP and cryoprecipitate can be thawed and available for transfusion in approximately 20–30 min. Since platelets are stored at room temperature, they can be immediately available for transfusion when required.

Administration of blood products

The process of transfusing blood products begins with the proper identification of the recipient, verification that the product to be transfused has been assigned to that recipient, and confirmation that the ABO type and Rh status of the blood product is appropriate for that recipient.

RBC products transfused intraoperatively may need to be warmed since they will have been kept at 1–6°C in the blood bank or stored on ice in the operating room. This may be accomplished by warming the WB or PRBC unit in a temperature-controlled water bath or by warming the RBCs as they flow through the intravenous (IV) tubing by using circulating water, forced air, or a heat exchanger. Warming these products prior to their administration attenuates not only the development of hypothermia but also any vasoconstriction and/or coagulopathy that may accompany hypothermia [170]. Care must be taken, however, to prevent excessive warming as this can lead to hemolysis [146]. FFP and cryoprecipitate will be warmed in the blood bank prior to their release, and platelets are stored at room temperature so further warming is not usually necessary prior to their administration.

If PRBCs need to be diluted to expedite their flow through IV tubing, 0.9% NaCl (normal saline) should be used. Calcium-containing solutions such as Ringer's lactate should be avoided for this purpose because calcium in excess of the chelating ability of the citrate anticoagulant in the PRBC unit will cause the formation of small clots. Hypotonic solutions should also be avoided because they may cause hemolysis of the RBCs. No medicines or other IV solutions should be infused through the same IV tubing being used for any blood products [146].

Screening filters with pore sizes of 170–200 μm should be used in the transfusion of WB, PRBCs, FFP, cryoprecipitate, and platelets to remove clots and aggregates. These filters are incorporated into all standard blood administration sets. There are no firm indications for using microaggregate filters (pore size 20–40 μm), although these are commonly used when reinfusing blood processed through a cell saver device. Microaggregate filters will trap platelets so should definitely not be used when transfusing platelet units. Finally, once any blood product is accessed for transfusion, its administration should be completed within 4 h to minimize the risk of bacterial contamination [146].

Indications/triggers for blood product transfusion

Blood products are used for the correction of anemia to improve oxygen-carrying capacity and for the treatment of coagulopathies to attenuate bleeding. The administration of blood products, however, is accompanied by infectious, immunological, and non-immunological risks that must be weighed against the anticipated benefits of their use. Therefore, insightful thought processes should guide any decision to transfuse these products [148].

Packed red blood cells

There is no single minimum hemoglobin level that serves as a transfusion trigger for all patients in all clinical scenarios [148,152,171]. To complicate this problem for pediatric caretakers, there is a dearth of randomized controlled trials on RBC transfusion thresholds for neonates, infants, and children [145]. Surveys of pediatric intensive care units (PICUs) have shown significant variations in hemoglobin levels that trigger RBC transfusion [172] as well as a variety of clinical factors other than hemoglobin level that are used to help make this decision [173]. The "10/30" rule for transfusion that was introduced in the 1940s has fallen into disfavor based on risk:benefit analyses [148], and hemoglobin levels are currently allowed to fall to levels much lower than 10 g/dL before PRBCs are administered in many clinical situations. Physiological signs such as tachycardia, hypotension, and, if available, low mixed venous oxygen saturations, increased oxygen extraction ratios, or development of lactic acidemia and metabolic acidosis are useful in providing objective evidence of the need to correct a given level of anemia [148].

In addressing specific hemoglobin levels, data from adults have shown that at a hemoglobin level less than 6 g/dL, coronary artery blood flow reserve may be exceeded and oxygen extraction may be compromised [148]. Studies in both adults and children in intensive care units using a restrictive transfusion strategy of only administering PRBCs when hemoglobin levels drop below 7 g/dL have shown reductions in number of patients transfused and units given with unchanged or improved morbidity and mortality rates when compared to more liberal strategies of transfusing at hemoglobin levels of 9.5 or 10 g/dL [174,175]. With these data in mind, recommendations to transfuse PRBCs for hemoglobin levels less than 7 g/dL seem appropriate. Transfusion for levels greater than 10 g/dL is probably unnecessary in the absence of ongoing blood loss or complicated clinical scenarios. Transfusions for hemoglobin levels between 7 and 10 g/dL should be triggered

by objective physiological signs of inadequate oxygen delivery to tissues [176]. These guidelines require modification for premature infants and for children with cyanotic congenital heart disease, congestive heart failure, or significant co-morbidities. Indeed, although not without controversy [177], the use of a restrictive transfusion threshold in premature infants may be associated with an increase in neurological morbidities that have been postulated to result from decreased oxygen delivery to the brain [178]. Practice parameters for these infants and children are even less evidence based than those previously described.

It typically has been taught that transfusing 10–15 mL of PRBCs per kg of bodyweight will raise the hemoglobin level by approximately 3 g/dL or the hematocrit by 10% [145]. Formulas have been developed to add more precision to determinations of volume of PRBCs to be transfused. One such formula is:

Volume of PRBCs to be transfused = total blood volume × (desired hemoglobin − actual hemoglobin) / hemoglobin of PRBC unit

Assumptions of total blood volume (TBV) are based on the age of the recipient: 90–100 mL/kg for preterm neonates, 80–90 mL/kg for full-term neonates, 80 mL/kg from 6 months to 2 years of age, and 70 mL/kg for children older than 2 years [179]. The hemoglobin of the PRBC unit depends on the anticoagulant/preservative solution used to store the unit [145]. The actual/predicted hemoglobin rise using this formula is 0.61–0.85 and is influenced by the TBV and PRBC hemoglobin values used. A new formula developed from a regression analysis of volume of PRBCs transfused versus bodyweight results in an actual/predicted hemoglobin rise of 0.95 that is valid across different age groups [180]:

$$\text{Volume of PRBCs to } be \text{ transfused} = 4.8 \times \text{weight}\,(kg) \times \text{desired rise in hemoglobin}\,(\text{g}/dL)$$
$$\text{or} = 1.6 \times \text{weight}\,(kg) \times \text{desired rise in hematocrit}\,(\%)$$

Use of this new formula may minimize the need for repeat transfusions.

Plasma

Generally agreed upon indications for transfusing FFP include the treatment of active microvascular bleeding associated with an acquired coagulopathy (disseminated intravascular coagulation, liver disease, massive transfusion, cardiac surgery, or liver transplantation) in the presence of an INR >2.0 or an aPTT >1.5 times normal or when an INR and an aPTT cannot be obtained in a timely manner; replacement of rare congenital coagulation factor deficiencies (II, V, X, XI, XIII, protein C) when specific concentrates are not available; emergent reversal of the anticoagulant effects of warfarin; replacement of AT deficiency in patients with heparin resistance when AT concentrate is not available; and replacement of C1 esterase inhibitor in patients with hereditary angioedema. FFP is not indicated for volume expansion, to augment albumin concentration, or when specific factor concentrates are available to correct documented deficiencies [145,152,176,181]. "Cryoprecipitate reduced plasma" is sometimes used in the management of thrombotic thrombocytopenic purpura (TTP), a condition where the breakdown of large multimers of vWF is inhibited thus leading to microvascular thromboses and tissue infarctions. Transfusion of this plasma product, which is devoid of vWF, replenishes the deficient enzyme (ADAMTS13) responsible for cleaving vWF and ameliorates the complications of TTP [145,146,182].

Ten to 15 mL of FFP per kg of bodyweight is the conventional volume transfused for the previously mentioned indications. This amount is reported to increase plasma levels of coagulation factors by 25–30% [1,3] and thus to exceed the factor level thresholds required for hemostasis (15% for factor V and 30% for all other factors) [183].

Cryoprecipitate

Transfusion of cryoprecipitate is indicated in the presence of microvascular bleeding when the fibrinogen level is <80–100 mg/dL or when the fibrinogen level cannot be measured in a timely fashion and in actively bleeding patients with congenital fibrinogen deficiencies. Cryoprecipitate is rarely indicated when the fibrinogen level exceeds 150 mg/dL but its use may be prudent with fibrinogen levels between 100 and 150 mg/dL when there is a risk of bleeding into a confined space such as the brain or the eye. Cryoprecipitate is not indicated as a first-line treatment for hemophilia A or B, factor XIII deficiency, or vWD, but may be used when purified or recombinant factor concentrates are not available or when vWD is unresponsive to the administration of DDAVP. In small children, 1 unit of cryoprecipitate per 5 kg of bodyweight is estimated to raise the fibrinogen level by 100 mg/dL. In older patients, one unit per 10 kg should increase the fibrinogen level by approximately 50–70 mg/dL [145,152,176].

Platelets

Platelet transfusions may be required because of low platelet counts or because of abnormal platelet function regardless of the number of platelets present. Controlled trials are lacking, and only general guidelines are available to help guide platelet replacement therapy. In the face of active bleeding in the perioperative period, it is prudent to maintain platelet counts above 50,000/μL. When microvascular bleeding is present, this level should probably be raised to 100,000/μL. When active bleeding occurs in the setting of platelet dysfunction (uremia, thrombasthenias, or ingestion of antiplatelet drugs), platelet transfusion will be required regardless of platelet counts. Even in the absence of bleeding, platelets are often transfused prophylactically when counts fall below 50,000/μL in the setting of sepsis, antibiotic use, or other coagulopathies, or when counts fall below 10,000/μL in patients who do not have these additional risk factors. Platelet counts greater than 30,000/μL are felt to be a safe level for most neonatal ICU patients if they have no other risk factors or previous intraventricular hemorrhage. Prior to invasive procedures such as surgery, central line placement, thoracentesis, endoscopy, or lumbar puncture, platelet counts should be raised to greater than 50,000/μL. For neurosurgical or ophthalmological procedures, or if bleeding in the central nervous system has occurred, platelet counts above 100,000/μL are preferred. Platelet transfusions are not typically indicated prior to bone marrow biopsies or in scenarios of increased platelet destruction (idiopathic thrombocytopenic purpura). Platelet administration will increase the risk of thrombosis in patients with TTP and heparin-induced thrombocytopenia [145,152,176,181].

When transfusing random donor platelets, 5–10 mL of platelets per kg of bodyweight in neonates and 0.1–0.2 units/kg in older infants and children should result in a platelet increment of 50,000–100,000/μL. When single donor apheresis platelet units are being transfused, a general rule is to administer 10 mL/kg to neonates, ¼ unit to children <15 kg, ½ unit to children between 15 and 30 kg, and a whole unit to children >30 kg. Response to these transfused volumes varies among patients and according to the platelet content of the unit transfused. Failure to achieve expected platelet increments after transfusion should prompt a search for causes of platelet refractoriness and may require the use of phenotypically matched platelets for future transfusions [145].

Massive transfusion

Trauma is the leading cause of death in children, and hemorrhage is the leading cause of preventable death in trauma victims [184]. Resuscitation of these patients, as well as patients with non-traumatic severe intraoperative bleeding, may require massive transfusion, classically (though arbitrarily) defined in children as the transfusion of one blood volume (70–80 mL/kg) in a 24 h period [185,186]. This amount of transfusion often follows significant crystalloid infusion and often is associated with a trauma-induced coagulopathy, part of the "lethal triad" of coagulopathy, acidosis, and hypothermia that often results in death in these patients [187,188]. Data derived from combat situations have shown that the use of fresh WB as part of "damage control resuscitation" attenuates this coagulopathy and improves survival rates in these patients [189]. Since WB is difficult to obtain in civilian settings, a balanced transfusion approach using predetermined ratios of RBCs, plasma, and platelets has been introduced and similarly found to reduce mortality in adult trauma victims [186,190]. Consequently, massive transfusion protocols (MTPs) have been proposed for use in hemorrhaging pediatric (mostly trauma) patients [191].

Goals of pediatric MTPs include maintenance of platelet counts above 50,000/μL and hemoglobin levels above 10 mg/dL and achievement of normal coagulation assays [192]. However, several questions surround the use of MTPs in the pediatric arena. Objective data to trigger the initiation of MTPs are elusive, but clinical concern for acute imminent blood loss or acute transfusion of 40 mL/kg of blood, a threshold shown to reliably predict mortality in children, has been suggested [193,194]. Variations in age, gender, and weight of children complicate the creation of universally applicable MTPs [184]. Optimal plasma and platelet to PRBC ratios have not been determined although 1:1 ratios of FFP and PRBCs are commonly sought, with platelets and cryoprecipitate included in subsequent rounds of the protocols [189,191,192,194] (Fig. 12.12). Benefits of using MTPs include not only allowing bedside physicians to focus on immediate patient care instead of the tedium of ordering blood products based on laboratory tests whose untimely results may no longer reflect the current clinical picture but also allowing the blood bank to more rapidly provide safe blood products for transfusion [186,195].

Neonate (1–5 kg)

Package	RBC	Plasma	PLTs	Cryo
1	½ unit	½ unit		
2	½ unit	½ unit	¼ apheresis	
3	½ unit	½ unit		1 unit
4	½ unit	½ unit	¼ apheresis	
5	½ unit	½ unit		1 unit

Infant (6–10 kg)

Package	RBC	Plasma	PLTs	Cryo
1	1 unit	1 unit		
2	1 unit	1 unit	½ apheresis	
3	1 unit	1 unit		2 units
4	1 unit	1 unit	½ apheresis	
5	1 unit	1 unit		2 units

Younger child (11–25 kg)

Package	RBC	Plasma	PLTs	Cryo
1	2 units	2 units		
2	2 units	2 units	1 apheresis	
3	2 units	2 units		4 units
4	2 units	2 units	1 apheresis	
5	2 units	2 units		4 units

Older child (26–50 kg)

Package	RBC	Plasma	PLTs	Cryo
1	3 units	3 units		
2	3 units	3 units	1 apheresis	
3	3 units	3 units		6 units
4	3 units	3 units	1 apheresis	
5	3 units	3 units		6 units

Adolescent (>50 kg)

Package	RBC	Plasma	PLTs	Cryo
1	5 units	5 units		
2	5 units	5 units	1 apheresis	
3	5 units	5 units		8 units
4	5 units	5 units	1 apheresis	
5	5 units	5 units		8 units

Figure 12.12 Pediatric massive transfusion protocol. Cryo, cryoprecipitate; PLTs, platelets; RBC, red blood cells. *Source:* Reproduced from Hendrickson et al [191] with permission of John Wiley & Sons.

MTP use in pediatric patients does not increase total blood product use and is not associated with morbidity from increased plasma or platelet transfusions. However, its use also has not yet been demonstrated to reduce overall mortality in massively transfused children [191,194].

KEY POINTS: TRANSFUSION THERAPY

- Blood groups are based on the presence or absence of inherited RBC surface antigens
- Cross-matching is required before PRBC transfusions but not before transfusions of plasma, cryoprecipitate, or platelets
- Specific factor concentrates may provide more targeted correction of coagulation problems while minimizing some transfusion-related issues
- Weight-adjusted massive transfusion protocols may be useful in resuscitating children during significant hemorrhage

Potential adverse effects of transfusion

The transfusion of blood products is not without risks. Additionally, the incidence of adverse reactions during blood product transfusion is three to four times greater in children compared to adults [196,197]. Transmission of infectious diseases and non-infectious immune- and non-immune-mediated hazards of transfusion are sources of ongoing concern and investigation (Box 12.3). Advances in blood donor selection, infectious disease testing of donated blood products, use of leukoreduction filters, and irradiation of blood components in defined situations have made today's blood supply safer than ever [145,198,199]. Nevertheless, vigilance must be maintained to identify known risks and to anticipate emerging risks in today's blood supply.

Transmission of infectious diseases

While the public may be unaware of many of the risks of transfusion, the risk of contracting an infectious disease from a blood product transfusion has not escaped its attention. Potentially transmissible agents include bacteria, viruses, parasites, and prions (Box 12.4).

Bacterial contamination is the most prevalent infectious risk. Platelet units are the most frequently contaminated blood product since they are stored at room temperature. *Staphylococcus* species are the most common contaminants of platelet units whereas gram-negative bacteria such as *Yersinia enterocolitica* that can replicate at cold temperatures are more commonly found as contaminants in PRBC units. The major sources of contamination are the donor's skin at the venipuncture collection site, donor bacteremia that is asymptomatic or undetected, unsterile collection packs, and violations of sterility during processing procedures [151,152,200–202].

Despite this, transmission of viral infections by blood product transfusions is more concerning because of potential long-term implications. Currently, donated blood products are regularly tested for human immunodeficiency virus (HIV), human T-lymphotrophic virus (HTLV), hepatitis B virus (HBV), hepatitis C virus (HCV), West Nile virus, and Zika virus using serological assays or nucleic acid amplification tests (NATs) [200,203–205] (Table 12.7). Early detection of viral DNA or RNA by NATs shortens the window period of these viruses, i.e. the time after a blood donor has become infected but before any donor screening tests are positive [151]. Consequently, the risk of transmitting several of these viruses through blood product transfusions has been drastically reduced [151,201,203,206]. NATs are not currently routinely performed for HBV detection since their use would reduce

Box 12.3: Potential hazards of transfusion

- Transmission of infectious diseases
- Immune-mediated risks
  - Hemolytic transfusion reactions
  - Febrile non-hemolytic transfusion reactions
  - Allergic reactions
  - Transfusion-related acute lung injury
  - Transfusion-associated graft versus host disease
  - Post-transfusion purpura
  - Transfusion-related immunomodulation
  - Alloimmunization
- Non-immune-mediated risks
  - Septic transfusion reactions
  - Non-immune hemolysis
  - Transfusion-associated circulatory overload
  - Metabolic derangements
  - Red blood cell storage lesions
  - Mistransfusion

Box 12.4: Infectious agents/diseases potentially transmissible by blood product transfusion

Viral
- HIV 1/2
- HTLV I/II
- Hepatitis A virus
- Hepatitis B virus
- Hepatitis C virus
- Hepatitis G virus
- Cytomegalovirus
- Epstein–Barr virus
- Parvovirus B19
- Human herpesvirus-8
- West Nile virus
- Enterovirus
- Zika virus

Bacterial
- Syphilis (*Treponema pallidum*)
- Rocky Mountain spotted fever (*Rickettsia rickettsii*)
- Contaminants

Parasitic
- Malaria (*Plasmodium* sp.)
- Babesiosis (*Babesia* sp.)
- Chagas disease (*Trypanosoma cruzi*)
- Toxoplasmosis (*Toxoplasma gondii*)
- Leishmaniasis (*Leishmania* sp.)

Prions
- Variant Creutzfeldt–Jakob disease

Table 12.7 Laboratory tests used to screen donated blood for pathogens

Pathogen	Laboratory tests
Human immunodeficiency virus (HIV) types 1 and 2	NAT for HIV-1 HIV-1 and HIV-2 antibody detection
Human T-lymphotropic virus (HTLV) types I and II	HTLV-I and HTLV-II antibody detection
Hepatitis B virus (HBV)	Hepatitis B surface antigen detection Hepatitis B core antibody detection
Hepatitis C virus (HCV)	NAT for HCV Hepatitis C virus antibody detection
West Nile virus (WNV)	NAT for WNV
Zika virus	NAT for Zika virus
Cytomegalovirus (CMV)	CMV antibody detection
Treponema pallidum (syphilis)	Treponemal antibody detection
Trypanosoma cruzi (Chagas disease)	*T. cruzi* antibody detection

NAT, nucleic acid amplification testing.
Source: Adapted from https://www.cdc.gov/bloodsafety/basics.html

Box 12.5: Estimated residual risks of transfusion-associated infections

- HIV: 1 in 2.3 million
- HTLV: 1 in 2 million
- Hepatitis B: 1 in 350,000
- Hepatitis C: 1 in 1.8 million

Source: Data from Hendrickson and Hillyer [201] with permission of Wolters Kluwer.

the window period only marginally compared to the most sensitive HBsAg screening tests [151,198]. Current estimated risks of transmitting some of these viral pathogens through blood product transfusion are detailed in Box 12.5.

Hepatitis A virus (HAV) is rarely transmitted by blood products because individuals are usually symptomatic when infected and thus excluded from donation, no chronic carrier state exists, and many people have developed antibodies either naturally from previous infection or by vaccination. The risk of CMV transmission to immunocompromised patients has been reduced by the use of leukoreduced cellular blood products (termed "CMV safe") or the use of CMV-seronegative cellular blood products [151]. Potential blood donors are also screened for *Treponema pallidum*, the causative agent of syphilis, and *Trypanosoma cruzi*, the parasite that causes Chagas disease, using serological tests to detect antibodies to these organisms [203,207].

The transfusion-associated transmission of other infectious agents for which no screening tests are currently available is also a concern. This includes human herpesvirus-8 (a causative agent of Kaposi sarcoma) and most of the parasitic diseases (malaria, babesiosis, toxoplasmosis, and leishmaniasis) [152,198,199,208]. Fortunately, transmission of parasitic diseases is rare in developed countries. However, potential transmission of hepatitis G virus, other as yet unknown viruses, and the prion causing variant Creutzfeldt–Jakob disease, the human equivalent of bovine spongiform encephalopathy ("mad cow disease"), is a significant concern [209]. Currently, potential blood donors who visited European countries affected by bovine spongiform encephalopathy between 1980 and 1996 are deferred from donating [203].

The risks of transfusion-associated transmission of infectious agents are not static because new agents continue to emerge and old agents change their properties and epidemiological patterns. A recent example is the development of a Zika virus screening test, and mandated testing of all blood donations in the United States for this virus [210].

Pathogen reduction technologies effective against most viruses, bacteria, and parasites are being developed to improve future safety, as are prion-retention filters [203,210]. Additionally, performance of NAT on individual units of blood rather than on minipools of samples, as is currently done, could be of benefit but would be extremely expensive [208]. Nevertheless, currently used screening methods are effective enough that non-infectious hazards of transfusion have now emerged as the leading complication of transfusion therapy [151,201,211].

Immune-mediated hazards of transfusion

Immune-mediated transfusion risks include hemolytic transfusion reactions, febrile non-hemolytic transfusion reactions, allergic reactions, transfusion-related acute lung injury, transfusion-associated graft versus host disease, post-transfusion purpura, transfusion-related immunomodulation, and alloimmunization [201] (Table 12.8).

Hemolytic transfusion reactions

Immune-mediated hemolytic transfusion reactions (HTRs) are caused by the transfusion of RBCs to patients with preexisting antibodies to antigens on those RBCs. The most serious HTRs are caused by the transfusion of ABO-incompatible RBCs and result in acute intravascular hemolysis. Clerical error is the most common cause of this mishap and, therefore, most are preventable. Electronic identification systems, including barcode scanning, have been demonstrated to reduce the incidence of transfusion of incompatible blood products [212].

Awake patients may manifest chills, fever, nausea, anxiety, and chest and flank pain but these may be masked in anesthetized patients. Tachycardia, hypotension, microvascular bleeding, and hemoglobinuria may be seen but need to be recognized as resulting from an HTR as opposed to a myriad of other potential causes in anesthetized patients. Once an acute immune-mediated HTR is suspected, the transfusion should be immediately stopped, the unit of blood should be returned to the blood bank for investigation, and steps should be taken to prevent or ameliorate acute renal failure and coagulopathy.

Delayed immune-mediated HTRs result from the transfusion of RBCs containing a non-ABO antigen to which the recipient has developed an antibody because of a previous transfusion or pregnancy. The antibody is usually present at such low levels that it is undetected during the screening procedure. However, a rapid anamnestic response follows the transfusion. A delayed HTR presents 3–10 days after transfusion as a falling hemoglobin level. No treatment is usually indicated but recognition of the problem, identification of the recipient's antibody, and future transfusion of blood negative for the corresponding antigen are necessary [145,152,201,203].

Table 12.8 Immune-mediated hazards of transfusion

	Etiology	Causative products	Prevention
Hemolytic transfusion reactions	Recipient antibodies to donor RBCs	Acute: ABO incompatible RBCs Delayed: non-ABO antigens on donor RBCs (anamnestic)	Acute: clerical error prevention Delayed: transfusion history and history of antibodies
Febrile non-hemolytic transfusion reactions	Leukocyte-derived cytokines in donor products Recipient antileukocyte antibodies against donor leukocytes	Platelets most commonly	Prestorage leukocyte reduction
Allergic reactions	Recipient antibodies against soluble donor plasma antigen Recipient anti-IgA antibodies against donor IgA	Plasma-containing products (FFP, apheresed platelets, and RBCs)	Washing cellular products (RBCs and platelets) to remove plasma Use of IgA-deficient plasma
Transfusion-related acute lung injury	Donor antileukocyte antibodies against recipient leukocytes Donor cytokine- or interleukin-induced activation of recipient leukocytes sequestered in lungs	Plasma rich products (FFP and apheresed platelets)	Avoidance of plasma products from multiparous female donors
Transfusion-associated graft versus host disease	Donor immunocompetent lymphocytes engraft in recipient	Cellular blood products (RBCs, platelets, granulocytes)	Irradiation of cellular blood products
Post-transfusion purpura	Recipient antibodies against donor platelet antigens	Platelets, RBCs, FFP	
Transfusion-related immunomodulation	Leukocytes?		Prestorage leukocyte reduction
Alloimmunization	Recipient antibodies to donor minor RBC, platelet, or leukocyte antigens	Cellular blood products (RBCs, platelets, leukocytes)	Extended antigen phenotyping Irradiation of HLA-matched platelets

FFP, fresh frozen plasma; RBC, red blood cells.

Febrile non-hemolytic transfusion reactions

A febrile non-hemolytic transfusion reaction (FNHTR) is defined as a 1°C increase in body temperature into the febrile range during or soon after a transfusion. These reactions are typically caused by leukocyte-derived cytokines that have been released into the blood product during storage or by the reaction of recipient antileukocyte antibodies (developed after previous transfusions or pregnancies) against donor leukocytes. They are most commonly seen in association with platelet transfusions but can also accompany RBC or plasma administration. FNHTR is a diagnosis of exclusion after other transfusion-associated causes of fever, such as acute HTRs, septic transfusion reactions, or transfusion-related acute lung injury, have been ruled out. The use of prestorage leukocyte reduction has significantly reduced the occurrence of these reactions [145,201,203].

Allergic reactions

Allergic reactions are the most common of all acute transfusion reactions and result from the reaction of an antibody in the recipient to a soluble plasma antigen in the donor. Leukocyte reduction of cellular blood products, therefore, does not decrease the occurrence of these reactions. However, pretransfusion washing of PRBCs or platelets removes plasma and associated antigens and thus does decrease the occurrence of allergic reactions. Treatment of allergic reactions involves stopping the transfusion and administering antihistamines. Some of these reactions are anaphylactic in nature and will require aggressive treatment, possibly including steroids, antihistamines, and epinephrine. IgA deficiency of the recipient should be considered after a severe allergic transfusion reaction has occurred. IgA-deficient individuals can develop anti-IgA antibodies that react with donor IgA resulting in an anaphylactic reaction. Use of IgA-deficient plasma or washed cellular products will be necessary for any future transfusions to recipients known to have IgA deficiency and anti-IgA antibodies [145,201].

Transfusion-related acute lung injury

Transfusion-related acute lung injury (TRALI) has historically been a leading cause of transfusion-related deaths [201]. TRALI is defined as new acute lung injury occurring during or within 6 h after a transfusion with a clear temporal relationship to the transfusion in patients with or without alternative risk factors for acute lung injury [213]. TRALI can occur after the administration of all types of blood components but is more likely after the transfusion of plasma-rich components such as FFP and apheresis platelets [214]. Two pathophysiological mechanisms have been proposed. In the "classical antibody mediated" mechanism (approximately 85% of cases), donor antileukocyte antibodies react with recipient leukocytes resulting in the release of inflammatory mediators that damage pulmonary alveolar epithelium and vascular endothelium leading to non-cardiogenic pulmonary edema. In approximately 15% of cases, however, no antibody can be detected. Systemic inflammatory conditions secondary to clinical scenarios such as major surgery, sepsis, trauma, aspiration, or massive transfusion lead to activation of leukocytes and pulmonary endothelium with subsequent leukocyte sequestration in the lungs. "Bioactive factors" such as cytokines, interleukins, or lipids in transfused products may then activate these sequestered leukocytes leading to lung injury and non-cardiogenic pulmonary edema [214].

The clinical presentation of TRALI mirrors that of acute respiratory distress syndrome (ARDS). Treatment is primarily supportive with recovery usually occurring within 96 h although the mortality rate is 5–10%. Diuresis does not improve symptoms and the role of steroids is unproven [152,214]. Plasma products from multiparous women have been implicated in the majority of cases of antibody-mediated TRALI because these donors may develop antileukocyte antibodies during pregnancies. Eliminating or minimizing the use of plasma products from these donors dramatically decreases the incidence of TRALI [145,214].

Transfusion-associated graft versus host disease

Transfusion-associated graft versus host disease (TA-GVHD) occurs when immunocompetent $CD8^+$ lymphocytes in transfused cellular blood products (RBCs, platelets, or granulocytes) engraft in a recipient, proliferate, and attack host tissues. This occurs when the recipient is immunocompromised and cannot eliminate the donor lymphocytes or when the recipient does not recognize the donor lymphocytes as foreign (biologically related donors or HLA-matched products) and thus does not eliminate them. Clinical manifestations include fever, rash, diarrhea, liver dysfunction, and pancytopenia and occur 1–6 weeks after transfusion. The diagnosis can be made by detecting donor DNA in a skin biopsy or in circulating lymphocytes taken from the recipient. Irradiating RBCs and platelets before their administration renders donor lymphocytes incapable of proliferating and thus eliminates the risk of the development of TA-GVHD. TA-GVHD is nearly uniformly fatal, with mortality rates approaching 90% [201,203].

Post-transfusion purpura

Post-transfusion purpura (PTP) is the development of severe thrombocytopenia after a transfusion in recipients who have developed antibodies against platelet-specific antigens as a result of previous transfusions or pregnancies. While PTP is a rare event, it can occur 5–10 days after the administration of RBCs, FFP, or platelets. Both transfused and autologous platelets are destroyed in this process thus severely decreasing the recipient's platelet count, even to below 10,000/μL. Recovery is usually spontaneous although treatment with steroids and IV immune globulin is indicated with plasmapheresis being a second-line intervention. Platelet transfusions are usually ineffective in raising the platelet count but, if felt necessary in the face of severe bleeding, may need to be administered in large doses since many of the transfused platelets also will be destroyed [201].

Transfusion-related immunomodulation

While the exact mechanism of transfusion-related immunomodulation (TRIM) has yet to be elucidated, modulation of the recipient's immune responses after transfusion may have both beneficial and harmful effects. Improved survival of transplanted kidneys has been documented in patients transfused before transplantation, as has survival of cardiac and liver transplant patients after pretransplant transfusion of donor-specific or HLA-DR-shared RBCs. TRIM may also decrease the recurrence rate of Crohn disease and of miscarriages in women who share HLA antigens with their mates. Evidence linking increased incidences of postoperative infections and cancer recurrence with transfusions, however, is controversial and not definitely proven. Theories of the etiology of TRIM indict leukocytes as major participants so harmful effects of transfusion that are blamed on TRIM may be ameliorated by prestorage leukocyte reduction of blood products [171,201,215].

Alloimmunization

Alloimmunization is the development of antibodies to minor RBC antigens or to platelet or leukocyte antigens after exposure by transfusion or pregnancy. Subsequent transfusion of blood products containing these antigens results in delayed HTRs or platelet refractoriness. Approximately two-thirds of clinically significant alloantibodies are directed toward Rh and Kell antigens on RBC surfaces. Up to 40% of children with sickle cell disease who are managed with chronic transfusion protocols develop alloantibodies. These children, therefore, should undergo extended RBC antigen phenotyping prior to the initiation of chronic transfusion therapy. Provision of PRBCs phenotypically matched for Rh and Kell antigens has been shown to decrease rates of alloimmunization from 3% per unit transfused to 0.5% per unit transfused [135]. Similarly, HLA-matched platelet units may be necessary for patients with platelet refractoriness and anti-HLA alloantibodies. These matched platelets, however, must be irradiated prior to transfusion to eliminate the risk of TA-GVHD due to the HLA similarity between donor and recipient [145,201,203].

Non-immune-mediated hazards of transfusion

Non-immune-mediated hazards of transfusion include septic transfusion reactions, non-immune hemolysis, transfusion-associated circulatory overload, metabolic derangements, complications from RBC storage lesions, and mistransfusion [201].

Septic transfusion reactions

Transfusion-associated bacterial sepsis occurs much less frequently than bacterial contamination of blood products. However, this is the most frequent cause of death from infectious agents acquired from blood product transfusion [202]. Gram-negative organisms are more likely to cause fatal infections. The institution in 2004 of mandatory testing of platelet units for bacterial contamination has resulted in a significant decrease in the incidence of post-transfusion sepsis. Ongoing improvements in blood component collection techniques and in the handling and storage of blood products have reduced this transfusion-related risk [151,152,200,201].

Non-immune hemolysis

Non-immune hemolysis of RBCs can result from improper storage of the blood unit, inadequate deglycerolization of frozen RBCs, thermal injury to RBCs by malfunctioning blood warmers, exposure of RBCs to hypotonic or hypertonic IV solutions, rapid transfusion through small-bore IV catheters, or processing techniques used during RBC salvage. This problem is usually preventable by strictly following established guidelines for storing, preparing, and transfusing RBCs [201].

Transfusion-associated circulatory overload

Transfusion-associated circulatory overload (TACO) is the development of cardiogenic pulmonary edema from volume

overload during transfusion. Infants and patients with cardiopulmonary compromise and renal failure are particularly susceptible to this risk. Diuretic administration, as well as slowing down the blood administration rate, may minimize TACO symptoms [201].

Metabolic derangements

Hyperkalemia, hypocalcemia, and hypothermia can accompany the transfusion of blood products. Hyperkalemia is a potential problem with PRBC administration because RBCs leak potassium into their storage solution over time. Potassium concentrations reach an average of 12 mEq/L after 7 days of storage and 32 mEq/L after 21 days of storage. Hyperkalemia can be a particular problem when transfusing neonates or in instances of massive transfusion because of the relative volume of PRBCs administered. Hyperkalemic cardiac arrest and deaths have been reported, due to faster rate of blood transfusion, rather than the total volume transfused [216].

The use of fresher PRBCs (<14 days old), transfusion into IV lines further away from the right atrium, correction of acidosis, administration of calcium to stabilize the myocardium, and administration of glucose and insulin to lower potassium levels are helpful with prevention and treatment.

Hypocalcemia from "citrate toxicity" may be a problem with administration of large volumes of plasma and platelets. These components have high citrate concentrations in their anticoagulant solutions. Citrate exerts its anticoagulant effect by binding ionized calcium. Neonates and infants are particularly prone to the development of hypocalcemia because their intracellular calcium reserves are limited. Treatment consists of the administration of calcium and slowing the infusion rate of the blood products. Citrate undergoes rapid hepatic metabolism so hypocalcemia associated with transfusion is a transient problem.

Hypothermia is a consequence of the rapid infusion of large amounts of inadequately warmed blood products. Hypothermia not only potentiates the cardiac toxicity of hyperkalemia and hypocalcemia but also is a component of the "lethal triad" of coagulopathy, hypothermia, and acidosis that can occur during massive hemorrhage and transfusion. Therefore, its occurrence should be aggressively prevented and/or treated [201].

Red blood cell storage lesions

The ability to store RBCs for up to 42 days provides blood distribution centers significant flexibility in managing the blood supply [199]. However, during this storage period, detrimental changes occur in RBCs themselves and in the RBC product as a unit. RBCs lose their deformability and increase their adhesiveness so that their passage through capillaries is impaired. Levels of 2,3-DPG fall so that the oxygen affinity of hemoglobin increases. Finally, concentrations of nitric oxide fall, possibly impairing vasodilation of blood vessels. Therefore, even though raising the hemoglobin level by transfusing RBCs allows more oxygen to be transported by blood, the sum of these effects may actually reduce the availability of this oxygen to tissues. These effects may be minimized by using PRBCs that are less than 14 days old [170,185,201].

Mistransfusion

Mistransfusion is the transfusion of the incorrect blood product to the incorrect recipient. It is the most common non-infectious complication of blood product transfusion. Approximately 30% of the errors leading to mistransfusion occur in the blood bank while 50% occur in clinical areas. Meticulous attention to detail when labeling blood samples and identifying blood products and recipients is critical to avoid the occurrence of this preventable hazard of blood transfusion [151,201]. As noted previously, electronic barcode identifying systems significantly reduce the incidence of this complication.

KEY POINTS: POTENTIAL HAZARDS OF TRANSFUSION

- Infectious disease transmission is now rare, but periodically new pathogens emerge, e.g. Zika virus
- Serious immune-mediated hemolytic transfusion reactions are most commonly due to clerical errors and can largely be prevented by electronic identification systems like barcoding
- Febrile non-hemolytic transfusion reactions, allergic reactions, transfusion-related acute lung injury, transfusion-associated graft versus host disease, transfusion-associated circulatory overload, and hyperkalemic cardiac arrest are additional risks of blood transfusion

Blood conservation

In light of the potential hazards posed by transfusing allogeneic blood products, efforts to minimize the necessity for transfusions should always be considered. These efforts may be especially important in patients who, for religious reasons (Jehovah's Witnesses), refuse blood product transfusion. Proactive blood conservation plans tailored to individual patients and their anticipated surgical procedures are essential for success but require significant forethought. Combining preoperative, intraoperative, and postoperative modalities will offer the best chance for a positive impact.

Preoperative modalities

Personal and family histories of bleeding disorders should be sought and investigated prior to surgery. Indicated laboratory tests should be performed well enough in advance to allow preoperative action based on the results. Causes of anemia should be investigated. Anticoagulant and antiplatelet drugs should be discontinued, if feasible, for an appropriate interval before surgery.

Preoperative anemia is a major risk factor in determining the need for perioperative allogeneic blood transfusion [171,217]. This risk may be reduced by the preoperative administration of erythropoietin, a hormone produced by the kidneys that acts on erythroblast precursor cells in the bone marrow to accelerate the production of mature erythrocytes and thus increase hemoglobin levels [218]. Recombinant human erythropoietin has been shown to increase preoperative hemoglobin levels in infants and children prior to a variety of surgical procedures [218–220]. However, it is expensive, it must be repeatedly injected intravenously or subcutaneously over a period of several weeks preoperatively, and its

use must be accompanied by iron supplementation. The most significant preoperative use of erythropoietin may be to increase hemoglobin levels in anticipation of preoperative autologous blood donation or intraoperative acute normovolemic hemodilution [220–223].

Preoperative autologous blood donation (PABD) is the preoperative collection of blood for transfusion back to the same donor in the perioperative period. PABD may be useful in children undergoing elective surgical procedures in which the likelihood of transfusion is substantial and in children who have rare blood groups or alloantibodies to high-incidence antigens. PABD decreases exposure to allogeneic blood products and has been used in a wide variety of surgical procedures in children as young as 3 months of age [221,224–226]. As with erythropoietin, the use of PABD requires time and forethought. Depending on the size of the child and the anticipated surgical blood loss, several donations may be collected but the donations should be completed far enough in advance of surgery to allow the patient's hemoglobin level to recover prior to surgery. Estimations of the volume of blood to be collected at each donation have been based on a percentage (15%) of estimated blood volume (EBV), a defined amount (10 mL) per kg bodyweight, a weight-corrected proportion of an adult unit of blood ([weight/50 kg] × 450 mL), and on formulas to keep the child's postdonation hematocrit above 30% (EBV × [initial Hct − 30]/average Hct with average Hct = (initial Hct − 30)/2) [224]. PABD should not be used in children with active infections, anemia, or limited cardiopulmonary reserves. Vascular access issues may limit the use of PABD in young infants [220,221]. This problem has been circumvented in some children prior to cardiac surgery by obtaining autologous blood from the large-bore vascular sheaths used during preoperative diagnostic catheterization [226]. The use of blood collected from PABD still carries risks from clerical errors and bacterial contamination, so appropriate indications should dictate its retransfusion while its automatic administration back to the donor without indications should be avoided [227].

Intraoperative modalities

Surgical technique obviously plays a role in limiting intraoperative blood loss and exposure to allogeneic blood transfusions. Direct control of bleeding vessels is essential and infiltration of local vasoconstrictors into surgical wound edges, use of tourniquets, patient positioning to elevate the surgical site, and use of topical clotting agents may all be important [215].

Anesthesiologists can also play helpful roles in minimizing perioperative exposure to allogeneic blood products. Maintenance of normothermia is important to prevent hypothermia-induced dysfunction of platelets and coagulation factors. Controlled hypotension techniques may help reduce intraoperative blood loss. Reinfusion of RBCs salvaged from the operative field may minimize effective blood loss but should not be used during cancer surgery, in patients with active infections, or after application of topical clotting agents. Tolerating lower hemoglobin levels and basing decisions to initiate transfusion on indicators such as the development of lactic acidosis or hemodynamic lability may avoid transfusion in some cases. Administration of increased inspired oxygen concentrations will increase dissolved oxygen in blood and help maintain adequate oxygen delivery to tissues when lower hemoglobin levels are being allowed. The use of acute normovolemic hemodilution (ANH) or antifibrinolytic agents may also be considered [171].

ANH involves the intraoperative collection of blood for reinfusion at the end of surgery. Blood is withdrawn from a patient after anesthetic induction while isovolemia is maintained by infusing crystalloid (3:1 volume replacement) and/or colloid (1:1 volume replacement). Subsequently, blood with a lower hemoglobin level is lost intraoperatively and safe, fresh autologous blood with a higher hemoglobin level and functioning coagulation factors and platelets is available for reinfusion once blood loss is controlled. The amount of blood to be withdrawn can be calculated using the formula EBV × (initial Hct − target Hct)/average Hct where average Hct = (initial Hct − target Hct)/2 [227]. ANH may be considered when surgical blood loss is anticipated to exceed 15% of a child's EBV and the child has a baseline hematocrit exceeding 35% and adequate cardiopulmonary reserve to tolerate lowering of the hematocrit. ANH has been used in children as young as 7 months of age and in surgeries ranging from posterior spinal fusions to abdominal surgery, cancer surgery, and bone marrow harvesting [224]. ANH offers advantages over PABD in that it may be performed on the day of surgery for both elective and emergency procedures, it may be performed after adequate vascular access is obtained in an anesthetized child, and it is associated with lower administrative costs [228]. Blood withdrawn during ANH may be stored for up to 8 h at room temperature and, if more than one bag of blood was withdrawn, should be reinfused in the reverse order of collection [224]. Therefore, blood with the highest hematocrit (the first unit collected) will be reinfused after bleeding has been controlled.

Antifibrinolytic agents include aprotinin and the lysine analogs, ε-aminocaproic acid (EACA) and tranexamic acid (TA). Although aprotinin, a serine protease inhibitor, is remarkably effective in reducing perioperative blood loss and transfusion exposure, its marketing was suspended in 2007 after concerns about adverse renal, cardiovascular, and cerebrovascular effects and increased postoperative mortality were raised in adults in whom it was administered during cardiac surgery [229–232]. Studies in neonates and children undergoing cardiac surgery have not documented similar concerns [233–236], and aprotinin has been relicensed for use in myocardial revascularization procedures in Europe and Canada [237]. We are still awaiting reconsideration of its use in children.

EACA and TA exert their antifibrinolytic effect most importantly by binding with the lysine-binding sites of plasminogen and plasmin. This reversible binding alters plasminogen's conformation, precludes its association with fibrin, and prevents its conversion to its active form, plasmin, while also inhibiting the activity of plasmin on fibrin [238,239]. These drugs have been shown to decrease blood loss and allogeneic blood transfusion in cyanotic children undergoing cardiac surgery [240–243], in children undergoing repeat sternotomies for cardiac surgery [142], and in children undergoing posterior spinal fusion for idiopathic or secondary scoliosis [244–246]. They have also been shown to have beneficial effects in adults undergoing liver transplantation [247,248] and total knee

replacement [249,250] and thus would probably be beneficial for similar types of surgeries in children. These drugs may also be helpful in preventing clot lysis in patients with vWD or hemophilia after hemostasis has been achieved with appropriate factor replacement therapy, especially with bleeding from mucous membranes [71,82]. Evidence points to TA being more effective than EACA in its hemostatic effects [251]. Appropriate dosing regimens remain an unresolved issue for both of these drugs. While no thrombotic complications have been reported with their use, an increased incidence of postoperative seizures has been reported with TA use in adults undergoing cardiac surgery [252,253].

Postoperative modalities

Efforts to minimize exposure to allogeneic blood products should continue into the postoperative period. Useful strategies include limiting blood sampling to necessary tests and continued use of restrictive transfusion thresholds to trigger RBC transfusions. Reinstitution of postoperative anticoagulant or antiplatelet therapies should begin only after correction of coagulopathies acquired intraoperatively. Future considerations include development of appropriate coagulation test-based transfusion algorithms to guide blood component use and the development of safe artificial oxygen carriers to limit RBC transfusions.

KEY POINTS: BLOOD CONSERVATION

- Combining preoperative, intraoperative, and postoperative blood conservation strategies creates maximal impact
- Preoperative approaches include the use of erythropoietin and autologous blood donation
- Intraoperatively, acute normovolemic hemodilution, RBC salvage, antifibrinolytic drugs, and controlled hypotensive techniques may be helpful
- Postoperative efforts include the use of restrictive transfusion thresholds and transfusion algorithms to guide component use

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A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 13
Cardiopulmonary Resuscitation

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Introduction

Pediatric cardiac arrest is not a rare event. While cardiac arrest survival outcomes have improved over the last decade, more than half of these children who initially have return of spontaneous circulation (ROSC) do not live to hospital discharge, and new significant neurofunctional morbidity is common among survivors [1–7]. Death from cardiac arrest accounts for the loss of up to 400,000 quality of life years annually in the United States. While research and quality improvement projects continue to improve the field, less than 5% of existing pediatric cardiopulmonary resuscitation (CPR) guidelines are supported by high-quality evidence [8]. Furthermore, despite mounting evidence that the immature brain's response to acute injury is markedly different than that of the mature brain, there is a paucity of research investigating secondary injury mechanisms specific to infants and children following cardiac arrest. This chapter focuses on pediatric cardiac arrest, cardiopulmonary resuscitation, and other therapeutic interventions that have been specifically designed to improve outcomes from pediatric cardiac arrest.

Epidemiology of pediatric cardiac arrest

Cardiovascular disease remains the most common cause of disease-related death in the United States, resulting in approximately one million deaths per year [9]. It is estimated that more than 400,000 Americans will suffer a cardiac arrest each year, nearly 90% in prehospital settings. The true incidence of pediatric cardiac arrest is difficult to determine due to inconsistencies in reporting, as well as difficulties with identifying and defining pediatric cardiac arrest. Specifically, the determination of pulselessness in children with poor perfusion is difficult [10] and the indication for beginning CPR for bradycardia with poor perfusion complicates definitions pertaining to pediatric in-hospital cardiac arrest (IHCA) [11]. Regardless, based on cardiac arrest registries and administrative databases, more than 6000 children receive CPR in the United States annually [12,13]. This amounts to 0.77 children receiving CPR per 1000 hospital admissions [12]. Due in part to the widespread implementation of rapid response systems in most children's hospitals [14–16] and the recognition of at-risk inpatients, >95% of CPR events in the United States occur in intensive care units (ICUs) [2]. The prevalence of CPR among one cohort of academic children's hospitals was 1.4% from 2010 to 2013, compared to 1.8% reported in the 1990s [13]. In pediatric cardiac ICUs, however, cardiac arrests are reported in 3–6% of patients [17,18].

Survival to hospital discharge following pediatric IHCA improved from 13.7% in the 1990s [13] to 22% in an American Heart Association (AHA) Get With The Guidelines-Resuscitation (GWTG-R) registry study from 2006 [19]. Additional GWTG-R data demonstrated an improvement in rates of ROSC from 39% to 78%, and survival to hospital discharge from 24% to 43% between 2001 and 2009 [4]. A more recent multicenter study of IHCA events in pediatric ICUs revealed that 78% of children attained ROSC and 45%

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

survived to hospital discharge [1]. Furthermore, while the likelihood of survival falls with increasing duration of CPR, the decision to end resuscitative efforts during a prolonged CPR event is complicated for practitioners. Due to improvements in CPR techniques, it is now clear that prolonged CPR is not uniformly futile. Factors that influence outcome from pediatric cardiac arrest include: (1) the pre-existing condition of the child; (2) the environment in which the arrest occurs; (3) the initial electrocardiographic (ECG) rhythm detected; (4) the duration of no-flow time (the time during an arrest without spontaneous circulation or CPR); (5) the quality of the life-supporting therapies provided during the resuscitation; and (6) the quality of life-supporting therapies following resuscitation [19–22].

The underlying etiologies of cardiac arrest and initial rhythm are closely related and have a substantial impact on outcome [1,20]. Whereas adult cardiac arrest is frequently associated with coronary ischemia and primary ventricular arrhythmias [23], pediatric IHCAs are most often due to progressive respiratory insufficiency and circulatory shock [1,20]. Additionally, the initial rhythm in pediatric CPR events is most commonly asystole, pulseless electrical activity (PEA), or bradycardia with poor perfusion [4,20]. Ventricular fibrillation (VF) or pulseless ventricular tachycardia (pVT) occurs as the initial cardiac arrest rhythm in 10–15% of pediatric IHCAs [4,20,24,25]. Notably, VF or pVT occurs as a secondary rhythm in approximately 15% of pediatric IHCAs. Whereas primary VF and pVT are favorable rhythms that are associated with improved rates of survival when compared to asystole or PEA, secondary VF or pVT carries the highest relative risk of mortality [20,25].

Not surprisingly, outcomes after pediatric out-of-hospital arrests are much worse than those after in-hospital arrests [26–36]. This may be due to the fact that there is a prolonged period of no flow in out-of-hospital arrests, where many of the pediatric cardiac arrests are not witnessed and only 30% of children are provided with bystander CPR. As a result of these factors, less than 10% of pediatric out-of-hospital cardiac arrests (OHCA) survive to hospital discharge, and among those who survive, severe neurological injury is common. These findings are especially troublesome given that bystander CPR more than doubles patient survival rates in adults [37]. An exciting prospective, nationwide, population-based cohort study from Japan similarly demonstrated more than doubling of survival rates for children who had OHCA and received bystander CPR either with conventional CPR (with rescue breathing) or chest compression-only CPR compared to no bystander CPR [38]. The same study then further stratified outcomes for OHCA into "cardiac" and "non-cardiac" causes for arrest, and defined the relative value of rescue breathing during CPR by bystanders. Pediatric patients who had OHCA with non-cardiac causes and received bystander conventional CPR (including rescue breathing) had an association with a higher frequency of favorable neurological outcomes at 1 month after arrest compared to compression-only bystander CPR or no bystander CPR. For pediatric arrests defined as "cardiac" in nature, bystander CPR (conventional or compression-only) was associated with a higher rate of favorable neurological outcomes 1 month after arrest compared to no bystander CPR. Interestingly, the two types of bystander CPR (conventional or compression-only) seemed to be similarly effective for pediatric cardiac arrests with cardiac causes, consistent with animal and adult studies [38].

Survival outcomes after IHCA are higher in the pediatric population compared with adults: 27% of children survive to hospital discharge compared with only 17% of adults [20]. For both children and adults, outcomes are better after arrhythmogenic arrests, from ventricular fibrillation/ventricular tachycardia (VF/VT). Importantly, pediatric IHCAs are less commonly caused by arrhythmias (10% of pediatric arrests versus 25% of adult arrests), and approximately one-third of children and adults with these arrhythmogenic arrests survive to hospital discharge. Interestingly, the superior pediatric survival rate following IHCA reflects a substantially higher survival rate among children with asystole or pulseless electrical activity (PEA) compared with adults (24% versus 11%). Further investigations have shown that the superior survival rate seen in children is mostly attributable to a much better survival rate among infants and preschool age children compared with older children [19]. Although speculative, the higher survival rates in children may be due to improved coronary and cerebral blood flow during CPR because of increased chest compliance in these younger arrest victims, with improved aortic diastolic pressure and venous return [39,40]. In addition, survival of pediatric patients from IHCA is more likely in hospitals staffed with dedicated pediatric physicians [41].

KEY POINTS: EPIDEMIOLOGY OF PEDIATRIC CARDIAC ARREST

- Cardiac arrest is reported in 1.4% of patients in pediatric ICUs, versus 3–6% of patients in pediatric cardiac ICUs
- Some 78% of children attained ROSC and 45% survived to hospital discharge after cardiac arrest in pediatric ICUs
- Due to improvements in CPR techniques, it is now clear that prolonged CPR is not uniformly futile
- The superior pediatric survival rate following in-hospital cardiac arrest reflects a substantially higher survival rate among children with asystole or pulseless electrical activity compared with adults (24% versus 11%)

Phases of resuscitation

The four distinct phases of cardiac arrest and CPR interventions are: (1) prearrest, (2) no flow (untreated cardiac arrest), (3) low flow (CPR), and (4) postresuscitation/arrest. Interventions to improve outcome of pediatric cardiac arrest should optimize therapies targeted to the time and phase of CPR, as suggested in Table 13.1.

Prearrest

The prearrest phase refers to any relevant pre-existing conditions of the child (e.g. neurological, cardiac, respiratory, or metabolic problems) and precipitating events (e.g. respiratory

Table 13.1 Phases of cardiac arrest and resuscitation

Phase	Interventions
Prearrest (Protect)	Optimize community education regarding child safety
	Optimize patient monitoring and rapid emergency response
	Train in-hospital METs and Rapid Response Teams
	Recognize and treat respiratory failure and/or shock to prevent cardiac arrest
	Transfer patients to skilled pediatric centers
Arrest (no-flow) (Preserve)	Minimize interval to BLS and ACLS (organized response)
	Minimize interval to defibrillation, when indicated
Low-flow (CPR) (Resuscitate)	Push hard, push fast
	Allow full chest recoil
	Minimize interruptions in compressions (15:2)
	Avoid overventilation
	Titrate CPR to optimize myocardial blood flow (coronary perfusion pressures and exhaled CO_2)
	Consider ECPR if standard CPR/ACLS not promptly successful (within 2–5 min) if available
Postresuscitation short-term (Metabolic Delivery)	Optimize cardiac output and cerebral perfusion
	Treat arrhythmias, if indicated
	Avoid hyperglycemia, hyperthermia, hyperventilation, hypoxemia, and hyperoxia
	Treat fever aggressively
	Continual quality improvement for future responses to emergencies
Postresuscitation phase	Early intervention with physical medicine and rehabilitation
Longer-term rehabilitation (Regenerate)	Bioengineering and technology interface
	Possible future role for stem cell transplantation

ACLS, advanced cardiac life support; BLS, basic life support; CPR, cardiopulmonary resuscitation; ECPR, extracorporeal membrane oxygenation assisted cardiopulmonary resuscitation; METs, medical emergency teams.

failure or shock) uncoupling metabolic delivery and metabolic demand. Pediatric patients who suffer an IHCA often have changes in their physiological status in the hours leading up to their arrest event [42,43]. Therefore, interventions during the prearrest phase focus on preventing the cardiac arrest, with special attention to early recognition and targeted treatment of respiratory failure and shock. Early recognition plays a key role in identifying a prearrest state in children, who unlike adults may be able to mount a prolonged physiological response to a worsening clinical picture. Medical Emergency Teams (METs) (also known as Rapid Response Teams) are in-hospital emergency teams designed specifically for this purpose. Front-line providers, and even parents, are encouraged to initiate evaluation by METs based on physiological protocol-driven parameters or even intuition. Patients are assessed by the METs and those at high risk of clinical decompensation are transferred to a pediatric intensive care unit if necessary, with the goal to prevent progression to full cardiac arrest or to decrease the response time to initiation of advanced life support, thereby limiting the no flow state. Implementation of METs decreases the frequency of cardiac arrests compared with retrospective control periods before MET initiation [16,44,45]. While early recognition protocols cannot identify all children at risk for cardiac arrest, it seems reasonable to assume that transferring critically ill children to an ICU early in their disease process for better monitoring and more aggressive interventions can improve resuscitative care and clinical outcomes. The caveat is that prearrest states must be identified to initiate monitoring and interventions that may inhibit the progression to an arrest. While a significant amount of research dollars and resources are spent on the other phases of cardiac arrest, particular focus on the prearrest state may yield the greatest improvement in survival and neurological outcomes.

In highly monitored settings such as a pediatric cardiac ICU, new approaches using real-time predictive analytics may be able to identify patients at highest risk for cardiopulmonary deterioration. Using a retrospective analysis of high-resolution physiological recordings, a risk index consisting of heart rate and heart rate variability, respiratory rate variability, ST segment variability, and SpO_2, a logistic regression model was created in 25 single-ventricle infants after neonatal cardiac surgery, mostly Stage I palliation for hypoplastic left heart syndrome. Twenty cardiorespiratory deterioration events (respiratory failure or arrest, or cardiac arrest) were identified in 13 patients, and an increased risk index 1–2 h before the event could detect an impending arrest with high reliability (receiver operator curve (ROC) area 0.91) [46]. In the same group of patients, utilizing three-dimensional ST-segment vector magnitude and instability alone in the 4 h window before arrest also predicted the event (ROC area 0.81) [47]. If these algorithms were validated prospectively to predict cardiac arrest in these vulnerable patients, crucial improvements in early warning could occur in monitored settings.

No flow/low flow

In order to improve outcomes from pediatric cardiac arrest, it is imperative to shorten the no-flow phase of untreated cardiac arrest. To that end, it is important to monitor high-risk patients to allow early recognition of the cardiac arrest and prompt initiation of basic and advanced life support. Effective CPR optimizes coronary perfusion pressure (by elevating aortic diastolic pressure relative to right atrial pressure) and cardiac output to critical organs to support vital organ viability (by elevating mean aortic pressure) during the low-flow phase. Important tenets of basic life support are: push hard, push fast, allow full chest recoil between compressions, and minimize interruptions of chest compression. The myocardium receives blood flow from the aortic root, mainly during diastole, via the coronary arteries. When the heart arrests and no blood flows through the aorta, coronary blood flow ceases. However, during chest compressions, aortic pressure rises at the same time as right atrial pressure and with the subsequent decompression phase of chest compressions, the right atrial pressure falls faster and lower than the aortic pressure, which generates a pressure gradient that perfuses the heart with oxygenated blood. Therefore, full elastic recoil (release) is critical to create a pressure difference between the aortic root and the right atrium. A coronary perfusion pressure (CPP) below 15 mmHg during CPR is a poor prognostic factor for ROSC. Higher values are associated with increased likelihood of ROSC in experimental and clinical settings

[48–51]. Thus, while chest compressions primarily serve to provide an interim source of cardiac output during cardiac arrest, vasopressor administration specifically targets the augmentation of systemic vascular resistance to increase CPP and facilitate ROSC. Achieving optimal CPP, exhaled CO_2 concentration, and cardiac output during the low-flow phase of CPR is consistently associated with an improved chance for ROSC and improved short- and long-term outcome in mature animal and human studies [48,51–57]. There is a critical need for research evaluating goal-directed CPR, both in immature animal models and pediatric patients. Other measures essential for truncating the no-flow phase during VF and pulseless VT are rapid detection and prompt defibrillation. Clearly, CPR alone is inadequate for successful resuscitation from these arrhythmias. For cardiac arrests resulting from asphyxia and/or ischemia, provision of adequate myocardial perfusion and myocardial oxygen delivery are the critical elements for ROSC.

Postarrest/resuscitation

The postarrest/resuscitation phase includes coordinated, skilled management of the immediate postresuscitation stage, the next few hours to days, and long-term rehabilitation. The immediate postresuscitation stage is a high-risk period for ventricular arrhythmias and other reperfusion injuries. Goals of interventions implemented during the immediate postresuscitation stage and the next few days include: adequate tissue oxygen delivery, treatment of postresuscitation myocardial dysfunction, and minimizing postresuscitation tissue injury (e.g. preventing postresuscitation hyperthermia and hypoglycemia; and, perhaps, initiating postresuscitation therapeutic hypothermia, preventing hyperglycemia, and avoiding hyperoxia). This postarrest/resuscitation phase may have the greatest potential for innovative advances in the understanding of cell injury (excitotoxicity, oxidative stress, metabolic stress) and cell death (apoptosis and necrosis) ultimately leading to novel molecular-targeted interventions. The rehabilitation stage concentrates on salvage of injured cells and support for reengineering of reflex and voluntary communications of these cell and organ systems to improve long-term functional outcome.

The specific phase of resuscitation dictates the focus of care. Interventions that improve outcome during one phase may be deleterious during another. For instance, intense vasoconstriction during the low-flow phase of cardiac arrest improves coronary perfusion pressure and the probability of ROSC. The same intense vasoconstriction during the postresuscitation phase increases left ventricular afterload and may worsen myocardial strain and dysfunction. Current understanding of the physiology of cardiac arrest and recovery allows us only to crudely manipulate blood pressure, oxygen delivery and consumption, body temperature, and other physiological parameters in our attempts to optimize outcome. Future strategies likely will take advantage of increasing knowledge of cellular injury, thrombosis, reperfusion, mediator cascades, cellular markers of injury and recovery, and transplantation technology, including stem cells.

KEY POINTS: PHASES OF RESUSCITATION

- The four phases of cardiac arrest and CPR are: (1) prearrest, (2) no flow (untreated cardiac arrest), (3) low flow (CPR), and (4) postresuscitation/arrest
- Interventions during the prearrest phase focus on preventing cardiac arrest, with early recognition and treatment of respiratory failure and shock
- The important tenets of basic life support are: push hard, push fast, allow full chest recoil between compressions, and minimize interruptions
- Goals during the postresuscitation stage include: adequate tissue oxygen delivery, treatment of myocardial dysfunction, and minimizing tissue injury (e.g. preventing hyperthermia and hypoglycemia, and preventing hyperglycemia and avoiding hyperoxia)

Interventions during the cardiac arrest (no-flow) and cardiopulmonary resuscitation (low-flow) phases

The components of high-quality CPR are: (1) ensuring adequate rate of chest compressions; (2) ensuring adequate depth of chest compressions; (3) allowing full chest recoil between chest compressions; (4) minimizing interruptions in chest compressions; and (5) avoiding excessive ventilation [58].

A-B-C or C-A-B

For OHCA victims, "compression-only" CPR has been associated with improved outcomes [59,60]. This is now the recommended modality for emergency medical service dispatcher instructing bystander CPR [61]. In a recent Japanese study, children with OHCA due to a primary cardiac etiology displayed an equivalent survival rate between compression-only CPR and classic CPR with rescue breaths. However, only 29% of patients had a cardiac cause of OHCA. Those with non-cardiac etiology in the overall cohort had a significantly worse survival rate with compression-only CPR, as compared to classic CPR with rescue breaths [40]. Additionally, in another nationwide Japanese OHCA registry study, compression-only CPR was superior to no bystander CPR at all but not to conventional CPR [62]. In a recent American OHCA registry study, children who received conventional bystander CPR with chest compressions and rescue breaths had improved rates of overall survival and survival with favorable outcomes as compared to those who did not receive CPR, whereas those receiving compression-only CPR did not fare any better than children not receiving CPR [63]. Thus, compression-only CPR is not recommended for children in either the inpatient or out-of-hospital setting, except in situations in which "rescuers are unwilling or unable to deliver breaths" [58].

Regardless, the prioritization of initial interventions during CPR has shifted from Airway-Breathing-Circulation ("A-B-C") to Circulation-Airway-Breathing ("C-A-B") in order to prevent harmful delays in the initiation of chest compressions and due to the relative complexity of the tasks involved in providing assisted ventilation. This is endorsed by both the

2010 and 2015 AHA BLS Guidelines [58,64]. However, a 2015 International Liaison Committee on Resuscitation consensus statement identified a paucity of pediatric-specific evidence to support this recommendation [65]. In our opinion, the approach is physiologically sound, especially given the association of delayed chest compression initiation with poor outcomes. With that said, the pediatric provider must consider the predominance of asphyxia and hypoxemia as precursors to cardiac arrest [1,20]. This is especially true in the ICU and operating room, where personnel and other resources frequently allow for simultaneous circulatory support with high-quality chest compressions as well as the provision of assisted ventilations by experienced personnel.

Airway and breathing

Establishing an airway with effective gas exchange as soon as possible is critical for the success of resuscitation. Establishing a patent airway with bag-valve-mask ventilation and 100% oxygen is an initial step in resuscitation, followed by endotracheal intubation as soon as possible, with minimal interruption in chest compressions. Colorimetric CO_2 detectors for exhaled gas are standard of care for pediatric CPR [41]. Absence of CO_{2in} exhaled gas may mean the endotracheal tube is in the esophagus, or that CPR is ineffective and there is no, or very low pulmonary blood flow for gas exchange to occur. If CO_2 is absent, direct laryngoscopy by an experienced clinician is performed immediately. If the tube is properly positioned in the trachea, attention is turned to the effectiveness of chest compresions. Persistence of adequate levels of end-tidal CO_2 during CPR is a favorable prognostic factor for ROSC [42,43].

During CPR, cardiac output and pulmonary blood flow are approximately 10–25% of those during normal sinus rhythm; therefore, a lower minute ventilation is necessary for adequate gas exchange from the blood traversing the pulmonary circulation. Animal and adult data indicate that hyperventilation ("overventilation" from exuberant rescue breathing) during CPR is common and can substantially compromise venous return and subsequently cardiac output [66–68]. These detrimental hemodynamic effects are compounded when one considers the effect of interruptions in CPR to provide airway management and rescue breathing and may contribute to worse survival outcomes [69–72]. While overventilation is problematic, in light of the fact that most pediatric arrests are asphyxial in nature (90% of arrests begin with respiratory insufficiency), immediate initiation of *adequate* ventilation is still important. The difference between arrhythmogenic and asphyxial arrests lies in the physiology. In animal models of sudden VF cardiac arrest, acceptable PaO_2 and $PaCO_2$ persist for 4–8 min during chest compressions without rescue breathing [73,74]. This is in part because aortic oxygen and CO_2 concentrations at the onset of the arrest do not vary much from the prearrest state with no blood flow and minimal aortic oxygen consumption. The lungs act as a reservoir of oxygen during the low-flow state of CPR; therefore, adequate oxygenation and ventilation can continue without rescue breathing. Several retrospective studies of witnessed VF cardiac arrest in adults have also shown that outcomes are similar after bystander-initiated CPR with either chest compressions alone or chest compressions plus rescue breathing [49]. However, during asphyxial arrest, peripheral and pulmonary blood flow continues during the prearrest state resulting in significant arterial and venous oxygen desaturation, elevated lactate levels, and depletion of the pulmonary oxygen reserve. Therefore, at the onset of CPR, there is substantial arterial hypoxemia and resulting acidemia. In this circumstance, rescue breathing with controlled ventilation can be a life-saving maneuver. In contrast, the adverse hemodynamic effects from overventilation during CPR combined with possible interruptions in chest compressions to open the airway and deliver rescue breathing are a lethal combination in certain circumstances such as VT/VF arrests. In short, the resuscitation technique should be titrated to the physiology of the patient to optimize patient outcome, with rapid, efficient, skilled airway management with minimal interruption of chest compressions a cornerstone of success in pediatric resuscitation.

Circulation

Optimizing blood flow during low-flow cardiopulmonary resuscitation: push hard, push fast

When the heart arrests, no blood flows to the aorta and coronary blood flow ceases immediately [49]. At that point, provision of high-quality CPR (push hard, push fast) is vital to re-establish coronary flow. The goal during CPR is to maximize the myocardial perfusion pressure (MPP). Related by the equation MPP = aortic diastolic blood pressure (AoDP) minus right atrial pressure (RAP), myocardial blood flow improves as the gradient between AoDP and RAP increases. During the downward compression phase, aortic pressure rises at the same time as RAP with little change in the MPP. However, during the decompression phase of chest compressions, RAP falls faster and lower than the aortic pressure, which generates a pressure gradient perfusing the heart with oxygenated blood during this artificial period of "diastole." Several animal and human studies have demonstrated, in both VT/VF and asphyxial models, the importance of establishing MPP as a predictor for short-term survival outcome (ROSC) [51,75–78]. Because there is no flow without chest compressions, it is important to minimize interruptions in chest compressions. To allow good venous return in the decompression phase of external cardiac massage, it is also important to allow full chest recoil and to avoid overventilation (preventing adequate venous return because of increased intrathoracic pressure).

Based on the equation in the previous paragraph, MPP can be improved by strategies that increase the pressure gradient between the aorta and the right atrium. As an example, the inspiratory impedence threshold device (ITD) is a small, disposable valve that can be connected directly to the tracheal tube or facemask to augment negative intrathoracic pressure during the inspiratory phase of spontaneous breathing and the decompression phase of CPR by impeding airflow into the lungs. Application in animal and adult human trials of CPR has established the ability of the ITD to improve vital organ perfusion pressures and myocardial blood flow [72,79–83]; however, in the only randomized trial during adult CPR, mortality benefit was limited to the subgroup of patients with PEA [83]. Additional evidence that augmentation of negative intrathoracic pressure can improve perfusion pressures

during CPR comes from the active compression-decompression device (ACD). The ACD is a handheld device that is fixed to the anterior chest of the victim by means of suction similar to a household plunger that can be used to apply active decompression forces during the release phase, thereby creating a vacuum within the thorax. By actively pulling during the decompression phase, blood is drawn back into the heart by the negative pressure [84]. Animal and adult studies have demonstrated that the combination of ACD and ITD acts in concert to further improve perfusion pressures during CPR compared to ACD alone [81]. In the end, while novel interventions such as the ITD and ACD are promising adjuncts to improve blood flow during CPR, the basic tenets of *push hard, push fast, allow full chest wall release, minimize interruptions, and don't overventilate* are still the dominant factors to improve blood flow during CPR and chance of survival.

Chest compression depth

The pediatric chest compression depth recommendation of at least one-third anterior–posterior (AP) chest depth (approximately 4 cm in infants and 5 cm in children) is based largely upon expert clinical consensus, using data extrapolated from animal, adult, and limited pediatric data. In a small study of six infants, chest compressions targeted to one-half AP chest depth resulted in improved systolic blood pressures compared to those targeted at one-third AP chest depth [85]. While only a small series with qualitatively estimated chest compression depths, this is the first study to collect actual data from children supporting the existing chest compression depth guidelines. In contrast, two studies using computed axial automated tomography (CT) [86,87] suggest that depth recommendations based on a relative percentage of AP chest compression depth are deeper than those recommended for adults, and that a depth of one-half AP chest depth will result in direct compression to the point of fully emptying the heart and requisite shifting of the heart because of inadequate AP diameter reserve in most children. Future studies that collect data from actual children and that associate quantitatively measured chest compression depths with short- and long-term clinical outcomes (arterial blood pressure, end tidal CO_2, ROSC, survival) are needed.

Compression/ventilation ratios

The amount of ventilation provided during CPR should match, but not exceed, perfusion and should be titrated to the amount of circulation during the specific phase of resuscitation as well as the metabolic demand of the tissues. Therefore, during the low-flow state of CPR when the amount of cardiac output is roughly 10–25% of normal, less ventilation is needed [88]. However, the best ratio of compressions to ventilations in pediatric patients is largely unknown and depends on many factors including the compression rate, the tidal volume, the blood flow generated by compressions, and the time that compressions are interrupted to perform ventilation. Recent evidence demonstrates that a compression/ventilation ratio of 15:2 delivers the same minute ventilation and increases the number of delivered chest compressions by 48% compared to CPR at a compression/ventilation ratio of 5:1 in a simulated pediatric arrest model [89,90]. This is important because, when chest compressions cease, the aortic pressure rapidly decreases and coronary perfusion pressure falls precipitously, thereby decreasing myocardial oxygen delivery [49]. Increasing the ratio of compressions to ventilations minimizes these interruptions, thus increasing coronary blood flow. The benefits of positive pressure ventilation (increased arterial content of oxygen and CO_2 elimination) must be balanced against the adverse consequence of decreased circulation. These findings are in part the reason why the AHA now recommends a pediatric compression/ventilation ratio of 15:2 for two rescuers and 30:2 for a single rescuer.

Duty cycle

In a model of human adult cardiac arrest, cardiac output and coronary blood flow are optimized when chest compressions last for 30% of the total cycle time (approximately 1:2 ratio of time in compression to time in relaxation) [91]. As the duration of CPR increases, the optimal duty cycle may increase to 50%. In a juvenile swine model, a relaxation period of 250–300 ms (duty cycle of 40–50% at a compression rate of 120 per min) correlates with improved cerebral perfusion pressures compared with shorter duty cycles of 30% [92].

Circumferential versus focal sternal compressions

In adult and animal models of cardiac arrest, circumferential (vest) CPR has been demonstrated to dramatically improve CPR hemodynamics [93]. In smaller infants, it is often possible to encircle the chest with both hands and depress the sternum with the thumbs, while compressing the thorax circumferentially (thoracic squeeze). In an infant animal model of CPR, this "two-thumb" method of compression with thoracic squeeze resulted in higher systolic and diastolic blood pressures and a higher pulse pressure than traditional two-finger compression of the sternum [94]. Although not rigorously studied, our clinical experience indicates that it is very difficult to attain adequate chest compression force and adequate aortic pressures with the two-finger technique, so we fully support the AHA guidelines for healthcare providers to perform CPR on infants with the two-thumb encircling hands technique [95].

Open-chest cardiopulmonary resuscitation

In animal models, high-quality standard, closed-chest CPR generates myocardial blood flow that is >50% of normal, cerebral blood flow that is approximately 50% of normal, and cardiac output ~10–25% of normal [49,76,96,97]. By contrast, open-chest CPR can generate myocardial and cerebral blood flow that approaches normal. Although open-chest massage improves coronary perfusion pressure and increases the chance of successful defibrillation in animals and humans [98–100], performing a thoracotomy to allow open-chest CPR is impractical in many situations. A retrospective review of 27 cases of CPR following pediatric blunt trauma (15 with open-chest CPR and 12 with closed-chest CPR) demonstrated that open-chest CPR increased hospital cost without altering rates of ROSC or survival to discharge. However, survival in both groups was 0%, indicating that the population may have been too severely injured or too late in the process to benefit from this aggressive therapy [101]. Open-chest CPR is often provided to children after open-heart cardiac surgery and sternotomy. Earlier institution of open-chest CPR may warrant reconsideration in selected special resuscitation circumstances.

Vascular access

Obtaining vascular access is obviously crucial to the success of resuscitation. Standard peripheral venous access is the first technique to consider. Ultrasound for guidance may also be used with teams that are proficient in the method. Infants and children, especially hospitalized children and those with multiple previous medical interventions, often have poor peripheral venous access, and it is not uncommon, even with IHCA, to encounter a patient without venous access. In this situation intraosseous (IO) infusion has become the recommended practice, supported by decades of animal study and clinical use [41,81]. Intraosseous needles (14, 16, and 18 gauge) should be kept on all CPR carts, and the flat surface of the proximal tibia is utilized. The needle is placed perpendicular to the bone and inserted with a twisting, "boring" motion until a loss of resistance heralding perforation of the bony cortex into cancellous bone. In infants and young children, active bone marrow hematopoiesis is occurring, and removal of the IO needle stylet and aspiration of bone marrow signifies successful placement. After rapid flush of 5–10 mL normal saline, resuscitation drugs and fluids can be administered IO, all followed by rapid flush with saline. These drugs include epinephrine, atropine, antiarrhythmic agents, naloxone, and dextrose. Fluids and blood can also be administered and blood samples can be obtained for laboratory studies. Caution must be exercised to detect extravasation of fluid into surrounding tissues. Standard venous access must be obtained as soon as possible. Central venous access is often difficult to obtain during resuscitation, and IO access is preferred. Venous access attempts should not interfere with chest compressions. See Chapter 19 for additional information about IO access.

Medications used to treat cardiac arrest

While animal studies have indicated that epinephrine can improve initial resuscitation success after both asphyxial and VF cardiac arrest, there are no prospective studies to support the use of epinephrine or any other medication to improve survival outcome from pediatric cardiac arrest. A variety of medications are used during pediatric resuscitation attempts including vasopressors (epinephrine and vasopressin), antiarrhythmics (amiodarone and lidocaine), and other drugs such as calcium chloride and sodium bicarbonate. Each will be discussed separately in this section.

Vasopressors

Epinephrine (adrenaline) is an endogenous catecholamine with potent α- and β-adrenergic stimulating properties. The α-adrenergic action (vasoconstriction) increases systemic and pulmonary vascular resistance. The resultant higher AoDP improves coronary perfusion pressure and myocardial blood flow even though it reduces global cardiac output during CPR; as noted above, adequacy of myocardial blood flow is a critical determinant of ROSC. Epinephrine also increases cerebral blood flow during good-quality CPR because peripheral vasoconstriction directs a greater proportion of flow to the cerebral circulation [102–104]. However, recent evidence suggests that epinephrine can decrease local cerebral microcirculatory blood flow at a time when global cerebral flow is increased [105]. The β-adrenergic effect increases myocardial contractility and heart rate, and relaxes smooth muscle in the skeletal muscle vascular bed and bronchi; however, the β-adrenergic effects are not observed in the peripheral vascular beds secondary to the high dose used in cardiac arrest. Epinephrine also increases the vigor and intensity of VF, increasing the likelihood of successful defibrillation. High-dose epinephrine (0.05–0.2 mg/kg) improves myocardial and cerebral blood flow during CPR more than standard-dose epinephrine (0.01–0.02 mg/kg) in animal models of cardiac arrest and may increase the incidence of initial ROSC [106,107]. However, prospective and retrospective studies have indicated that the use of high-dose epinephrine in adults or children does not improve survival and may be associated with worse neurological outcome [108,109]. A randomized, blinded, controlled trial of rescue high-dose epinephrine versus standard-dose epinephrine after failed initial standard-dose epinephrine in pediatric IHCA demonstrated a worse 24 h survival in the high-dose epinephrine group (1 of 27 survivors versus 6 of 23 survivors, $p < 0.05$) [110]. Based on these clinical studies, high-dose epinephrine cannot be recommended routinely for either initial or rescue therapy. Importantly, these studies indicate that high-dose epinephrine can worsen a patient's postresuscitation hemodynamic condition and likelihood of survival.

Vasopressin is a long-acting endogenous hormone that acts at specific receptors to mediate systemic vasoconstriction (V_1 receptor) and reabsorption of water in the renal tubule (V_2 receptor). Vasoconstrictive properties are most intense in the skeletal muscle and skin vascular beds. Unlike epinephrine, vasopressin is not a pulmonary vasoconstrictor. In experimental models of cardiac arrest, vasopressin increases blood flow to the heart and brain and improves long-term survival compared with epinephrine. However, vasopressin was formerly recommended as an alternative to epinephrine in adult cardiac arrest [111], but was removed from 2015 guidelines due to a lack of survival advantage over epinephrine alone [112,113]. Due to a paucity of pediatric data and an association with lower rates of ROSC in an AHA GWTG-R study [114], vasopressin has not been recommended during cardiac arrest in children. Although there are potentially candidates with epinephrine-refractory low systemic vascular resistance during CPR that could benefit from the addition of vasopressin, this has not yet been elucidated.

Antiarrhythmic medications

Amiodarone has been the long-standing first-line agent for shock-refractory VF or pVT [115]. In a 2014 GWTG-R registry study, the use of lidocaine in these circumstances was associated with an increased likelihood of ROSC [116]. It is still unclear if one therapeutic has a clear advantage over the other. Current AHA guidelines now recommend either amiodarone or lidocaine for shock-refractory VF or pVT [8].

Calcium

Calcium is used frequently in cases of pediatric cardiac arrest, despite the lack of evidence for efficacy. In the absence of a documented clinical indication (i.e. hypocalcemia, calcium channel blocker overdose, hypermagnesemia, or hyperkalemia), administration of calcium does not improve outcomes from cardiac arrest [117–125]. To the contrary, three pediatric studies have suggested a potential for harm, as routine calcium administration was associated with decreased survival rates and/or worse neurological outcomes [117–125]. Despite limited clinical

data to support the use of calcium during CPR, it is reasonable to consider calcium administration during CPR for cardiac arrest patients at high risk of hypocalcemia (e.g. renal failure, shock associated with massive transfusion) and in combination with laboratory values obtained during arrest.

Buffer solutions

There are no randomized controlled studies in children examining the use of sodium bicarbonate for management of pediatric cardiac arrest. Two randomized controlled studies have examined the value of sodium bicarbonate in the management of adult cardiac arrest [126] and in neonates with respiratory arrest in the delivery room [127]. Neither study was associated with improved survival. In fact, one multicenter retrospective in-hospital pediatric study found that sodium bicarbonate administered during cardiac arrest was associated with decreased survival, even after controlling for age, gender, and first documented cardiac rhythm [124]. Therefore, the routine use of sodium bicarbonate is not recommended during pediatric cardiac arrest resuscitation. Clinical trials involving critically ill adults with severe metabolic acidosis do not demonstrate a beneficial effect of sodium bicarbonate on hemodynamics despite correction of acidosis [128,129]. This is somewhat surprising in light of data that severe acidosis may depress the action of catecholamines and worsen myocardial function [130,131]. Nevertheless, the common use of sodium bicarbonate during CPR is not supported by clinical data. Pediatric patients with implanted cardiac pacemakers may have an increased threshold for myocardial electrical stimulation when acidotic [132], therefore administration of bicarbonate or another buffer is appropriate for management of severe documented acidosis in these children. Administration of sodium bicarbonate also is indicated in the patient with a tricyclic antidepressant overdose, hyperkalemia, hypermagnesemia, or sodium channel blocker poisoning. The buffering action of bicarbonate occurs when a hydrogen cation and a bicarbonate anion combine to form carbon dioxide and water. Carbon dioxide must be cleared through adequate minute ventilation; thus, if ventilation is impaired during sodium bicarbonate administration, carbon dioxide build-up may negate the buffering effect of bicarbonate. Because carbon dioxide readily penetrates cell membranes, intracellular acidosis may paradoxically increase after sodium bicarbonate administration without adequate ventilation. Therefore, bicarbonate should not be used for management of respiratory acidosis.

KEY POINTS: INTERVENTIONS DURING CARDIAC ARREST AND CPR

- Compression-only CPR is not recommended for children, except in situations in which "rescuers are unwilling or unable to deliver breaths"
- Resuscitation technique should aim to optimize patient outcome, with rapid, efficient, skilled airway management and minimal interruption of chest compressions
- The basic tenets of CPR are: *push hard, push fast, allow full chest wall release, minimize interruptions, and don't overventilate*
- Current AHA guidelines recommend either amiodarone or lidocaine for shock-refractory VF or pVT

Postresuscitation interventions

Temperature management

Observational studies of children treated with therapeutic hypothermia have not demonstrated improvement in mortality or neurological outcomes [133,134], although fever after cardiac arrest is common and associated with worsened neurological outcomes [135]. The Therapeutic Hypothermia After Cardiac Arrest (THAPCA) trial in pediatric OHCA reported no improvement with hypothermia as compared to normothermia, although there was a non-significant trend toward improved rates of survival with hypothermia [136]. The IHCA arm of THAPCA likewise failed to demonstrate a benefit in survival with favorable functional outcome with hypothermia as compared to normothermia, and was terminated because of futility [137]. Current pediatric advanced life support (PALS) guidelines for the temperature management of comatose patients call for the aggressive treatment of post-ROSC fever (>38°C) and 5 days of normothermia (36–37.5°C). In OHCA specifically, 2 days of hypothermia (32–34°C) followed by 3 additional days of normothermia can be considered, although evidence is lacking to support hypothermia over normothermia. Continuous temperature monitoring and aggressive treatment of post-ROSC fever are Class I recommendations [8].

Glucose control

Both hyperglycemia and hypoglycemia following cardiac arrest are associated with worse neurological outcome [138–141]. While it seems intuitive that hypoglycemia would be associated with worse neurological outcome, whether hyperglycemia *per se* is harmful or is simply a marker of the severity of the stress hormone response from prolonged ischemia is not clear. In critically ill adult patients, tight glucose control using an insulin infusion was associated with improved survival [142,143]. However, subsequent studies of non-surgical adult populations and neonatal/pediatric trials have demonstrated no survival benefit and the potential for harm from attempts at tight glucose control because of high rates of inadvertent hypoglycemia [138,144–150]. In summary, there is insufficient evidence to formulate a strong recommendation on the management of hyperglycemia in children with ROSC following cardiac arrest. If hyperglycemia is treated following ROSC in pediatric patients, blood glucose concentrations should be carefully monitored to avoid hypoglycemia.

Blood pressure management

A patient with ROSC may have substantial variability in blood pressure following cardiac arrest. Postarrest/resuscitation myocardial dysfunction is very common and is often associated with hypotension) [151–162]. In addition, hypertension may occur, especially if the patient receives vasoactive infusions for postarrest myocardial dysfunction. Optimization of blood pressure post arrest is critical to maintain adequate perfusion pressure to vital organs that may have already been injured from the "no-flow" and "low--flow" states during initial cardiac arrest and CPR. Cerebral blood flow in healthy patients is tightly controlled over a wide range of mean arterial blood pressure via the cerebral neurovascular bundle

(autoregulation); however, adults resuscitated from cardiac arrest have demonstrated impaired autoregulation of cerebral blood flow and this may also be the case in children [163]. Dysautoregulation of the cerebral neurovascular bundle following cardiac arrest may limit the brain's ability to regulate excessive blood flow and microvascular perfusion pressure, thereby leading to reperfusion injury during systemic hypertension. However, in animal models, brief induced hypertension following resuscitation results in improved neurological outcome compared with normotensive reperfusion [164,165]. Conversely, systemic hypotension may perpetuate neurological metabolic crisis following ischemic injury by uncoupling bioenergetic demand and delivery. Therefore, a practical approach to blood pressure management following cardiac arrest is to attempt to minimize blood pressure variability in this high-risk period following resuscitation.

Postresuscitation myocardial dysfunction

Postarrest myocardial stunning and arterial hypotension occur commonly after successful resuscitation in both animals and humans [151–162]. Animal studies demonstrate that postarrest myocardial stunning is a global phenomenon with biventricular systolic and diastolic dysfunction. Postarrest myocardial stunning is pathophysiologically and physiologically similar to sepsis-related myocardial dysfunction and post-cardiopulmonary bypass myocardial dysfunction, including increases in inflammatory mediators and nitric oxide production [154,157,158,160]. Because cardiac function is essential to reperfusion following cardiac arrest, management of postarrest myocardial dysfunction may be important to improving survival. The classes of agents used to maintain circulatory function (i.e. inotropes, vasopressors, and vasodilators) must be carefully titrated during the postresuscitation phase to the patient's cardiovascular physiology. Although the optimal management of post-cardiac arrest hypotension and myocardial dysfunction has not been established, data suggest that aggressive hemodynamic support may improve outcomes. Controlled trials in animal models have shown that dobutamine, milrinone, and levosimendan can effectively ameliorate post-cardiac arrest myocardial dysfunction [151,152,166,167]. In clinical observational studies, fluid resuscitation has been provided for patients with hypotension and concomitant low central venous pressure, and various vasoactive infusions, including epinephrine, dobutamine, and dopamine, have been used to treat the myocardial dysfunction syndrome [155–159,161,162]. In the end, optimal use of these agents involves close goal-directed titration, and the use of invasive hemodynamic monitoring may be appropriate. General critical care principles suggest that appropriate therapeutic goals are adequate blood pressures and adequate oxygen delivery. However, the definition of "adequate" is elusive. Studies in large animals have shown that with even optimal resuscitation there is still persistent mitochondrial and metabolic injury from ischemia and reperfusion [168,169]. Reasonable interventions for vasodilatory shock with low central venous pressure include fluid resuscitation and vasoactive infusions. Appropriate considerations for left ventricular myocardial dysfunction include euvolemia, inotropic infusions, and afterload reduction.

Neuromonitoring

Continuous neuromonitoring and goal-directed intervention following cardiac arrest is an exciting frontier with great promise in improving neurological outcomes post-cardiac arrest [170]. Continuous electroencephalography (cEEG) monitoring is an increasingly instituted modality for neuromonitoring of critically ill patients, especially to diagnose non-convulsive seizures (NCS) and seizures in patients receiving muscle relaxants. cEEG monitoring is non-invasive, performed at the bedside, and permits continuous assessment of cortical function. Interpretation of continuous EEG is usually performed by a neurologist from a remote location, and not bedside critical care physicians. However, advances in quantitative EEG tools may allow bedside caregivers to identify important electrographic events, such as seizures or abrupt background changes, to potentially permit real-time analysis and intervention [171]. In a prospective study of cEEG in children, non-convulsive seizures were detected in 39% (12 of 31) children following cardiac arrest [172]. In a partially overlapping cohort of 19 children, NCS were common in children undergoing therapeutic hypothermia after cardiac arrest [172]. NCS seems to be a common occurrence following cardiac arrests in children. Although the relationship of NCS to worse outcomes has not been established in pediatric patients following cardiac arrest, it has been associated with worse outcomes among critically ill adults and neonates [173–179]. We believe that cEEG should be considered for children post-cardiac arrest and that patients with NCS (especially status epilepticus with NCS) should be treated with anticonvulsant medication. Further study is warranted to better establish frequency of NCS and potential benefit in outcomes with anticonvulsant therapy.

Oxidative injury may be greatest in the early phases of postresuscitation therapy following cardiac arrest [180]. Interestingly, the use of 100% oxygen (compared to room air) during and immediately following resuscitation in animal models may potentiate oxidative injury to key mitochondrial enzymes (pyruvate dehydrogenase or manganese superoxide) or mitochondrial lipids (cardiolipin) and is associated with worse neurological outcomes [181–184]. Experimental protocols in large animals using peripheral pulse oximetry to titrate oxygenation in the postresuscitation phase can reduce postresuscitation hyperoxia and significantly improve neuropathology and neurobehavioral outcomes [185]. Consistent with these experimental findings, arterial hyperoxia (PaO_2 ≥300 mmHg) was independently associated with in-hospital mortality compared with either hypoxia or normoxia in an observational study among critically ill adult patients admitted to the ICU within 24 h of a cardiac arrest [186]. We believe it is prudent to titrate oxygenation during and following pediatric cardiac arrest. Although the optimal SpO_2 is not known, we recommend titration of FiO_2 to the lowest amount necessary to assure SpO_2 >94%. Perhaps the future of postarrest care will include more aggressive neurocritical care monitoring, such as near-infrared spectroscopy, cerebral microdialysis, brain tissue oxygen saturation ($PbtO_2$), cerebral blood flow, and even bedside analysis of mitochondrial dysfunction. A non-invasive technology, cerebral oximetry, uses near-infrared (NIR) light to measure brain tissue perfusion [187]. Commercially available near-infrared spectroscopy (NIRS) devices emit a continuous wave of light from a source probe

and measure the returning light at a detector probe on the patient's forehead. Cerebral oximetry monitoring during cardiac arrest may be feasible and may not necessarily distract from high-quality CPR [188–191]. Parnia and colleagues performed a multicenter prospective observational study in 2016, representing the largest cohort of adults with cerebral oximetry in place during cardiac arrest [192]. Patients with sustained ROSC had higher overall rSO_2 during CPR (51.8% versus 40.9%, p <0.0001) during this study involving IHCA. Furthermore, patients who survived to hospital discharge with a favorable neurological outcome had higher rSO_2 than those who died in hospital but obtained ROSC (mean rSO_2 56.1% and 50.6%, respectively, p<0.001) and no patients with rSO_2 <25% achieved ROSC. In a meta-analysis performed by Sanfilippo and colleagues in 2015 which included mostly OHCA patients, average rSO_2 for those who achieved ROSC was 44.9%, compared to 29.4% in those who did not have ROSC [193]. Given the variety and technical limitations of commercially-available devices, rSO_2 measurements should be interpreted cautiously. Optimal values of cerebral oxygen saturation are not known. These devices have not been validated against gold-standard measures in the cardiac arrest setting and may not be accurate during periods of diminished blood flow and oxygenation [193–196].

KEY POINTS: POSTRESUSCITATION INTERVENTIONS

- Continuous temperature monitoring and aggressive treatment of post-ROSC fever are Class I recommendations
- If hyperglycemia is treated following ROSC in pediatric patients, blood glucose concentrations should be carefully monitored to avoid hypoglycemia
- Systemic hypotension may perpetuate neurological metabolic crisis following ischemic injury by uncoupling bioenergetic demand and delivery
- General critical care principles suggest that appropriate therapeutic goals are adequate blood pressures and adequate oxygen delivery
- Although the optimal SpO_2 is not known, we recommend titration of FiO_2 to the lowest amount necessary to assure SpO_2 >94%

Other considerations

Quality of cardiopulmonary resuscitation

Despite evidence-based guidelines, extensive provider training, and provider credentialing in resuscitation medicine, the quality of CPR is typically poor. CPR guidelines recommend target values for selected CPR parameters related to rate and depth of chest compressions and ventilations, avoidance of CPR-free intervals, and complete release of sternal pressure between compressions [197]. Slow compression rates, inadequate depth of compression, and substantial pauses are the norm. The approach "*push hard, push fast, minimize interruptions, allow full chest recoil and don't overventilate*" can markedly improve myocardial, cerebral, and systemic perfusion, and will likely improve outcomes [71]. Quality of postresuscitative management has also been demonstrated to be critically important to improve resuscitation survival outcomes [155]. The importance of measuring the quality of CPR and avoiding overventilation during cardiac arrest resuscitation has recently been re-emphasized by consensus of the International Liaison Committee on Resuscitation and the American Heart Association [198]. Although the correct amount, timing, intensity, and duration of ventilation required during CPR are controversial, there is no controversy that measurement and titration of the amount of ventilation to the amount of blood perfusion are desirable. Thus, additional technology that is safe, accurate, and practical would improve detection and feedback of the "quality of CPR."

Recent technology has been developed that monitors quality of CPR by force sensors and accelerometers and can provide verbal feedback to the CPR administrator regarding the frequency and depth of chest compressions and the volume of ventilations. Recent pediatric data illustrate that intensive training and real-time corrective feedback can help chest compression quality approach age-specific AHA CPR guideline targets [199–201]. Moreover, improvements in postresuscitation care can improve resuscitation survival outcomes [155].

Extracorporeal membrane life-saving cardiopulmonary resuscitation

The use of extracorporeal membrane oxygenation (ECMO) life-saving (extracorporeal life support – ECLS) devices as a rescue therapy for refractory cardiac arrest (ECPR) is an exciting topic in resuscitation science. In children with medical or surgical cardiac diseases, ECPR has been shown to improve survival to hospital discharge [202] and can be effective even after more than 50 min of CPR [203]. However, at this time observational data have not consistently demonstrated a survival benefit of ECPR compared to conventional CPR across broad populations [204,205]. Children with primary cardiac disease may have a survival advantage due to these disease processes being amenable to a bridge with ECLS – either to recovery, surgery, or transplantation. There may be an underlying advantage for these patients as well, stemming from predominantly single-organ failure compared to patients with non-cardiac etiologies of cardiac arrest, allowing for a greater chance of full recovery after resuscitation [206]. Importantly, in these observational studies, ECPR is used as a rescue therapy in patients who likely would have died with continued conventional resuscitation efforts [206]. In fact, in a GWTG-R study that looked at both cardiac and non-cardiac patients with >10 min of CPR, those who received ECPR had improved survival and favorable neurological outcome at discharge [207]. The finding of a lack of survival advantage across broad populations in observational studies, even when controlling for confounding factors, is flawed by the nature of these studies [208]. In the absence of randomized controlled trials that specifically compare early initiation of ECPR and conventional CPR, it is probably reasonable to consider ECPR as a rescue therapy in patients with potentially reversible underlying disease processes. However, as noted in PALS guidelines, any

reasonable chance of success requires a setting with "existing ECMO protocols, expertise, and equipment" [8], and dedicated teams that train for efficient cannulation under difficult circumstances. Therefore, timely, quality ECPR may be an exciting adjuvant to conventional CPR for pediatric patients. Future frontiers will define patient populations and optimize the clinical approach to extracorporeal support; however, clinicians providing CPR should consider ECPR early in the course of a resuscitation not responding to conventional CPR. Perhaps after failure to attain ROSC within 5 min, clinicians should ask themselves: (1) does the patient have a potentially reversible process, (2) would ECMO be a "bridge" to a potentially good outcome, and (3) do we have the personnel and resources to provide EMCO promptly? If the answers to all three are "yes," prompt implementation of ECPR should be considered.

Ventricular fibrillation and ventricular tachycardia in children

Pediatric VF or VT has been an underappreciated pediatric problem. Recent studies indicate that VF and VT (i.e. shockable rhythms) occur in 27% of IHCAs at some time during the resuscitation [25]. In a population of pediatric cardiac ICU patients, as many as 41% of arrests were associated with VF or VT [208]. According to the National Registry of Cardiopulmonary Resuscitation (NRCPR) database (https://www.heart.org/en/professional/quality-improvement/get-with-the-guidelines/get-with-the-guidelines-resuscitation/get-with-the-guidelines-resuscitation-overview), 10% of children with IHCA had an initial rhythm of VF/VT. In all, 27% of the children had VF/VT at some time during the resuscitation [209]. The incidence of VF varies by setting and age [210]. In special circumstances, such as tricyclic antidepressant overdose, cardiomyopathy, post cardiac surgery, and prolonged QT syndromes, VF and pVT are more likely.

The treatment of choice for short-duration VF is prompt defibrillation. In general, the mortality rate increases by 7–10% per minute of delay to defibrillation. Because VF must be considered before defibrillation can be provided, early determination of the rhythm by electrocardiography is critical. An attitude that VF is rare in children can be a self-fulfilling prophecy with a uniformly fatal outcome. The recommended defibrillation dose is 2 J/kg, but the data supporting this recommendation are not optimal and are based on old monophasic defibrillators. In the mid-1970s, authoritative sources recommended starting doses of 60–200 J for all children. Because of concerns for myocardial damage and animal data suggesting that shock doses ranging from 0.5 to 1 J/kg were adequate for defibrillation in a variety of species, Gutgesell et al evaluated the efficacy of their strategy to defibrillate with 2 J/kg monophasic shocks. Seventy-one transthoracic defibrillations in 27 children were evaluated. Shocks within 10 J of 2 J/kg resulted in successful defibrillation (i.e. termination of fibrillation) in 91% of defibrillation attempts. More recent data demonstrate that an initial shock dose of 2 J/kg terminates fibrillation in <60% of children, suggesting that a higher dose may be needed [30, 211]. Despite five decades of clinical experience with pediatric defibrillation, the optimal dose remains unknown.

Pediatric automated external defibrillators

Automated external defibrillators (AEDs) have improved adult survival from VF [212,213]. AEDs are recommended for use in children 8 years or older with cardiac arrest [95,214]. The available data suggest that some AEDs can accurately diagnose VF in children of all ages, but many AEDs are limited because the defibrillation pads and energy dosage are geared for adults. Adapters having smaller defibrillation pads that dampen the amount of energy delivered have been developed as attachments to adult AEDs, allowing their use in children. However, it is important that the AED diagnostic algorithm is sensitive and specific for pediatric VF and VT. The diagnostic algorithms from several AED manufacturers have been tested for such sensitivity and specificity and therefore can be reasonably used in younger children.

Simulation and pediatric cardiopulmonary resuscitation

Simulation has achieved an increasingly important place in medical education and training in pediatric anesthesiology and critical care, with resuscitation scenarios among the most frequent programs provided by pediatric simulation centers [185]. Simulation scenarios can reveal gaps in knowledge and technique for physicians. In a study of 20 anesthesia residents in a scenario of hyperkalemic cardiac arrest during anesthesia for a craniotomy for tumor incision in a 1-year-old patient weighing 10 kg resulting in pulseless electrical activity, only one-third of the residents performed chest compressions properly and administered the correct dose of epinephrine. Only one-fourth of the residents considered hyperkalemia as a cause of the arrest, and none asked for dosing aids [186]. In a study of *in situ* simulation training for effective chest compressions in a pediatric ICU, healthcare providers with more frequent exposure to these sessions correctly demonstrated proper chest compressions in significantly less time than those with less frequent exposure to these sessions [169]. See Chapter 47 for a thorough discussion of simulation in pediatric anesthesia.

Intraoperative cardiac arrest

See Chapter 45 for a detailed discussion of the causes of intraoperative cardiac arrest.

When should cardiopulmonary resuscitation be discontinued?

Several factors determine the likelihood of survival after cardiac arrest, including the mechanism of the arrest (e.g. traumatic, asphyxial, progression from circulatory shock), location (e.g. IHCA or OHCA), response (i.e. witnessed or unwitnessed, with or without bystander CPR), underlying pathophysiology (i.e. cardiomyopathy, congenital defect, drug toxicity, or metabolic derangement), and the potential reversibility of underlying diseases. These factors should all be considered before deciding to terminate resuscitative efforts. Continuation of CPR has been traditionally considered futile beyond 15 min or when more than two doses of epinephrine are needed [215]. Presumably in part because of improvements in CPR quality and postresuscitation care, improved outcomes from in-hospital CPR efforts beyond 15 min or two doses of epinephrine are increasingly the norm [20,21]. The potential for excellent outcomes despite prolonged CPR has been highlighted by the ECPR data noted previously [203,216–219]. Recently, Berg and colleagues reported 98% rates of ROSC in patients receiving 1–3 min of CPR as compared to 56% in patients receiving >30 min of CPR. At hospital discharge, survival rates were 66% and 28%, respectively [1]. In a GWTG-R study, children with CPR lasting >35 min had a 16% chance of survival to hospital discharge [220]. While these data may seem discouraging, it is important to consider that these children requiring prolonged CPR actually have better outcomes than pediatric IHCA victims with average durations of CPR just a decade earlier [4]. Thus, we believe that decisions regarding futility of continuing resuscitation efforts should not be based on duration alone.

Quality improvement in cardiac arrest

The 2015 Institute of Medicine report, *Strategies to Improve Cardiac Arrest Survival: A Time to Act*, recommended the adoption of continuous quality improvement programs to improve outcomes from cardiac arrest [221]. Use of quality improvement strategies has been associated with improved outcomes [222]. For example, the provision of formalized non-punitive feedback and the implementation of multidisciplinary postarrest debriefing have been effective at improving CPR quality and are associated with improved rates of survival to discharge in pediatric IHCA [223,224].

Postarrest prognostication

Following ROSC, a number of findings have been associated with survival and neurological outcomes. These include pupillary responses [225,226] serum biomarkers such as neuron-specific enolase and S100B [227,228], serum lactate levels [229], EEG findings [225,230], somatosensory evoked potentials [231], neuroimaging studies [232], non-invasive cerebral tissue oxygenation [192,233], and the presence or absence of hypotension [234]. Importantly, the data supporting the application of these tools as prognosticators are not as robust in children as they are in adults, and each patient's overall clinical status after cardiac arrest must be considered over any one finding.

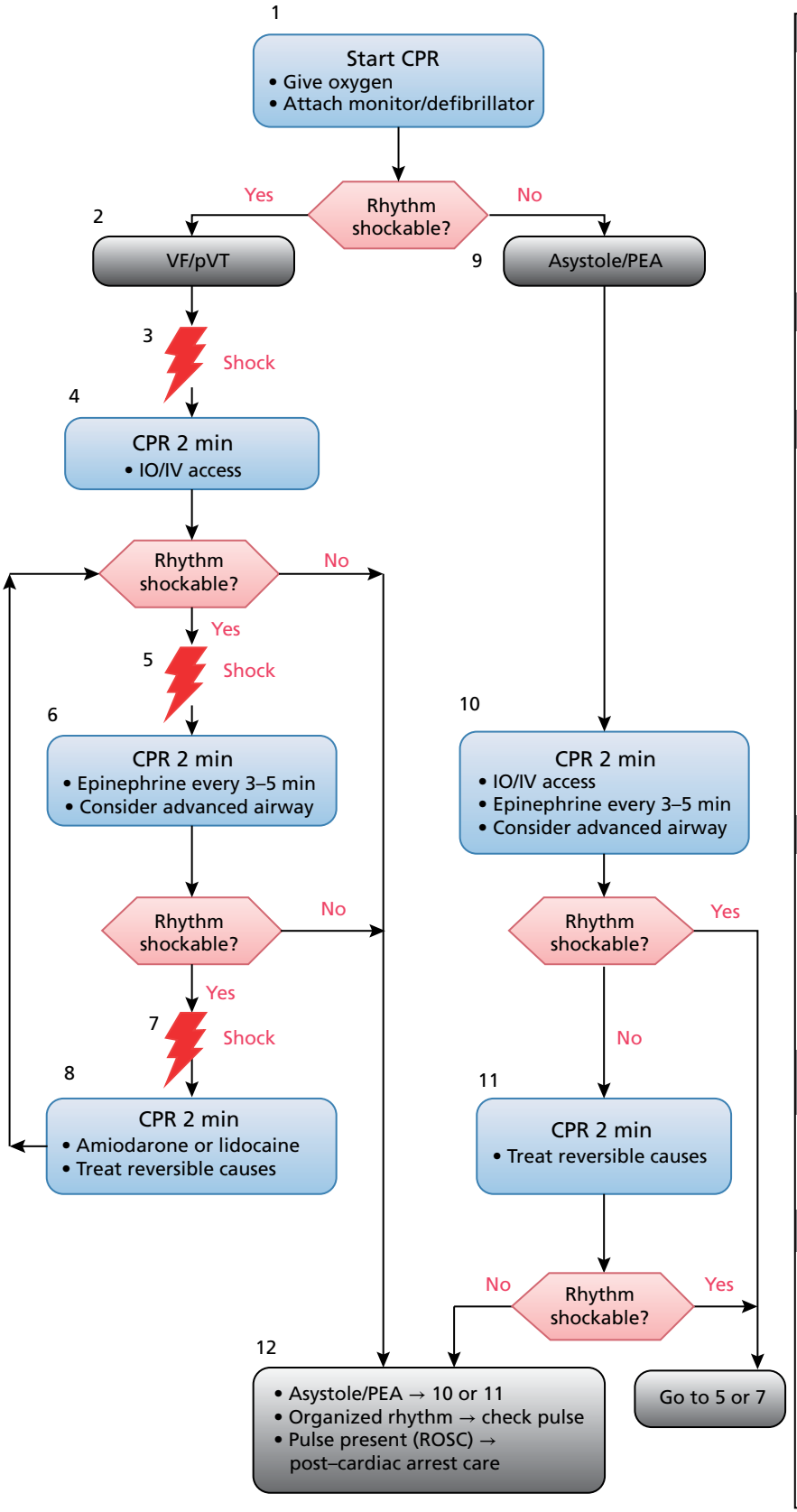
KEY POINTS: OTHER CONSIDERATIONS

- Quality ECPR may be an exciting adjuvant to conventional CPR, and future frontiers will define patient populations and optimize the clinical approach to extracorporeal support
- An initial shock dose of 2 J/kg terminates fibrillation in <60% of children, suggesting that a higher dose may be needed
- Some AEDs can accurately diagnose VF in children of all ages
- Children with CPR lasting >35 min had a 16% chance of survival to hospital discharge
- Non-punitive feedback and postarrest debriefing have been effective at improving CPR quality and are associated with improved rates of survival to discharge

Conclusion

Figures 13.1 through 13.8 summarize the most recent American Heart Association guidelines for PALS (2015) [235]. The reader is advised that new guidelines are published every few years, and the most recent guidelines should be sought out and followed.

Outcomes from pediatric cardiac arrest and CPR appear to be improving, however many patients are still left with devastating neurological injury. Perhaps the evolving understanding of pathophysiological events during and after pediatric cardiac arrest and the developing fields of pediatric critical care and pediatric emergency medicine have contributed to these apparent improvements. In addition, exciting breakthroughs in basic and applied science laboratories are on the immediate horizon for study in specific subpopulations of cardiac arrest victims. ECPR and CPR optimized to the individual patient and pathophysiology is the future of resuscitation. By strategically focusing therapies to specific phases of cardiac arrest, there is great promise that critical care interventions will lead the way to more successful cardiopulmonary and cerebral resuscitation in children.



CPR Quality

- Push hard (≥⅓ of anteroposterior diameter of chest) and fast (100–120/min) and allow Complete chest recoil.
- Minimize interruptions in compressions.
- Avoid excessive ventilation.
- Rotate compressor every 2 minutes, or sooner if fatigued.
- If no advanced airway, 15:2 compression-ventilation ratio.

Shock Energy for Defibrillation

First shock 2 J/kg, second shock 4 J/kg, subsequent shocks ≥4 J/kg, maximum 10 J/kg or adult dose

Drug Therapy

- **Epinephrine IO/IV dose:** 0.01 mg/kg (0.1 mL/kg of the 0.1 mg/mL concentration). Repeat every 3–5 minutes. If no IO/IV access, may give endotracheal dose: 0.1 mg/kg (0.1 mL/kg of the 1 mg/mL concentration).
- **Amiodarone IO/IV dose:** 5 mg/kg bolus during cardiac arrest. May repeat up to 2 times for refractory VF/pulseless VT.
- **Lidocaine IO/IV dose:** Initial: 1 mg/kg loading dose. Maintenance: 20–50 mcg/kg per minute infusion (repeat bolus dose in infusion initiated >15 minutes after initial bolus therapy).

Advanced Airway

- Endotracheal intubation or supraglottic advanced airway
- Waveform capnography or capnometry to confirm and monitor ET tube placement
- Once advanced airway in place, give 1 breath every 6 seconds (10 breaths/min) with continuous chest compressions

Return of Spontaneous Circulation (ROSC)

- Pulse and blood pressure
- Spontaneous arterial pressure waves with intra-arterial monitoring

Reversible Causes

- **H**ypovolemia
- **H**ypoxia
- **H**ydrogen ion (acidosis)
- **H**ypoglycemia
- **H**ypo-/hyperkalemia
- **H**ypothermia
- **T**ension pneumothorax
- **T**amponade, cardiac
- **T**oxins
- **T**hrombosis, pulmonary
- **T**hrombosis, coronary

Figure 13.1 Pediatric cardiac arrest algorithm. CPR, cardiopulmonary resuscitation; ET, endotracheal; IO, intraosseous; IV, intravenous; PEA, pulseless electrical activity; pVT, pulseless ventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia. *Source:* Reprinted with permission ©2015 American Heart Association, Inc.

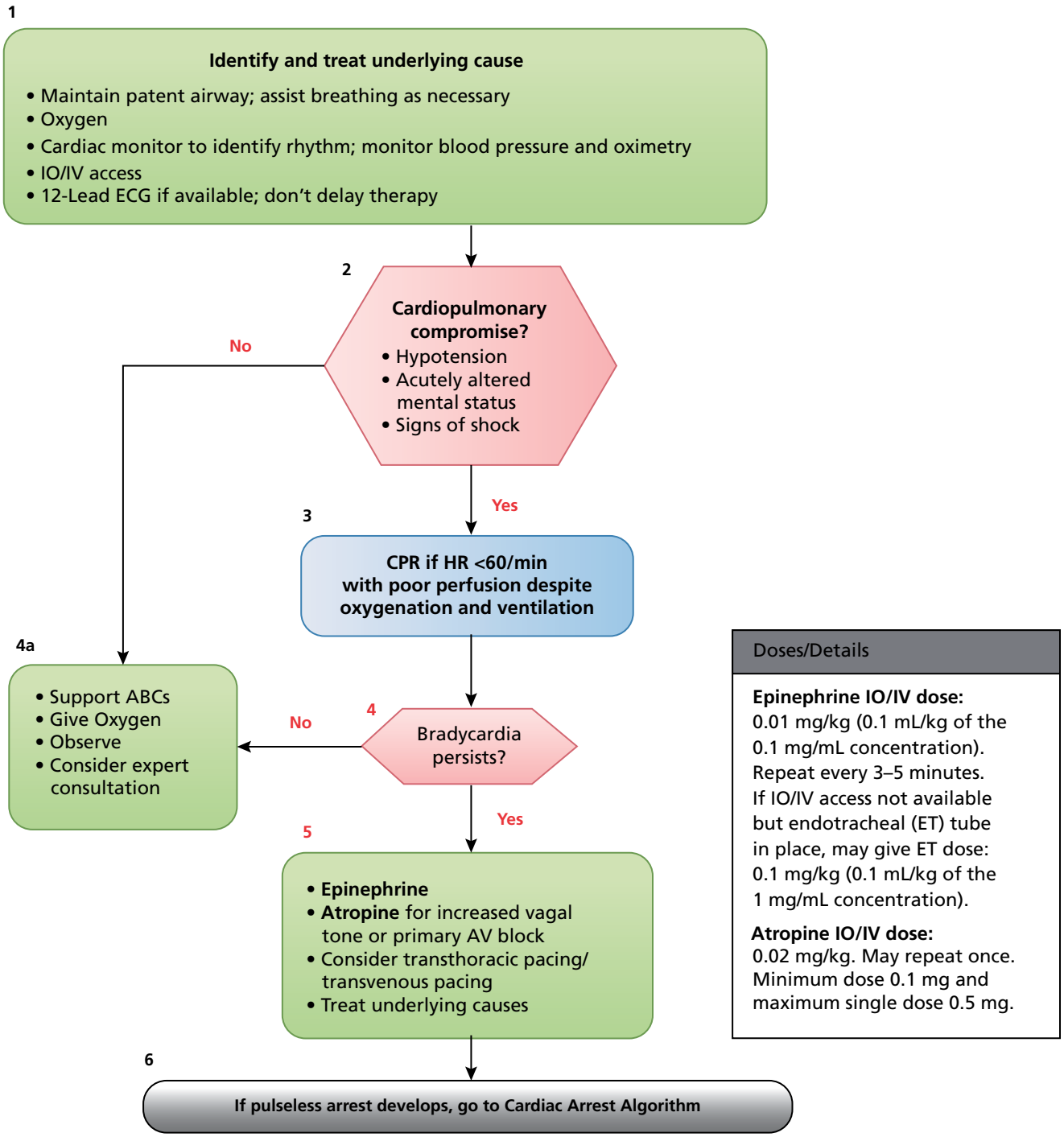


Figure 13.2 Pediatric bradycardia with a pulse and poor perfusion algorithm. AV, atrioventricular; CPR, cardiopulmonary resuscitation; ECG, electrocardiogram; HR, heart rate; IO, intraosseous; IV, intravenous. *Source:* Reprinted with permission ©2015 American Heart Association, Inc.

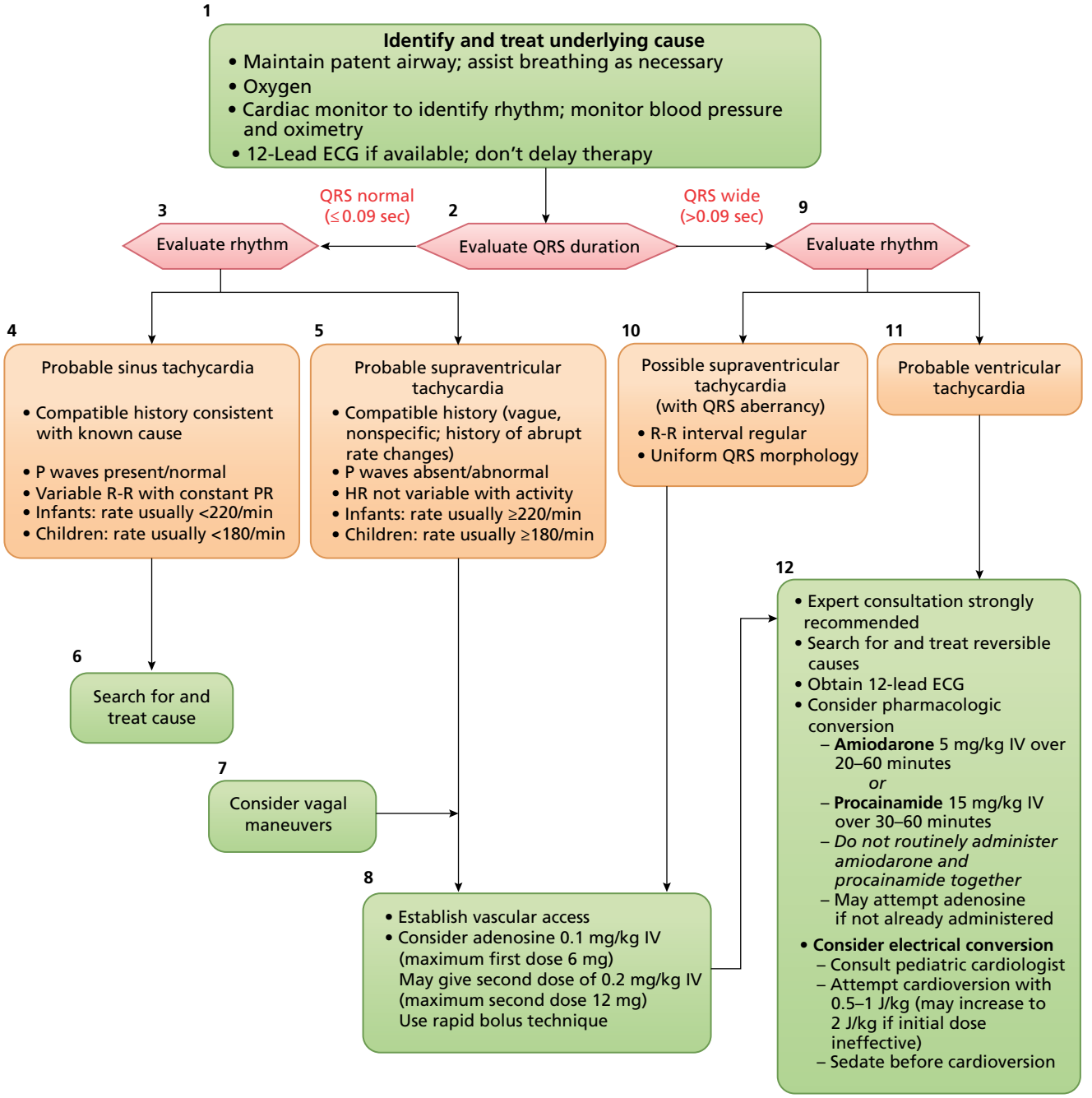


Figure 13.3 Pediatric tachycardia with a pulse and adequate perfusion algorithm. ECG, electrocardiogram; HR, heart rate; IV, intravenous; PR, pulse rate. *Source:* Reprinted with permission ©2015 American Heart Association, Inc.

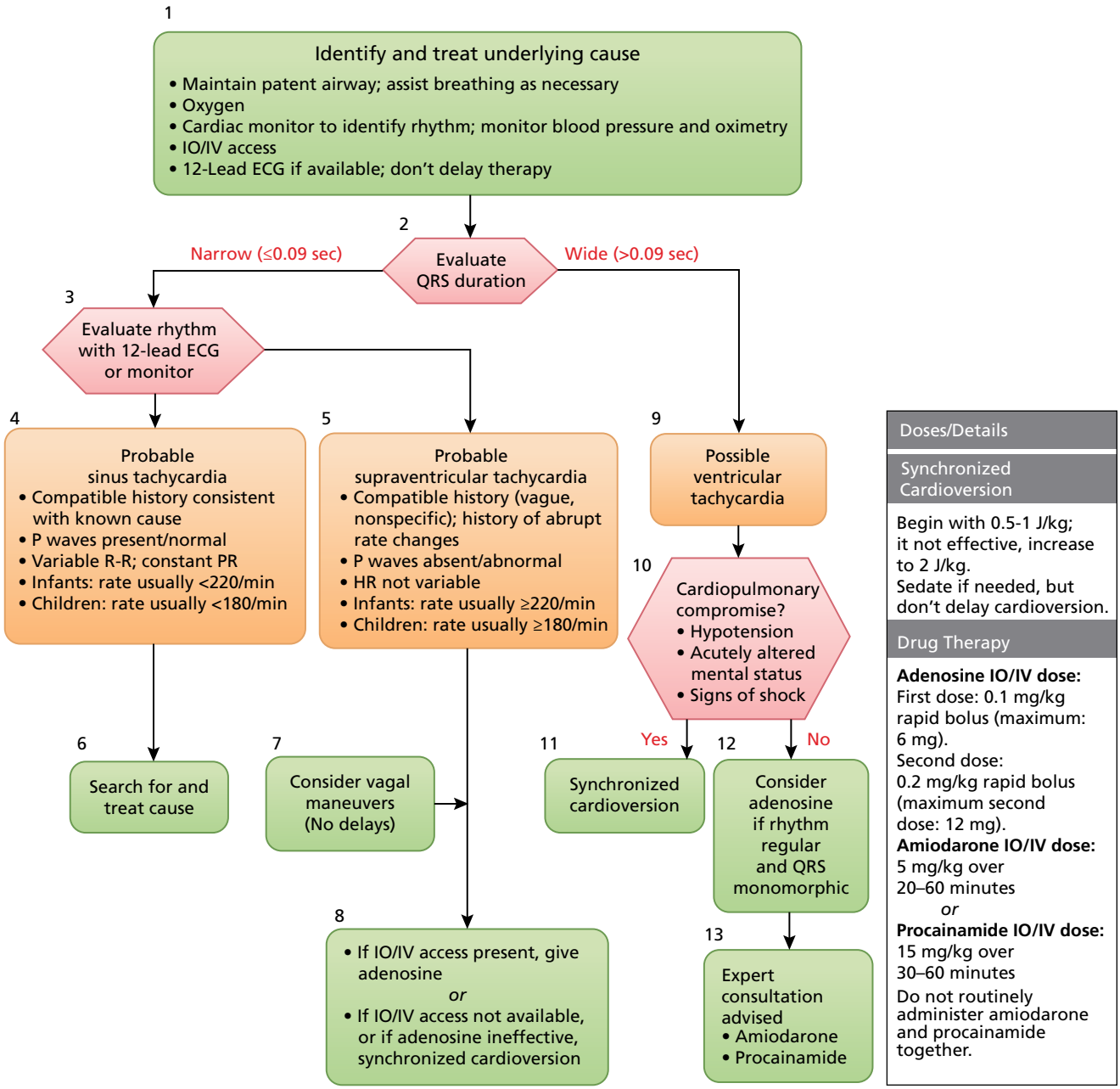


Figure 13.4 Pediatric tachycardia with a pulse and poor perfusion algorithm. ECG, electrocardiogram; HR, heart rate; IO, intraosseous; IV, intravenous; PR, pulse rate. *Source:* Reprinted with permission ©2015 American Heart Association, Inc.

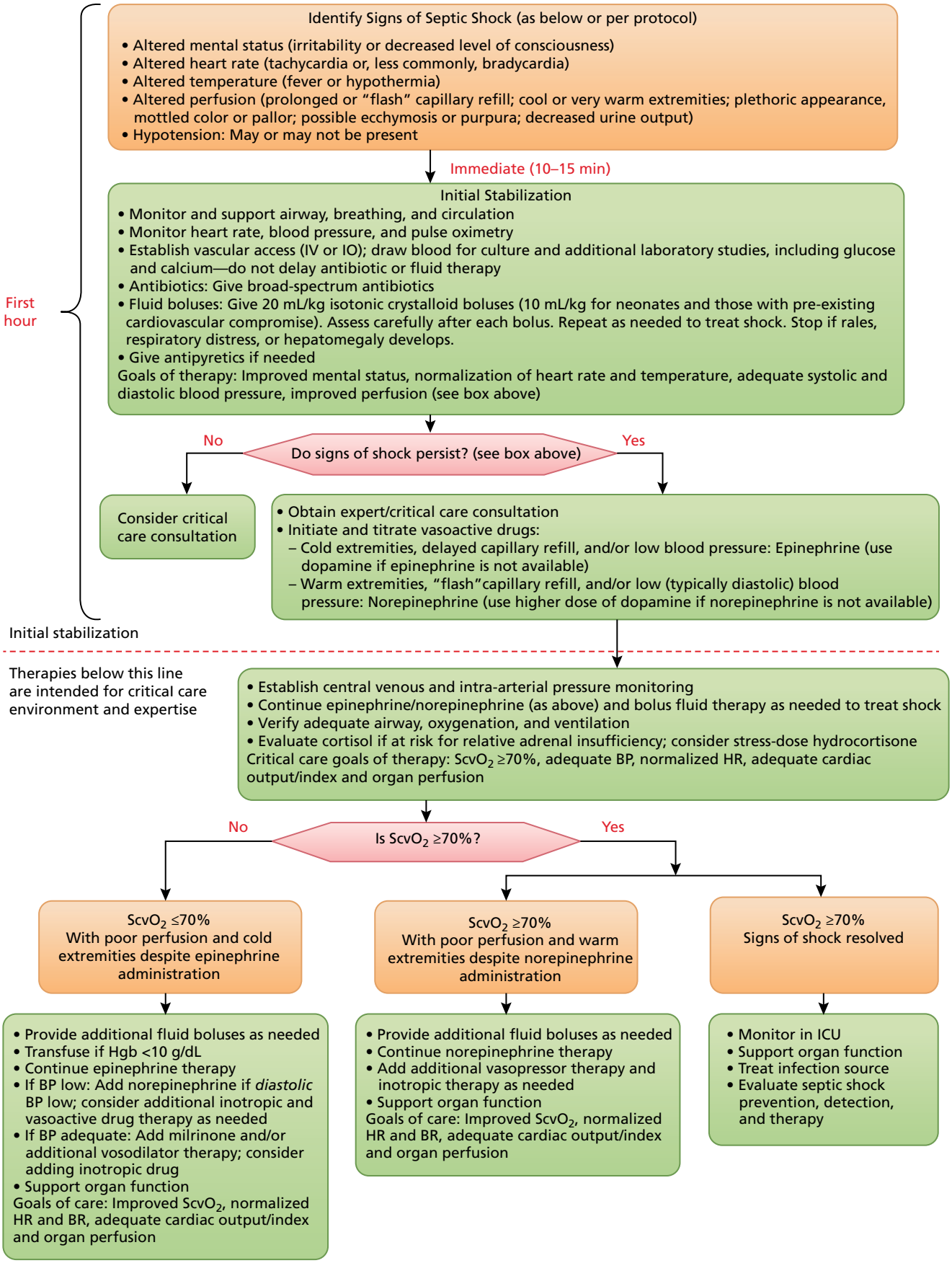


Figure 13.5 Pediatric septic shock algorithm. BP, blood pressure; HR, heart rate; ICU, intensive care unit. *Source:* Reprinted with permission ©2015 American Heart Association, Inc.

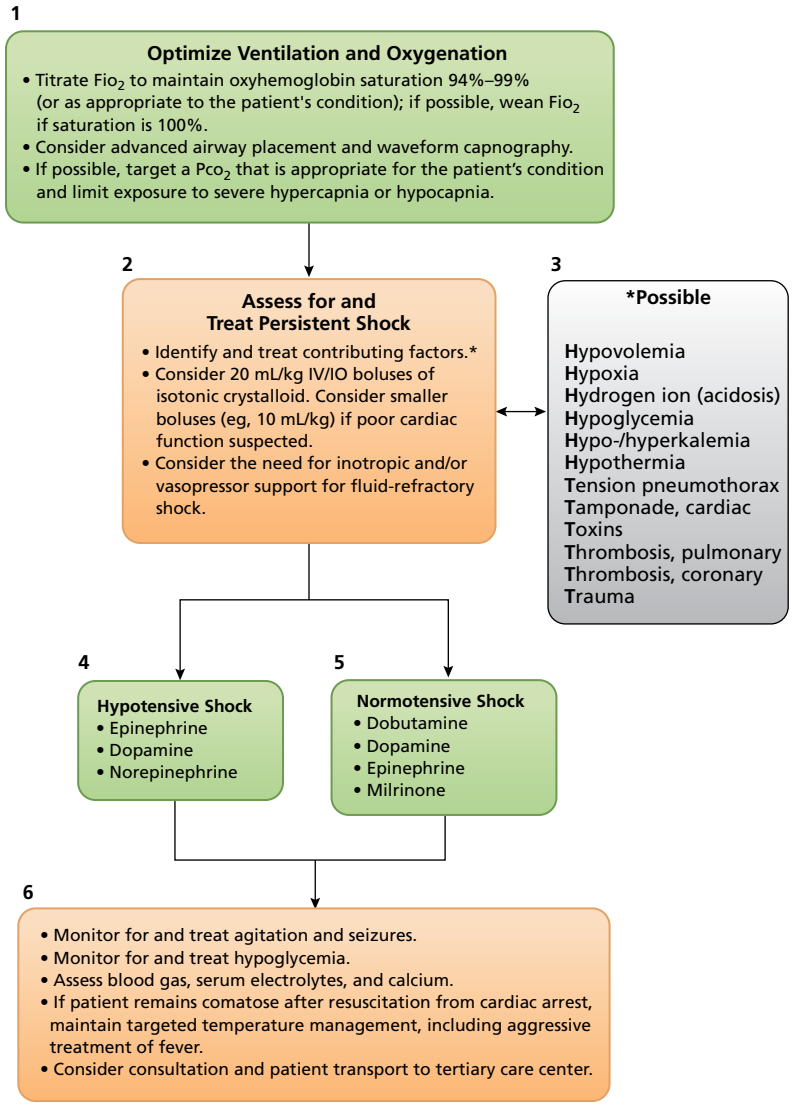


Figure 13.6 Pediatric postresuscitation care. IO, intraosseous; IV, intravenous. *Source:* Reprinted with permission ©2015 American Heart Association, Inc.

Equipment	GRAY* 3–5 kg	PINK Small Infant 6–7 kg	RED Infant 8–9 kg	PURPLE Toddler 10–11 kg	YELLOW Small Child 12–14 kg	WHITE Child 15–18 kg	Blue Child 19–23 kg	ORANGE Large Child 24–29 kg	GREEN Adult 30–36 kg
Resuscitation bag		Infant/child	Infant/child	Child	Child	Child	Child	Child	Adult
Oxygen mask (NRB)		Pediatric	Pediatric	Pediatric	Pediatric	Pediatric	Pediatric	Pediatric	Pediatric/ adult
Oral airway (mm)		50	50	60	60	60	70	80	80
Laryngoscope blade (size)		1 Straight	1 Straight	1 Straight	2 Straight	2 Straight	2 Straight or curved	2 Straight or curved	3 Straight or curved
ET tube (mm)†		3.5 Uncuffed 3.0 Cuffed	3.5 Uncuffed 3.0 Cuffed	4.0 Uncuffed 3.5 Cuffed	4.5 Uncuffed 4.0 Cuffed	5.0 Uncuffed 4.5 Cuffed	5.5 Uncuffed 5.0 Cuffed	6.0 Cuffed	6.5 Cuffed
ET tube insertion length (cm)	3 kg 9–9.5 4 kg 9.5–10 5 kg 10–10.5	10.5–11	10.5–11	11–12	13.5	14–15	16.5	17–18	18.5–19.5
Suction catheter (F)		8	8	10	10	10	10	10	10–12
BP cuff	Neonatal #5/infant	Infant/child	Infant/child	Child	Child	Child	Child	Child	Small adult
IV catheter (ga)		22–24	22–24	20–24	18–22	18–22	18–20	18–20	16–20
IO (ga)		18/15	18/15	15	15	15	15	15	15
NG tube (F)		5–8	5–8	8–10	10	10	12–14	14–18	16–18
Urinary catheter (F)	5	8	8	8–10	10	10–12	10–12	12	12
Chest tube (F)		10–12	10–12	16–20	20–24	20–24	24–32	28–32	32–38

Abbreviations: BP, blood pressure: ET, endotracheal; F, French; IO, intraosseous; IV, intravenous; NG, nasogastric; NRB nonrebreathing.
*For Gray column, use Pink or Red equipment sizes if no size is listed.
†Per 2010 *AHA Guidelines*, in the hospital cuffed or uncuffed tubes may be used.

Figure 13.7 Pediatric color-coded length-based resuscitation tape. *Source:* Reprinted with permission ©2015 American Heart Association, Inc.

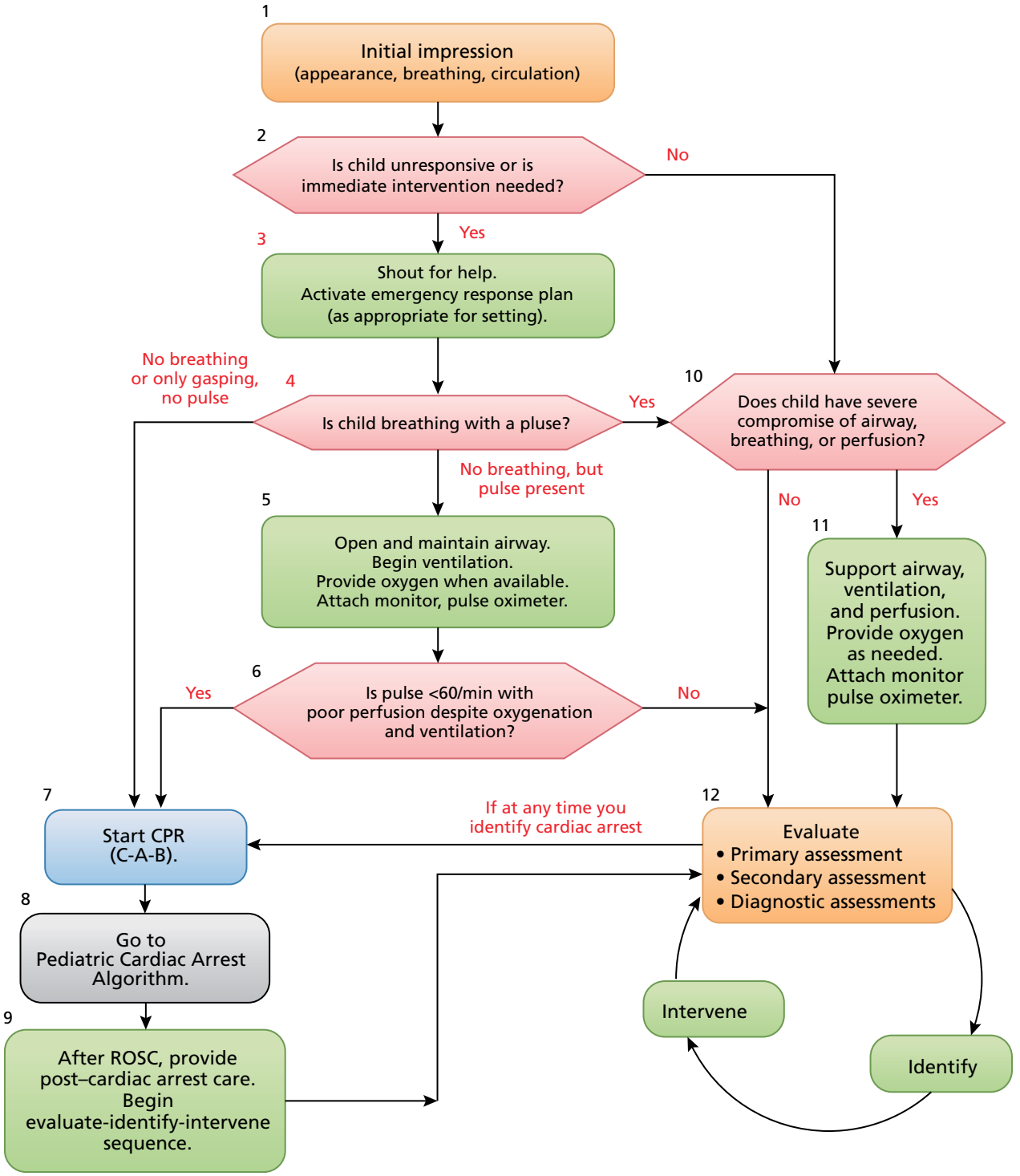


Figure 13.8 PALS systematic approach algorithm. CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation. *Source:* Reprinted with permission ©2015 American Heart Association, Inc.

CASE STUDY

A 5-year-old girl was found floating at the bottom of a swimming pool after not being seen by her parents for approximately 10 min. She was pulled from the water by a lifeguard. He noted that she was apneic and had no signs of life. Rescue breaths were given and chest compressions were initiated. The lifeguard gave rescue breaths coordinated with chest compressions at a cycle of 15:2 while emergency medical services (EMS) were called. Upon arrival of EMS, an endotracheal tube was placed while in-line neck stabilization was provided. Following intubation the child was hand ventilated at a rate of 10–12 breaths per min and received compressions at a rate of 100 per min simultaneously. An AED was placed and did not advise shocking. The EMS providers placed a cervical collar and inserted an intraosseous needle in her proximal right tibia. They infused an intraosseous bolus of 2 mL epinephrine 1:10,000 (0.1 mL/kg based on a presumed weight of 20 kg) every 3 min × 3. She was transported to an outside hospital emergency department (ED), with return of spontaneous circulation noted on arrival.

In the ED she had a rectal temperature of 36°C, a heart rate of 170 beats per minute, a blood pressure of 120/60, and SpO_2 of 100% with FiO_2 1.0. Her end-tidal CO_2 was 65 mmHg. Her pupils were 4 mm bilaterally and reactive and she had intermittent extensor posturing with stimulation, but no purposeful movement. Two peripheral intravenous lines were placed. Her initial venous blood gas revealed a pH 6.9, PCO_2 65 mmHg, PaO_2 25 mmHg, bicarbonate 12 meq/L, a base deficit of -22 meq/L, and an ionized calcium of 1.02 mmol/L. A complete blood count had a white blood cell count of 15,000/mm^3 hemoglobin of 12 g/dL, and a platelet count of 242,000/mm^3. A chemistry panel showed a sodium of 138 meq/L, potassium 7 meq/L, chloride of 103 meq/L, BUN of 15 mg/dL, and a creatinine of 0.3 mg/dL. The glucose was 345 mg/dL. The initial chest x-ray showed an endotracheal tube in the mid trachea with bilateral hazy infiltrates. Secondary to hyperkalemia in the face of a severe metabolic and mild respiratory acidosis, the patient was hyperventilated at a rate of 22 breaths per minute. She received 2 meq/kg of sodium bicarbonate as well as 50 mg/kg of calcium gluconate intravenously. She also received 20 mL/kg of normal saline, 20 µg of fentanyl, and 1 mg of midazolam for posturing and twitching with resolution of her twitching. The head CT showed no intracranial injury. She was then transferred to the ICU for further management.

On arrival in the ICU her vital signs were notable for a rectal temperature of 35.5°C, a heart rate of 150 beats per min, a blood pressure of 90/40, and a SpO_2 of 100% on FiO_2 1.0 with hand ventilation. She had an end tidal CO_2 of 50 mmHg. She was placed on initial ventilator settings of tidal volume 160 mL, a positive end expiratory pressure of 10 cmH_2O and a rate of 22 breaths per min with FiO_2 1.0. To avoid hyperoxia, her supplemental oxygen was weaned to maintain her SpO_2 >94%. Her ventilation rate was titrated to maintain normocarbia.

Simultaneously she had an esophageal and bladder temperature probe placed for core temperature monitoring. The esophageal probe was placed through the mouth and measured to terminate at the distal end of the esophagus. The temperature-sensing Foley catheter was placed for urinary output monitoring as well as continuous core temperature monitoring. A 5 French, 12 cm triple lumen right subclavian catheter was placed under sterile conditions. This catheter was placed for continuous medication administration as well as co-oximetry monitoring and central venous pressure monitoring. A repeat chest x-ray was obtained which showed the catheter to terminate at the right atrial–superior vena caval junction. There was no evidence of pneumothorax and the esophageal probe terminated at the distal esophagus. She also had a right radial arterial line placed under sterile conditions for continuous arterial blood pressure monitoring and frequent lab sampling.

Following these procedures, the patient remained tachycardic with a heart rate of 140 bpm, and became hypotensive with a blood pressure of 70/40. Her central venous pressure was 2, and her repeat venous blood gas was pH 7.13/PCO_2 45/PO_2 38/base deficit -12/lactate 6. She received another 20 mL/kg of normal saline × 2 with improvement in her central venous pressure to 6, however despite fluid boluses she remained persistently hypotensive at 80/40. At that time the intensivist decided to initiate vasopressor therapy to improve her cerebral perfusion pressure. Dopamine was infused at 5 µg/kg/min, resulting in a blood pressure of 102/55 mmHg and a urine output of approximately 5 mL/kg/h.

Labs were sent to further evaluate end-organ perfusion. Her troponin was 1.5 µg/L, creatine kinase (CK) was 2023 units/L and her CK-myocardial band percentage was 7%. Her amylase, lipase, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were within normal limits. Her glucose was 327 mg/dL. She remained comatose with a Glasgow Coma Score of 7 Total (Eye opening 1, Verbal response 0 (intubated), Motor response 5).

At that time the clinical team placed her on a cooling blanket with the goal of maintaining her temperature between 36 and 37°C to avoid hyperthermia. She was initiated on maintenance fluids without dextrose due to hyperglycemia. An insulin infusion was ordered to start at 0.01 units/kg/h

to maintain her blood glucose <180 and prevent excessive urine output from osmotic diuresis. Because of hypotension and the known risk of post-cardiac arrest myocardial depression, an echocardiogram was obtained at the bedside, which showed a shortening fraction of 40% and a hyperdynamic myocardium. Because of intermittent posturing and tachycardia, which resolved after IV midazolam treatment, a continuous electroencephalogram was performed to monitor for post-cardiac arrest seizure activity. The neurologist noted non-convulsive seizure activity on the electroencephalogram, and the patient was loaded with 20 mg/kg of intravenous fosphenytoin. She was sedated with fentanyl and midazolam infusions to decrease metabolic demand immediately post arrest.

During the 3 days following her cardiac arrest, her temperature was maintained between 36 and 37°C, her blood pressure was maintained within normal limits for age, and she was weaned off dopamine, her $PaCO_2$ was maintained in the 40s, and her SpO_2 was maintained >95%. Within 36 h post arrest, trophic feeds were initiated and slowly titrated to goal caloric needs via a naso-duodenal feeding tube. On post-cardiac arrest day 3, her neurological exam revealed: bilateral reactive pupils, a cough and gag, spontaneous respiratory effort, and she was localizing to noxious stimuli. Her seizures were controlled with phenytoin and EEG monitoring was discontinued at 72 h with no new seizures evident. On day 4 post arrest her temperature-sensing Foley and esophageal probes were removed so that she could go to MRI for evaluation of her brain and cervical spine. Her cervical spine showed no evidence of bony or ligamentous injury and her cervical collar was removed. Her brain MRI showed evidence of subtle acute hypoxic ischemic injury in the cerebral cortex bilaterally. On day 5 her sedation infusions were discontinued and she was extubated. On day 6 her central line and arterial line were discontinued and she was transferred to the inpatient rehabilitation ward for intensive therapies.

Three months following her cardiac arrest she was verbal and interactive. She was able to ambulate with assistance. She had had no seizures and was maintained on phenytoin with plans to wean it off at 6 months post arrest if there was no new seizure activity.

1. The chain of survival includes early, good-quality CPR, early defibrillation if appropriate, aggressive postresuscitative care and rehabilitation services.
2. Prompt bystander CPR was provided with chest compressions and rescue breathing.
3. Postresuscitative care requires a multidisciplinary approach and focus on details of avoiding secondary injuries from hyperoxia, hyperthermia, hypotension, and acidosis.
4. Post cardiac arrest, patients often exhibit intravascular volume depletion and have a systemic inflammatory response syndrome (SIRS) and myocardial depression. Therefore, close hemodynamic monitoring and cardiovascular supportive care are necessary for optimal postresuscitative care.

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A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 14

Anxiety, Psychological Preparation, Awareness, and Behavior Change

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Introduction

Millions of children undergo general anesthesia (GA) and, regrettably, many experience perioperative anxiety [1]. Sometimes the anxiety is severe enough to increase analgesic requirements and to cause psychological or behavioral disturbances; for a few patients, these problems may continue long after discharge from hospital [2].

Delivering healthcare in the 21st century is no longer limited to optimization of physiological parameters and clinical treatment of disease. The World Health Organization defines health as: "A state of complete physical, mental and social well-being not merely the absence of disease" [3]. This promotes a holistic approach to caring for patients of all ages [4]. Part of our role, as anesthesiologists, is to try to both reduce the distress of anxiety and prevent its long-term consequences.

Figure 14.1 illustrates the important interactions observed between perioperative anxiety, awareness, behavioral changes, and the potential value of psychological preparation. For example, perioperative anxiety may lead to behavioral changes later on, which may have been prevented or minimized by preoperative psychological preparation. Also, experiences of accidental awareness under general anesthesia (AAGA) itself may lead to anxiety about future anesthetics and other psychological consequences.

This chapter explores some important issues surrounding anxiety related to GA including the main causes and associated factors, and how psychological preparation can help. We will address the special problem of AAGA and consider its severity and how the related distress can be managed. Finally the behavioral consequences of GA and their significance in both the short and long term will be discussed.

Anxiety

Anxiety is defined as an *uncomfortable feeling of nervousness or worry about something that is happening or might happen in the future* [5]. It is an unpleasant emotional experience but it is an inevitable part of normal everyday life. It is estimated that 30–50% of children undergoing GA will be distressed preoperatively [6,7] and up to a quarter require some degree of physical restraint at induction [8].

The consequences of perioperative anxiety can be far-reaching. There is a strong association with emergence delirium [9] and other negative behavioral changes in recovery which may persist for weeks and months [10]. An anxious child is likely to worry already apprehensive parents which, in turn, can heighten the anxiety of the child. Anesthetizing a child who is anxious, distressed, and uncooperative requires consideration of interventions such as non-pharmacological techniques (i.e. play therapy and other behavioral and psychological interventions) and anxiolytic or sedative premedication. Such interventions however are time-consuming and impact on the efficiency of operating schedules. If all children were anxious, all would need these interventions and operating lists would be more predictable. However, in the authors' experience, only a few children are anxious enough to need special management and these children cannot always be identified beforehand. The behavior of children is notoriously difficult to predict and this leads to inevitable difficulties within a busy operating room schedule.

Anxiety may be associated with physical complications. In adults, pre-existing anxiety or depression increases the probability of developing a wound complication after undergoing common orthopedic or general surgical procedures [11]. This may be caused by stress-related elevations in glucocorticoid

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

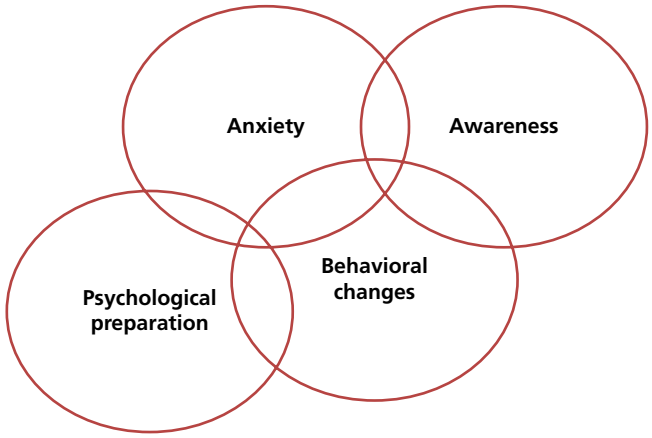

Figure 14.1 Interactions between perioperative anxiety, awareness, behavioral changes, and psychological preparation.

and catecholamine hormones, which suppress the immune system [12,13]. Additionally, increased anxiety may reduce tolerance of pain [14].

Risk factors

The ability to predict preoperative anxiety is important if it is to be effectively managed. In the past 20 years there has been much research not only to measure the frequency, range, and severity of anxiety but also to identify risk factors that could be used to predict behavior and guide interventions. Box 14.1 identifies internal and external risk factors.

Age

Children of differing ages, and thus developmental stages, have distinct triggers for their anxiety and require different management.

Infants (0–1 year)

Infants are too young to appreciate the circumstances and become anxious. Preoperative fasting is more likely to be a cause of crying than fear. Separation anxiety may become a factor after 6 months of age [15] but this will be nullified if parents remain with them during induction of GA. Parental anxiety is a related but separate problem.

Preschool children (1–5 years)

Preschool children are more likely to experience distress and anxiety during admission to hospital for an operation than any other age group [15]. There may be many reasons for this. They are less able to rationalize the reasons for their operation than older children and they have a unique perception of the world related to their imagination. They may therefore develop imaginary concepts and fears about reasons for their admission [16]. In a study of 90 4- to 6-year-olds, 90% reported at least one hospital-related fear and more than a third reported at least seven separate triggering factors for anxiety. The majority of these fears related to pain (e.g. of injections), being left alone, imaginary fears (such as monsters), noises, unfamiliar surroundings, and separation from their parents [16]. Children in this age group have a thinking style that is syncretic in nature in that they do not make deductions or reason beyond what is seen or experienced. They lack rational thought and therefore cannot understand the reasons why they are in hospital. In our experience most children in this age group, and many older children too, can be calmed by the presence of kind and friendly hospital staff in an environment that suits the needs of the child. For small children, a play area staffed by "play specialists" is extremely useful.

Box 14.1: Risk factors for perioperative anxiety in children[7,57,91]

Internal
- Younger age
- Child temperament

External
- Previous experiences in hospital
- Parental anxiety levels

School-aged children (5–12 years)

Children of this age have developed language skills and begin to apply logical thinking to situations [4]. Their anxieties include those related to their condition or the procedure (GA and/or operation). They want information and participation. Simple explanations can help to reassure younger children, while older children will ask questions and require more complex descriptions [15].

Adolescents

Adolescents are high-functioning individuals who can skilfully analyze situations and apply abstract thought [4]. However, their ability to cope and make decisions independently varies considerably depending on their maturity. They will often rely on the support of caretakers but will need to be fully involved in any discussion and decision-making including and especially that related to the method of anaesthetic induction. Adolescents have a fully developed body image and their privacy should be respected. Their fears are consistent with those of adults and these include loss of control, pain, and AAGA [15].

Child temperament

Children who display a greater degree of sociability and social-adaptive capacity are less likely to be anxious [17]. Those who are emotional, impulsive, and socially inhibited are more likely to have preoperative distress and postoperative negative behavioral changes [9]. Moreover, it is accepted that those with higher levels of baseline anxiety (so-called "trait" anxiety) are more likely to experience higher levels of anxiety during times of stress (so-called "state" anxiety) [18].

Previous experience

Children (4- to 6-year-olds) who have been admitted to hospital in the past have more hospital-related fears than their counterparts with no prior experience [16]. Moreover previous traumatic hospital experiences or distress after vaccinations have been shown to be significant predictors for preoperative anxiety [19]. These risk factors can be cumulative [20].

Parental anxiety

Parental anxiety has been consistently associated with distress at induction [7]. This is most pronounced in young

children, and may be a result of a phenomenon called "social referencing" when a child follows a parent's facial expression to guide their own behavior in an unfamiliar situation. It has been demonstrated when infants observe their mother taking part in a stressful interaction with a stranger; they will mirror these responses in their own interaction with this individual [21]. It may therefore be beneficial to use an intervention to calm parents before anesthesia. For example, the children of mothers who received auricular acupuncture compared to sham control acupuncture 30 minutes prior to induction were calmer and more compliant [22]. That a parent's anxiety is the main cause of their children's anxiety, however, is difficult to prove.

Other factors

The type of induction may be a risk factor but evidence remains inconclusive. When 100 children, sedated with midazolam and separated from their parents, were randomized to receive either an inhalational or intravenous induction, significantly more were anxious in the intravenous group [23]. This study was in children having routine ear, nose, and throat surgery and may not be applicable to other groups. In another study, unpremedicated children aged 2–10 years were equally anxious about an inhalational or intravenous induction [24]. In both studies parents were not present at induction, which may or may not have been important.

The location of the induction may also be relevant. In the UK almost all hospitals use separate anesthetic rooms (AR) next to the operating room (OR). To date, no difference has been demonstrated between using an AR or OR in respect of either children's distress or the parents' satisfaction. Furthermore, no difference has been demonstrated in operating schedule efficiency [25]. A change in a child's disposition is often observed as they enter the OR or the AR and we believe that any unfamiliar environment, especially if it involves separation from parents and apprehension about forthcoming events, is the main trigger for anxiety-related behavior. When faced with a frightened child the anesthesiologist needs to be patient, sympathetic, and able to distract and entertain the child while being skilful in the chosen induction technique.

Assessment and measurement

Various scales and scoring systems have been developed to measure and evaluate anxiety. These are not only valuable in a clinical setting but also important tools in providing quantitative data for statistical analysis in research studies.

The State-Trait Anxiety Inventory for Children (STAIC) has long been considered the gold standard for assessing perioperative anxiety. It consists of a self-report scale with 40 statements assessing how the child feels at a particular moment in time (state) and their tendency to feel anxious (trait) [26]. However, this scale may not be practical for anxiety related to induction as it takes approximately 5–10 min to complete. Also, because it is completed by the patient, only children over 5 years old can use it. It is probably impractical in a high-turnover operating schedule and in children who are extremely anxious.

Consequently, The Yale Preoperative Anxiety Scale (YPAS) was developed and revised by Kain et al [27] to become the modified YPAS (mYPAS). The mYPAS is a rapid observational scoring tool that can be applied to children over 2 years of age at any stage of the patient perioperative journey. It had, initially, five categories: activity, emotional expressivity, state of arousal, vocalization, and use of parents. The latter category was eliminated in the mYPAS because of content overlap and inconsistencies with parental presence at time of scoring. It was initially applied at four points during the perioperative period but has since been rationalized to waiting in the preoperative holding area and at the time of showing the child the anaesthetic mask: this creates the mYPAS-Short Form (mYPAS-SF) [28] (Table 14.1).

Compared with the STAIC scoring system, the mYPAS demonstrated good observer reliability and validity for anxiety throughout the perioperative period [27]. Even though the

Table 14.1 mYPAS short form

Category	Scores
Activity	1. Looking around, curious playing/reading. Moves around room toward toys/parents
	2. Not exploring/playing. May look down/fidget/suck thumb. May sit close to parent. Play has a manic quality
	3. Moving from toy to parent in unfocused manner/frenzied/squirming movements. May push mask away/cling to parent
	4. Actively trying to escape using all four limbs. Not engaging with toys. Desperate clinging to parent
Vocalization	1. Reading, asking/answering questions, laughing, babbling (as appropriate to age)
	2. Responding to questions but only whispering/head nodding
	3. Quiet, no responses to adults
	4. Whimpering, moaning, silent crying
	5. Crying or screaming
	6. Sustained loud crying or screaming
Emotional expressivity	1. Happy/smiling or playing contentedly
	2. Neutral, no facial expression
	3. Worried, frightened, or tearful
	4. Distressed, extremely upset
State of arousal	1. Alert, looks around, notices what anesthesiologist does
	2. Withdrawn, sitting still, may have face turned into adult
	3. Vigilant, looking around quickly. Eyes wide, body tense
	4. Panicked, may be crying, pushing others away

Source: Reproduced from Kain et al [27] with permission of Elsevier.

mYPAS scoring system is simple it still requires time to assess the child. Using the FACES pain scale instead is quicker and has been proposed as a rapid screening tool to identify anxious children at the preoperative assessment clinic [18]. When tested against the STAIC scoring system, this method demonstrated poor specificity and sensitivity, but it may be useful in identifying extremely anxious children [18].

Induction of anesthesia in the uncooperative child

Despite efforts to identify and prepare anxious children, it is common for children to be unexpectedly distressed and difficult to manage at induction. In this situation, the first option available to the anesthesiologist that must be considered, albeit carefully, is postponement of the procedure to allow adequate psychological preparation. A discussion should take place at this stage with the operating team and the parents about what is in the best interests of the child. Delaying the procedure may not be sensible in many circumstances, for example those involving oncological, cardiac, or acute neurological conditions. Long waiting times and financial implications for families traveling significant distances for specialized treatment are other reasons not to delay. This is a challenging scenario and the anesthesiologist should endeavor to safely induce anesthesia while minimizing distress. The following methods of reducing distress may be considered.

Non-pharmacological

A range of behavioral techniques and psychological approaches are possible. Many of these are time consuming and may not be effective although the specialist pediatric anesthesiologist should have some knowledge and experience of simple behavioral methods to reduce anxiety. These will be appropriate to the age of the child and the reader is referred to a full discussion of the subject elsewhere [29]. Parents should also be helped to deal with this difficult situation as they will need to agree with any proposed course of action.

Pharmacological

A full discussion of the range of sedative and anxiolytic drugs can be found in *Pharmacology for Anaesthesia and Intensive Care* [30]. In the authors' hospital, four groups of drugs, used either alone or in combination, are in current use. In children predicted to need premedication, midazolam is usually given orally (to be swallowed or held in the mouth) as a first-line agent. Other potentially useful drugs (all oral) include morphine, clonidine, and ketamine. We think that it is important to maximize the chance of the premedication being effective by ensuring the timing is appropriate to gain the maximum sedative effect (e.g. oral midazolam may have a window of effective time between 30 and 60 min after its administration). Also, the child should, ideally, be first on the operating schedule to make premedication timing easier, avoid the anxiety of waiting, and minimize the period of fasting. In the scenario of an unexpected need for sedation in the OR, midazolam (sublingual or nasal) and ketamine (nasal) are sometimes necessary.

If intravenous anesthesia is not possible because the child is too uncooperative, induction of anesthesia will usually involve inhalation of sevoflurane. If this is impractical then an intramuscular injection may be considered. Ketamine, at a dose of 4–5 mg/kg, provides effective sedation to facilitate an intravenous cannula insertion or inhalational induction within 5 min, but the injection is itself painful and should be necessary only in very rare circumstances [31].

Physical restraint

Physical restraint varies according to the size of the child and may only involve tight cuddling of an infant or a toddler [32]. Physical restraint of older children should only be attempted as a last resort. Situations where it may be considered include vital and urgent surgery for a child with behavioral problems who cannot be reasoned with, who does not respond to non-pharmacological methods, and in whom pharmacological methods are impractical or ineffective. In the UK, the Department of Health has published guidelines for restraint of children in a healthcare setting [33].

The issue of physical restraint remains controversial. This was demonstrated in surveys in the UK and US that revealed a wide range of opinions as to what constitutes restraint and when it may be appropriate. In general, the tendency for it to be utilized decreased with increasing age of the child [34,35].

Parents also express general dissatisfaction after being involved in restraining their child for an anesthetic, with 62% of parents in one survey stating they would prefer a sedative premedication for their child in future [36]. Nevertheless, restraint may be appropriate to some situations. In our hospital a recent feedback survey showed that out of over 700 children approximately 20% of parents reported they needed to restrain their child to help the anesthesiologist and fewer than 5% thought that this was not the best approach [37].

Legality

Laws vary around the world; here we present the situation relevant to the UK and some principles that may be applicable widely. In the UK, a child who does not have capacity can be anesthetized against their will providing there is parental consent [34]. Capacity is defined as the ability to use and understand information to make a decision, and communicate any decision made [38]. Young children, usually, do not have capacity, but "people aged 16 years or over are entitled to consent to their own treatment, and this can only be overruled in exceptional circumstances" [38]. Children younger than 16 can also consent provided they have capacity. This is usually termed "assent" in a child younger than legal age of consent, and for developmentally normal children the age at which they are assumed to have capacity to give assent is usually 7 years. Refusal to give consent is more complicated. If a child has capacity their refusal should be respected and the GA and operation should be delayed. It may take time to persuade the child and every effort should be made to do so. In extreme circumstances caretakers can follow a legal process which would enable them to act in the best interests of the child albeit against their wish. If consent is withdrawn during induction the anesthesiologist is permitted to proceed if they believe that stopping would be unsafe[34].

Summary

Anxiety prior to GA is a complex, varied, and challenging problem occurring in up to half of all children [6,7]. Anxiety is a normal and appropriate behavioral response and only a few

children show appreciable distress and need a special intervention. Distress caused by anxiety is often multifactorial; management begins with identifying vulnerable children beforehand. A poor patient experience may influence the child's reaction to future admissions.

KEY POINTS: ANXIETY

- Preoperative anxiety can have clinical and psychological consequences
- A large proportion of children experience anxiety preoperatively
- The healthcare environment and caretakers should be child friendly
- Only a minority of children need a special intervention
- Children at risk should be identified
- Previous encounters have important influences on future experiences
- Restraint is a last resort in the non-compliant, combative child

Psychological preparation

The effect of preoperative anxiety and a negative perioperative experience can have important short- and long-term effects. It has been estimated that a 10-point increase in the mYPAS score is associated with an increase in emergence delirium or maladaptive behavioral changes by 10% and 12.5% respectively [9]. The following strategies may be useful before children arrive in the OR to help them to adapt more effectively to potentially intimidating and bewildering situations thus reducing anxiety and negative behaviors. The strategies covered include not only non-pharmacological techniques of calming a child but also the pharmacological methods (anxiolytic premedication drugs) in common use.

Non-pharmacological

A Cochrane review in 2015 of various non-pharmacological interventions included 28 trials and a total of 2681 children. It found that there were major inconsistencies in the measured effects of non-pharmacological interventions [39]. Many of the studies had small sample sizes and were not adequately blinded, leading to a risk of bias. This shows that high-quality research is rare and probably very difficult in this area. Conclusions should therefore be drawn cautiously. Nevertheless, some of the strategies show promising results and are worthy of having their wider application tested.

Coping

Coping is the patient's ability to manage and minimize stress. There are various coping strategies appropriate to age and maturity of the child. Children less than 4 years of age can use distraction such as play. This is a type of "emotion-focused" coping which involves trying to directly reduce the negative feelings associated with a stressful event. More mature children may use "cognitive" coping where the perception of the situation guides the individual's ability to cope [4]. As the child grows, he or she will ask more questions and attempt to have "cognitive mastery" of a situation. For example, if they are attached to a heart monitor they seek reassurance by learning about the heart and the monitor [17]. Mature children try to problem-solve and will begin to seek support from their peers rather than their parents [16]. All of these coping methods are more likely to be effective if they are discussed before the day of surgery [40].

Preoperative preparation programs

Many hospitals offer preparation leaflets and videos to children and their parents to explain what will happen to them during their admission. A visit to the hospital may help the child to gain familiarity with the surroundings. There is some evidence to support preoperative visits and programs but the types of intervention and their effects vary. Generally, they are considered useful but they require parent involvement and extra healthcare resources.

In the Advance trial [41], a preoperative program was developed which consisted of a group of family-centred interventions 5–7 days prior to surgery, including information videos and leaflets and the opportunity to practice an inhalational induction by playing with a facemask, followed by distraction therapy on the morning of surgery and at induction with parents being present the entire time. There were 400 children aged 2–12 years randomized to control groups (consisting of standard care with or without parent presence or midazolam premedication) or to receive the intervention. Children in the Advance group were significantly less anxious in the holding area, had less emergence delirium and lower analgesic requirements, and were discharged from recovery earlier than those children in any of the three control groups [41]. Anxiety levels at induction were comparable to those receiving premedication with midazolam and lower than those receiving standard care with or without parental presence. The two elements with the greatest impact on reducing anxiety were practicing with the facemask at home and the parents' adherence to the agreed distraction methods [42].

In another study, age-appropriate comic-book leaflets were given to the children 1 week beforehand and this significantly reduced the anxiety scores compared to a control group [40]. Third, in support of preparation programs, a further study showed that when an illustrated children's book was provided at the preoperative visit, parents were less anxious and children were calmer during the admission [43]. Finally, attendance at a preoperative workshop 2 weeks beforehand, at which toy models and figurines were used to explain the perioperative process, was associated with less preoperative anxiety and fewer postoperative negative behavior changes [44].

Preoperative explanation and communication also helps parents [41]. Parents want in-depth information about GA, and this has been shown to reduce their own anxiety [45]. Likewise, children are inquisitive by nature and studies generally support the concept that children want more, not less, information. In a US study of 143 children, anxious children wanted more information, especially about pain; children less than 12 years said they wanted to know more about the operating theatre environment [46]. At the preoperative visit the anesthesiologist may focus on communication with the parent, possibly with the intention of not discussing potentially distressing details with the child. Evidence, however,

suggests that information does not usually upset children and could be helpful to them to improve their coping.

Overall, the evidence supports that negative behavioral changes can be decreased by preoperative programs and preparation [41,44], however the grade of evidence is not strong due to problems with randomization and selection bias.

Distraction therapy

Distraction therapy, for example using clown doctors, has been shown to significantly reduce anxiety in 5- to 12-year-olds [47]. It is unclear, however, whether it is specific distraction or general interaction that is effective. Other distraction techniques using entertainment videos played during induction [48,49] have been shown to reduce anxiety scores when compared with controls or with parental presence alone. Conversely, other studies have shown no effect. In one study video distraction therapy failed to calm children of 2–7 years [50]. This may have been because the children were too young and too anxious. Interventions therefore may be valuable for some children, but not universally applicable. In a study of 84 ASA I and II patients aged 4–8 years, children receiving a smartphone with age-appropriate applications to play with in the preoperative holding area and continued until inhaled induction was completed had significantly lower mYPAS scores than children who received no preparation but whose parents had verbal and written orientation to the anesthetic procedures [51]. In another study of 135 patients aged 2–12 years, children were given a portable digital video disk (DVD) player in the preoperative holding area to watch age-appropriate animated movies and compared to a group who received oral midazolam premedication and a third group with both DVD and oral premedication. There was no difference in mYPAS and visual analog score for anxiety, from the holding area until parental separation, between groups [52].

The environment is also potentially important. Anesthetizing children in a dimly lit room with soft background music and only one person talking to the child can reduce anxiety scores [53]. Music, alone, has not been shown to be of appreciable benefit. Interestingly there is also a "therapist effect" [54] in that some people are more able to calm children than others. Hypnotherapy may be helpful and has been associated with fewer children having negative behaviors postoperatively [55].

Parental presence

Anxious parents make their children more anxious [56,57]. Calm parents ought to reduce anxiety in their children, however research has consistently failed to demonstrate this [39]. In the UK, almost all parents want to accompany their child to the anesthetic room and are present until the child is asleep. Parental satisfaction is generally higher when they accompany their children, even (or especially) when the surgery is high risk. In one study, 97% of parents thought that being present was a positive experience for both themselves and their children [58]. In the UK, parental presence is generally seen as a positive experience for all; although it has not been shown to dramatically reduce anxiety in the child, it does not have a negative impact and increases parental satisfaction. The family's expectations may need to be discussed beforehand. Having a separate anesthetic induction room removes any barrier to parental presence. In our view, parents should be made welcome and helped with guidance and preparation.

Timing and selection

A preoperative visit on the day of surgery may have little effect on a child's anxiety [40], probably because the need for psychological preparation is related to many factors [59] and the timing of a psychological intervention may be relevant. In an observational study of 143 children undergoing day-case surgery, a preoperative preparation program had no effect overall. However a reduction in anxiety was seen in children who had participated in the program 5–7 days before admission. Children who had participated only 1 day before admission were made more anxious by the program [59]. In addition, children under 3 years old who had had previous experience of hospitalization seemed to be made more anxious by the program irrespective of the time [59]. These findings contrast with those of a study in Sweden which found that psychological preparation was most successful in children younger than 5 years old with a previous experience of hospitalization [20]. The methodological differences between the studies may be important. In the Swedish study all children had premedication intramuscularly, which was identified by the researchers at the time to be a major triggering factor in itself for development of anxiety. The timing of the preparation program varied and the psychological preparation was based on role play which may not be suitable for all ages of children [20]. These points show that it is difficult to be certain of the efficacy of psychological interventions and indicates the importance of tailoring different strategies to different children.

The person who delivers a psychological intervention may also be very important. A study in Sweden showed that if the nurse who had met the child at the preoperative assessment was present at induction and in the recovery unit, salivary cortisol levels (a potential biological marker for anxiety) were significantly lower compared to children who were seen by different healthcare professionals [60]. This supports the idea that trust and rapport are important factors.

Pharmacological

Despite our best efforts, anxiety may need to be managed with an anxiolytic or sedative "premedication" drug. An ideal agent for premedication should have the following properties:

- rapid onset time
- short recovery period
- no airway effects
- no cardiovascular instability
- analgesia and amnesia
- no paradoxical agitation
- simple and painless administration
- pleasant taste and smell
- no nausea or vomiting.

The perfect agent does not exist but the common classes of anxiolytic premedication in current use include benzodiazepines, opioids, α_2-agonists and N-methyl-D-aspartate (NDMA)-receptor antagonists. The principles by which the drugs may be selected are discussed below and a summary of important pharmacological effects can be found in Table 14.2. Dose ranges are provided but the correct dose depends upon

Table 14.2 Comparison of classes of drugs available for premedication [31,133–140]

Class of drug	Advantages	Disadvantages
Benzodiazepines	Rapid onset/offset time	Intranasal burning/bitter taste
Midazolam	Amnesia	Potentiates opioid-mediated respiratory depression
Oral 0.5 mg/kg		
Buccal 0.2–0.3 mg/kg		Paradoxical disinhibition
Intranasal 0.3 mg/kg		No analgesia
Rectal 0.3–0.5 mg/kg		Hiccups
Opioid	Analgesia	Respiratory depression
Morphine		PONV
Oral (0.2 mg/kg)		
Fentanyl		
Transmucosal 15–20 μg/kg		
α_2 agonists	Preserved airway reflexes	Cardiovascular depression – hypotension/bradycardia
Clonidine	No respiratory depression	
Intranasal 2 μg/kg	Tasteless	Prolonged onset and duration of action
Oral 2–4 μg/kg	Reduction in PONV	
Dexmedetomidine	Sedation more similar to sleep	
Intranasal 1–2 μg/kg	No disinhibition	
	Reduced shivering	
	Analgesia	
	Antisialagog	
NDMA receptor antagonists	Analgesia	Excess salivation
Ketamine	Preserved airway reflexes	PONV
Oral 3–8 mg/kg	No respiratory depression	Hallucinations
Intramuscular 4–5 mg/kg		

NMDA, N-methyl-D-aspartate; PONV, postoperative nausea/vomiting.

many factors and the reader should consult their hospital formulary for guidance.

Benzodiazepines

Benzodiazepines act via the gamma-aminobutyric acid-A ($GABA_A$) receptor, GABA being the main inhibitory neurotransmitter in the central nervous system. The most common member of the class of drugs used for premedication is midazolam because it is water soluble and has a rapid onset and short half-life [30]. Given orally, this drug is usually effective within 30 minutes. Occasionally children have paradoxical excitement, and this can be reversed with flumazenil.

α_2 Agonists

The main α_2 agonists available are clonidine and dexmedetomidine. Dexmedetomidine has eight times greater affinity for the α_2 receptor than clonidine. It acts at the locus coeruleus (LC) in the pons [61] which is the nucleus responsible for promoting arousal. The majority of noradrenaline synthesis in the brain is at the LC where there is a dense array of excitatory projections to the cerebral cortex inhibiting input to GABAergic neurons [62]. The inhibition of the release of noradrenaline at this location will therefore produce sedation. Dexmedetomidine acts at the LC to cause a natural, physiological sleep quality in contrast to propofol and midazolam [61]. This is supported by EEG findings that show that dexmedetomidine produces EEG patterns similar to natural sleep [61]. Clonidine has some analgesic properties.

NDMA-receptor antagonists

Ketamine is a phenylcyclidine derivative and a non-competitive inhibitor at the N-methyl-D-aspartate (NMDA) receptor, where glutamate, the brain's main excitatory neurotransmitter, acts. It is a potent analgesic and usually creates a calm state. Occasionally it causes distressing hallucinations. It can be administered into the nose using an atomizer or spray device and this method has rapid effect. By mouth the drug has a slow and variable onset. The intramuscular route is most reliable for this drug, but the injection itself is painful, distressing and, in our opinion, should be used only in exceptional circumstances. Others have suggested that, in the scenario of an uncooperative child, a ketamine injection has advantages over a forced inhalational induction with sevoflurane because it may be performed on the admission ward and the sedation is more rapidly achieved, thus minimizing duration of restraint [15].

Opioids

Opioids are rarely a first-line choice for anxiolysis, mainly due to the increased risk of respiratory depression and the side-effects of nausea and vomiting. They may however be useful for anxious older children who may need a combination of two drugs.

Studies comparing these drug classes show that α_2 agonists are superior to benzodiazepines in terms of greater sedation, reduced emergence delirium, and improved postoperative pain relief [63]. Intranasal dexmedetomidine (2 μg/kg) can produce similar sedation to oral midazolam (0.5 mg/kg) [64], but 1 μg/kg of dexmedetomidine has a slower and less reliable onset [65].

There are problems to consider and overcome if a premedication drug is ordered. It may be difficult to persuade a child to take the anxiolytic premedication, especially if they have a behavioral disorder. Once taken, the drugs can take 30–45 min to achieve their full effect and this will have an impact on the operating schedule. All the drugs have a variable effect and some children may become too deeply sedated with standard

doses. It is important to be aware that a sedated child can develop airway obstruction and respiratory depression (cardiovascular compromise is rare but possible in dehydrated children or those with severe cardiac dysfunction). All sedated children should be monitored and observed by a vigilant person trained to prevent, recognize, and manage complications. Other premedication problems are disinhibition, delayed emergence, and postoperative drowsiness.

Summary

There are many tools at our disposal to prevent or minimize negative psychological effects of hospital admissions. However, the efficacy of the interventions is variable and patient selection is important. Preschool children have the greater chance of being anxious and having emergence delirium, and further research is needed to help this patient group. Premedication still plays a significant part in facilitating the induction process for many children.

KEY POINTS: PSYCHOLOGICAL PREPARATION

- Children adapt to stressful situations differently according to their age and maturity
- Psychological preparation programs can be valuable for some children
- Parental presence at induction may be expected by parents and their children
- Premedication should be reserved for children for whom other strategies have been ineffective

Awareness

General anesthesia is the abolition of consciousness, memory, and involuntary reflexes in order to create safe, stable surgical operating conditions and prevent pain and distress. Accidental awareness during general anesthesia (AAGA) is defined as the explicit recall of intraoperative events. The manifestations of AAGA are broad and vary from minor auditory and tactile sensations to major horrific pain and a feeling of being unable to move. The distress and psychological consequences of AAGA will vary. Children commonly recall tactile and auditory experiences but, fortunately, the severe distress of pain and immobility is reported rarely [66].

Incidence

The incidence of AAGA depends on the method used to identify recall. AAGA is a well-reported subject in adults and the common method to identify it is by a postoperative interview of consecutive patients using a series of questions devised by Brice et al [67]. The postoperative questionnaire, known as the Brice questionnaire [67], is typically administered on the first postoperative day and again on day 3–7 and day 30. It is thought to be the best method of detection of AAGA [68]. Using the Brice method in adults, the overall incidence has been reported to be between 0.1 and 0.2% [69–71]; this rate varies however with types of patients and operations (Box 14.2). The 5th National Audit Project of the Royal College of Anaesthetists and the Association of Anaesthetists of Great Britain and Ireland (NAP 5) was a survey of spontaneous first reports in UK National Health Service patients over 12 months in 2012–2013. It is the largest and most comprehensive audit of AAGA to date and it found that the overall incidence was 0.005%. This incidence, being of spontaneous reporting, is strikingly lower than the postoperative interview method [72] and this difference suggests that only a minority of patients who have AAGA spontaneously disclose it.

Box 14.2: Risk factors for awareness under general anesthesia

Patient risk factors
- Hemodynamic instability
- Difficult airway
- Advancing ASA grade
- Obesity
- Female gender
- Younger age (not including children)

Anesthetic risk factors
- Total intravenous technique
- Neuromuscular blockade
- Junior anesthesiologist

Surgical risk factors
- Cardiothoracic
- Obstetrics
- Emergency surgery

Source: Reproduced from Pandit et al [72] with permission of Elsevier.

Fewer data are available concerning pediatric AAGA. There are five recent cohort studies using the postoperative interview method. Combining data from these, the overall rate of AAGA in children was 0.74% [66], which is much higher than rates reported for adults. Interestingly, the NAP5 study found that AAGA was reported much less frequently (0.002%) by children than by adults [73] (Fig. 14.2). This suggests that an even smaller proportion of children who have AAGA report it spontaneously.

In our own survey of patient feedback in our hospital, in which 241 children completed a confidential written questionnaire, we found that 16.2% reported something that they thought took place after the induction and before the end of the operation [37]. That all these methods yield different

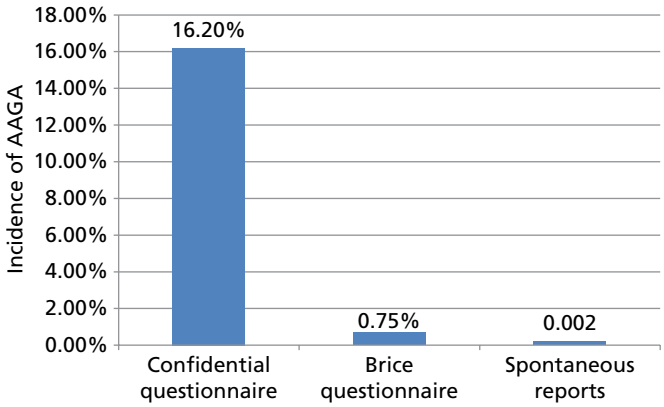

Figure 14.2 Comparison of incidences obtained from differing methods of accidental awareness under general anesthesia detection in children.

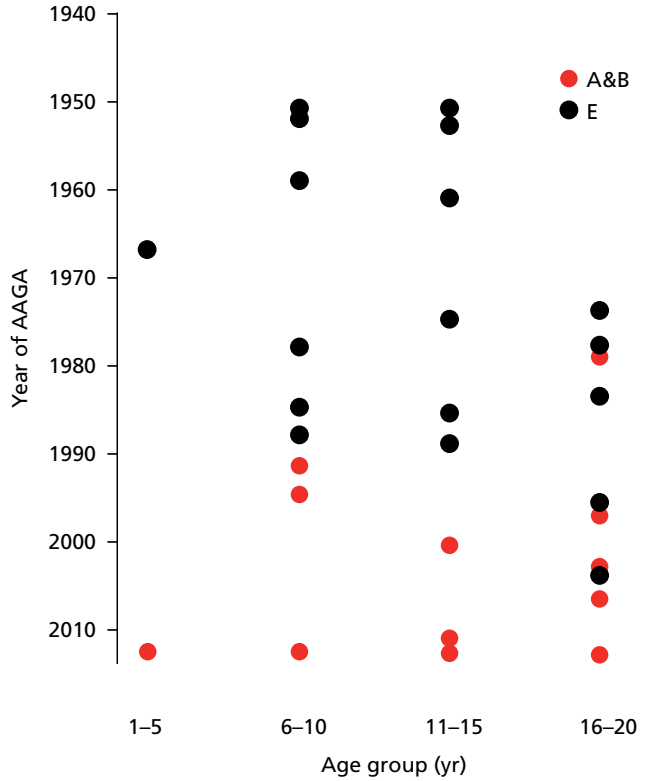

Figure 14.3 Year of accidental awareness under general anesthesia first reported to the National Audit Project 5 in 2013 [72]. Red circles, accepted and verifiable reports; black circles, not verifiable as records not available. *Source:* Reproduced with permission from the Royal College of Anaesthetists. Originally published in the report and findings of the 5th National Audit Project: Accidental Awareness during General Anaesthesia in the United Kingdom and Ireland, September 2014.

results may be explained if children are too frightened to reveal or report AAGA; on the other hand, the questionnaire method, without an interview, may not distinguish the experience of awakening in recovery from that of true AAGA [74].

The timing of the AAGA report in relation to the GA is particularly interesting in children. NAP5 found that there is often a long delay, perhaps 30–40 years. This supports the idea that some children are reluctant to report AAGA [73,75] (Fig. 14.3). The reasons why many children do not report their experiences and why others delay their disclosures are unclear. It may be that the experiences are not considered important by the child or it may be that the experiences are too distressing. A few children were not believed by their parents. Furthermore, a child's ability to correctly interpret their experiences, thereby appreciating the significance and meaning of such an event, distinguish them from dreams, and form explicit memory is dependent on age and individual cognitive abilities. Younger children may also struggle to express these events to adults due to a limited vocabulary.

Furthermore, AAGA requires a patient to recall intraoperative events; however, it is possible that memory and consciousness become uncoupled during GA and a patient could be aware but not be able to recall the experience [68]. This is illustrated by studies using the isolated forearm technique in which the patient's arm is kept free from the effects of a neuromuscular blocking drug (NMB). As the anesthetic is lightened (albeit to a dose that is considered compatible with unconsciousness) the patient responds to commands by moving their isolated arm, yet they cannot recall doing so [76]. In a survey of children under isoflurane anesthesia Andrade and colleagues found that only 2 of 181 children responded and neither had memory of it [77].

Memory

The ability to process information and retain memories is closely linked. It is generally accepted that a wide variety of new information is selected for cerebral processing and is held in the area of the brain dealing with short-term or working memory. The interpretation of new information will be dependent on prior knowledge and previous experiences already held in the long-term memory [78]. Key to this process are a child's age, cognitive abilities, and prior experiences. Children's brains are rapidly developing and growing and their cognitive abilities and proficiency in forming memory are therefore evolving.

Implicit memory

Implicit memory is that which occurs subconsciously and manifests as changes in behavior. It develops early and stabilizes by 3 years old [79]. Age has little effect thereafter. Implicit memory is hard to demonstrate in young children. One example is that when children of 3 years old are read a children's book, 3 months later they show no recognition of the pictures they had seen before, but can point to blurred similar images of the same pictures more quickly than children in a control group [80]. Infants are thought to have implicit memory before their explicit memory has developed [81].

Explicit memory

Explicit memory involves the conscious recollection of true events. Explicit memory develops throughout childhood. Few adults can recall events of their childhood before the age of 5 years. Nevertheless there is evidence of explicit memory developing in infants and toddlers. Groups of infants aged 8–10 months have been observed to imitate the sequence of actions with toys to generate a rewarding outcome, for example the finding of a toy behind a door [82]. The advancement in explicit memory may be a continuous steady process or it may have abrupt development phases [83].

Episodic memory

Episodic memory is a form of explicit memory of specific events and contextual features such as times, places, and people. It has been demonstrated in children by asking them to recall facts presented a week previously. Recollection of the facts (and the circumstances of when, where, and who told them the fact) improves markedly between the ages of 4 and 6 years [84]. The specific areas of brain development leading to these changes are thought to be related to the maturity of the medial temporal lobe including the hippocampus and the neural connections with the frontal cortex [79].

Dreaming

There may be a weak association between dreaming under GA and AAGA. Huang et al, in a prospective cohort study of 864 5- to 12-year-olds, found an incidence of dreaming of

10.4%. It was significantly more common in younger children and associated with anxiety in their parents [85]. Children in this study who did dream were significantly more likely to have also experienced AAGA. This may be because dreaming occurs under shallow depths of anesthesia [85]. Dreams, however, were not associated with negative behaviors [85].

Implications

What does this mean for anesthesiologists? How can higher awareness rates in children be explained and how can we reduce the probability of AAGA? The existence of explicit, specifically episodic, memory is pertinent in children as it relates to the child's ability to recall personal experiences. Based on current understanding, children of preschool age are unlikely to retain memories of AAGA. The implicit memory is functional at this age and unpleasant AAGA may contribute, in theory, to anxiety and other negative behaviors later. Reliable detection of AAGA with certainty in this population of children, however, is not possible.

Studies have failed to identify specific risk factors for children [75]. In contrast to adults, NMBs are not associated with AAGA [66,75]. In one prospective study, six out of 928 children reported awareness, and although four of these received a NMB, none reported being unable to move [75]. Davidson et al analyzed anesthesia factors in 4486 children and found associations with the use of tracheal tubes and nitrous oxide [66]. Associations, however, are not necessarily causation.

Reducing accidental awareness under general anesthesia

The higher awareness rates in children suggest we should be more proactive to reduce AAGA. The use of EEG monitoring such as Bispectral Index (BIS) is, to some, a logical step and it is used increasingly in the UK. Evidence of efficacy however is not compelling. The B-aware trial of 2004 [86] found that using BIS significantly reduced the rate of AAGA awareness in high-risk adults. In contrast, the B-unaware trial in 2008 [71] showed that expired breath monitoring of volatile anesthetics was equivalent to BIS. A Cochrane review in 2014 [87] concluded that BIS may provide some protection from awareness when clinical signs alone are used, but it was not superior to expired breath monitoring. In the UK, BIS is being used most frequently in adults receiving a total intravenous technique and NMBs [88].

The BIS algorithm was developed from EEG data from adults. Its validity in children has therefore been questioned. Given the limited use of BIS in predominantly volatile-based GA, this mode of monitoring may only have a small role to play in preventing awareness in children.

The NAP5 project concluded that the causes of AAG were likely to be the same in children and adults. Common causes were mistakes in technique and related to NMBs at induction and emergence [73].

Management

When a child reports AAGA, a meeting with the child and parents should be offered as soon as possible. The child should be believed although other explanations unrelated to AAGA may be considered. An apology and an explanation are courteous and appropriate, and not necessarily an admission of fault. The timing of the awareness should be checked against the anesthetic record. NAP5 suggests that there are four signs that may indicate psychological sequelae: nightmares, flashbacks, new anxiety, and depression. These should be sought in the first 24 hours and followed up at 2 weeks. A referral to a psychologist should be made if these signs persist [88,89]. AAGA in children tends to be less distressing in the short term than AAGA in adults [75].

KEY POINTS: AWARENESS

- Implicit memory develops by 3 years of age, but explicit memory begins to develop later
- AAGA rates, as detected by interviews, are higher in children
- Children are less likely to report awareness than adults
- Specific risk factors for children are unknown
- Children are less likely to suffer psychological sequelae in the short term than adults

Behavior change

Short-term negative behavioral change

Negative behavioral change in children after GA has been acknowledged since the 1940s [90]. Despite improvements in quality of anesthesia care, this problem has continued. Common short-term behavioral problems include separation anxiety, defiance towards authority, temper tantrums, nightmares, and nocturnal enuresis [1], which may persist for over 12 months in 7.3% of children [1]. Longer-term consequences are unknown.

Evaluating behavioral change of children relies on the completion of questionnaires by parents. The Post-Hospitalization Behavior Questionnaire (PHBQ) was developed over 50 years ago and is still in use. Examples of questions include: Does your child have bad dreams at night or wake up and cry? Does your child follow you everywhere around the house? [91]. The following studies show interesting and consistent results.

In a large cohort study of over 800 children, significant negative behavior changes (i.e. seven or more changes reported with the PHBQ) were noted in 24% of children aged 3–12 years undergoing a variety of surgical procedures. These changes persisted to 30 days in 8%. Anxious parents, older siblings, being young, and a previous bad hospital experience were associated factors [92].

Behavioral changes were demonstrated amongst 551 children in Finland aged 4 months to 13 years. Problems occurred in 47% and mostly in children aged 1–3 years. Associated factors were postoperative pain and previous negative experience of healthcare. Nine percent of children still had problems 4 weeks after the operation [10].

A study from three UK hospitals involving 131 2- to 12-year-olds showed that pain and behavioral change were still evident in 25% and 32%, respectively, by 4 weeks. Again, younger age, anxiety, pain, and poor previous hospital experience were associated factors [93].

Furthermore, 80% of children had negative behavioral changes the day after tonsillectomy or adenoidectomy, which remained in 30% 2 weeks later [92]. Apathy and withdrawal were more common than other problems in the first few days and separation anxiety predominated at 7–14 days. Postoperative pain was the strongest risk factor [94].

Behavioral changes may also be related to culture or community. Hispanic Spanish-speaking parents have reported significantly fewer negative behavioral changes than White English-speaking parents [95].

Identifying children at risk of postoperative negative behavior change could help to focus preventative strategies. Certainly pain at home is often undermanaged by parents and this could be improved with out-of-hospital support [96].

Even though associated "risk" factors have been identified in these studies, it is not possible to be sure about whether the anesthesia is responsible or whether it is the surgery or even the hospital episode overall that is more important. Certainly, the method of induction of GA, either inhalational or intravenous, made no difference to behavioral disturbances 2 weeks postoperatively [23].

Psychological instabilities have been demonstrated in children after a medical admission not involving GA. A study found no difference in incidence of problem behaviors in children who had caustic esophageal injury (requiring repeated dilatations under GA) compared with children with chronic renal disease requiring hemodialysis. Neither group, however, may have been comparable with children undergoing minor elective surgery [97]. Disruption of family life and chronic pain are probably important factors generating stress and behavioral problems [97].

Emergence delirium

Emergence delirium (ED) occurs on awakening from GA and was first described in the 1960s [98]. It is characterized by a state of dissociation with inconsolable crying, excitation, and agitation. It lasts for less than 15 min in 70% of cases but can continue for up to an hour [99]. The child is always distressed and may be restless enough to cause self-injury, including damage to the surgical site. Negative behaviors are weakly associated with ED: one study found that children were 1.43 times more likely to develop negative behavior if they had ED [9].

Assessment

Children awakening after GA may be in pain or hungry or confused (possibly related to hypoxia, hypoglycaemia, or drugs) which is often difficult to distinguish from ED. Studies have shown considerable variation in the incidence of ED, ranging from 10% to 80% [100]. To help evaluate ED the following scoring systems have been developed.

Pediatric Anesthesia Emergence Delirium (PAED) scale

The PAED scale (Table 14.3), developed in 2004, is considered to be a reliable and validated tool. It is more detailed than other ED scales and hence its main limitation is that it takes time to complete [101]. A score of 10 was shown to have reasonable sensitivity and specificity for ED [99]. Given that there is overlap in the behavioral items of ED and pain, observers have suggested that lack of eye contact and lack of awareness of surroundings are important markers of ED [99,102].

Cravero scale

The Cravero scale has five levels, each combining consciousness, crying, and restlessness. ED is defined as crying and restlessness lasting more than 5 min [103].

Watcha scale

The Watcha scale has four points and a simple design [104]. It defines ED as inconsolable crying or agitated and thrashing behavior for any length of time [105]. This scale correlates best with the PAED scale [105].

Potential risk factors

Age

ED is most common in toddlers and young children, and this may relate to their psychological maturity and cognitive ability [106]. Eighteen percent of 3- to 7-year-olds have ED [106].

Preoperative anxiety

The rate of ED increases by 10% for every increment of 10 points in the child's mYPAS score [9]. This suggests that modification of anxiety may reduce ED.

Type of anesthesia

ED can occur after any GA technique but sevoflurane is considered to be the most commonly associated drug [107]. A Cochrane review in 2014 concluded that within 158 studies involving 14,045 children ED was more common in anaesthetics maintained with sevoflurane as opposed to halothane or propofol, with it occurring in 50–75% more cases when sevoflurane was used. There was no conclusive evidence indicating the effect of maintenance with desflurane or isoflurane [108].

Table 14.3 The pediatric anesthesia emergence delirium (PAED) scale

Behavior	Not at all	Just a little	Quite a bit	Very much	Extremely
The child makes eye contact	4	3	2	1	0
The child's actions are purposeful	4	3	2	1	0
The child is aware of their surroundings	0	1	2	3	4
The child is restless	0	1	2	3	4
The child is inconsolable	0	1	2	3	4

Reverse scoring applied for items 1 and 2.
Source: Reproduced from Bajwa et al [105] with permission of Elsevier.

Rapid awakening was thought to be a possible factor [106]. However, desflurane has a shorter duration of action than sevoflurane and has not been shown to have higher rates of ED [108–110]. When 110 children induced with sevoflurane were randomized to receive sevoflurane or isoflurane for maintenance, there were significantly more children with ED in the group who were continued with sevoflurane for the entire anesthetic with awakening times similar on average [111]. In a study in which the emergence time of sevoflurane was controlled, the incidence of ED was the same irrespective of fast or slow emergence [112]. Depth of anesthesia is also not thought to be a major factor in the development of ED [113].

Given that induction GA with sevoflurane often has an excitement phase, some have suggested that sevoflurane may have a paradoxical excitatory effect at emergence also [114]. Contrary to this, however, ED existed long before the introduction of sevoflurane [98].

Postoperative pain

In a study of children undergoing inguinal hernia repair, fewer had ED after an effective caudal local anesthesia block [115]. Surgical pain is not an essential or even an important factor in the causation of ED because ED is also common after anesthesia for painless imaging [107].

Non-surgical site pain such as sore throat, headache, or the pain from a cannula site may be contributory. Although pain is not a causative factor, its presence may heighten central nervous system excitation thus lowering the threshold for agitation.

Type of surgery

The rates of ED are highest in children undergoing ophthalmic and ENT procedures [106].

Prevention

ED may be reduced if anxiety and pain are minimized [115]. Meta-analyses have shown that the administration of supplemental bolus doses of propofol, fentanyl, ketamine, clonidine, or dexmedetomidine just before emergence reduces the rate of ED [108,116]. As with all meta-analyses, their validity is limited both by the quality and power of the included studies and by the inability to include unpublished data.

Propofol

Propofol has a beneficial role either when given as a continuous infusion to maintain GA [117] or when given as a bolus at the end of the procedure [118]. A single bolus dose shortly after induction was shown to be ineffective [116].

Benzodiazepines

Midazolam given before or after induction has not been shown to reduce ED [116]. The 2014 Cochrane review concluded that midazolam has a positive effect when given as a bolus at the end of the procedure [108].

Opiates

A small (1 μg/kg) dose of fentanyl just before the end of a painless imaging scan reduces ED [103]. The contribution of analgesia in reducing ED is uncertain.

α_2 Agonists

Children undergoing circumcision with sevoflurane and a penile block developed significantly less ED if they received an intravenous bolus of clonidine at the start of the procedure [119]. Intranasal dexmedetomidine may be better than clonidine in reducing ED although recovery times are longer [120]. In a randomized trial, intranasal dexmedetomidine was shown to significantly reduce ED rates in a dose-dependent manner [121]. Dexmedetomidine may be better than propofol in reducing ED [122].

Ketamine

During eye surgery ketamine has been shown to be superior to midazolam [123] and similar to dexmedetomidine [124] in reducing ED.

Others

A magnesium infusion has been shown to significantly reduce the occurrence of ED in a study of 70 children, apparently without delaying recovery [125]. Acupuncture may be useful too: anesthetized children randomly assigned to have wrist stimulation during surgery had significantly less ED [126].

Management

The initial challenge is correct diagnosis. It is important to treat pain if it exists and to be sure that the child is not confused from an organic cause, e.g. hypoxemia or hypoglycemia. The treatment of ED will depend on its severity and whether the child is in danger of harm by his/her restlessness. Parents themselves seem to have a calming effect for many children. If ED requires treatment, small doses of sedative agents, for example propofol, fentanyl, midazolam, or dexmedetomidine, may be considered. Little evidence exists for the superiority of one drug over another to treat ED. The authors recommend subanesthetic doses of propofol (managed, always, by trained personnel).

Post-traumatic stress disorder

AAGA, in adults, has resulted in significant and long-term psychological sequelae such as anxiety, sleep disturbances, nightmares, flashback, and post-traumatic stress disorder (PTSD) [127]. Children may suffer similarly although the evidence for PTSD after GA (with or without AAGA) is sparse [128]. There is evidence to suggest that PTSD from all causes, including those unrelated to anesthesia, occurs less commonly than in adults. The British National Survey of Mental Health reported that of over 10,000 children 0.4% of those aged 11–15 years had PTSD and in those less than 10 years it was very rare [129]. Also, the diagnosis of PTSD in children less than 5 years old is uncertain because of communication difficulties [128].

Lopez et al followed up seven children 1 year after AAGA and found no psychological symptoms. Furthermore, none had negative descriptions of the events in question, in contrast to adults who often offer accounts of helplessness, pain, and fear [130]. In the five cohort studies of AAGA in children, approximately 25% of children reported fear or pain at the time of AAGA but they were not distressed afterwards [66]. Phelan and colleagues interviewed four

families whose child experienced AAGA and all denied significant psychological impact [131]. In the NAP5 report 12 adults reported AAGA remembered from when they had their GA as a child. Of these, five were anxious about future anesthesia and two had complex anxiety symptoms and recurrent nightmares [71]. This is supported by Osterman et al, who reported adults with PTSD who had had AAGA in childhood [132].

Summary

Negative changes in behavior are observed frequently after GA. Some anxious children and those who had previous poor hospital experiences may be at higher risk. Other factors such as the fear of surgery and pain may also be important. Attention to good-quality anesthesia and analgesia is important to prevent these problems. ED can occur after any anesthesia technique but is most common after sevoflurane: its incidence and severity can be reduced by other sedative and analgesic agents. PTSD does occur in children, but is rare after AAGA [75,128]. Nevertheless, PTSD related to anesthesia may occur in adults and could be related to AAGA suffered in childhood.

KEY POINTS: BEHAVIOR CHANGE

- Negative behavioral changes are associated with younger age, anxiety, previous negative experiences, and emergence delirium
- Emergence delirium:
  - is usually short-lived and self-limiting
  - is more likely with sevoflurane
  - may be reduced by good-quality analgesia and sedative agents
- PTSD after AAGA in children is rare but psychological effects may be delayed until adulthood

Conclusion

A holistic approach to anesthetic care not only focuses on the physiological and pharmacological requirements of the child but also attends to the psychological implications these events may elicit due to high levels of anxiety, unintended awareness, and negative behavioral changes. Consequently, our responsibility to the children we anesthetize extends to the prevention, evaluation, and alleviation of anxiety and distress throughout the perioperative period.

We must identify those children with increased vulnerability and implement appropriate strategies to promote coping strategies and facilitate resilience in all children we treat.

The challenge of pediatric anesthesia is to establish relationships with children and their families based on trust and humanity. Such an approach should be the foundation of promoting cooperation and reducing anxiety in children.

CASE STUDY

A healthy 4-year-old girl presents to your pre-assessment clinic with her parents 2 weeks prior to an admission for an inguinal hernia repair. Her parents describe a stormy perioperative course 18 months ago during an admission for a tonsillectomy.

According to her mother she was extremely distressed in the preoperative ward, and worsened on entering the OR. She clung to her mother and hid her face in her shoulder. She was resistant to encouragement by anesthesiologists and nurses and screamed when the mask was held to her face until she fell asleep.

When she awoke, her mother reports being told by the recovery nurses that she cried from when she opened her eyes. When her parents saw her in the recovery area she was thrashing around on her bed and pulled out her intravenous cannula. She was inconsolable by her parents and they both report that she did not seem to recognize them for the first hour. This episode only resolved when the anesthesiologist returned to review her. Her cannula had to be re-inserted, which caused further distress, and he gave an intravenous medication that settled her after a few minutes.

Two weeks after the procedure she was still displaying some signs of separation anxiety and sleep disturbance with some minor disobedient behavior out of character for her. Her parents felt guilty after this overall experience and are feeling extremely anxious about the forthcoming admission. On further questioning you elicit that when she had her vaccinations at 1 year old she was a lot more distressed than her older brother. Your summary of the situation is that the child has suffered a severe case of emergence delirium after her previous surgery with some longer-term behavioral changes, possibly contributed to by her anxiety prior to entering the anesthetic room and a previous negative experience in a healthcare setting. You feel that she is at high risk of a difficult induction and recovery this time which may be exacerbated by her parents' heightened anxiety on this occasion.

You arrange for a tour of the operating room complex and ward she will be admitted to, in order to familiarize her with the environment. You also provide her parents with a cartoon-based children's book explaining the perioperative process, which you advise they should read with her two or three times prior to admission. You discuss the option of premedication on the day of surgery and advise the parents to engage her in distractive activities on admission with toys or a tablet computer which should be continued in the OR. You make a note that due to the likelihood of emergence delirium she may benefit from a bolus dose of propofol, fentanyl, or an α_2 agonist prior to emergence.

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A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 15

Principles of the Pediatric Perioperative Surgical Home

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Introduction

The perioperative surgical home (PSH) is a patient-centered, innovative model of delivering healthcare during the entire patient surgical/procedural experience, from the time the decision for surgery is made until the patient has recovered and returned to the care of his or her patient-centered medical home or primary care provider. High-performing care coordination addresses interrelated medical, social, developmental, behavioral, educational, and financial needs to achieve the best possible health and wellness outcomes [1]. The modern concept of the pediatric perioperative surgical home (PPSH) renders obsolete the old practice of asking the primary care pediatrician to "clear" the patient for surgery and anesthesia. Instead the patient is evaluated in the context of an overarching perioperative episode which integrates the care provided by the perioperative care team with the patient's ongoing providers for the benefit of the family, patient, and health system [2–4]. A PPSH model must organize around each patient's condition rather than each physician's medical specialty and allow successful transition for the patient between outpatient care and episodes of procedural care. Care must be integrated across specialties and facilities, with the patient and family positioned at the center, so that the shift from volume to value may be achieved. This is especially important in the population of children with chronic conditions, an important segment of the population for whom care delivery is often fragmented.

Traditional volume-based care for a discreet surgical procedure has resulted in fragmentation of care and a diminished patient experience throughout the entire surgical or procedural episode. Too often, perioperative care plans are variable and disjointed. The need for surgery frequently disconnects patients from their routine medical care and as a result surgical patients may experience lapses in care, duplication of tests, and preventable harm. Costs rise, complications occur, physicians and other healthcare team members are frustrated, and the patient and family experience a lower quality of care. The transition back from perioperative surgical care to medical home or primary care may also be accompanied by lapses [5,6]. The goals defined for future healthcare are represented in the triple aim of high-quality care, a focus on population health, and reduced expenditures. The redesign of practice models represents a disruptive innovation in which the benefits offered are simpler, less expensive, and of equal or higher quality than current fee-for-service models [7]. A key strategy for meeting these goals is the implementation of measurable, evidence-informed, standardized activities that provide optimization of care coordination.

Goal and objectives

A comprehensive PSH provides coordination of care throughout all of the clinical microsystems of care and embeds the strategic principles outlined previously into its framework. The key elements of the PSH as defined in the literature are illustrated in Figure 15.1. As these new practice models evolve, it will be essential to monitor progress and performance by designing measures that will successfully gauge the value provided by the portfolio of care coordination activities and functions, as the guidelines for reimbursement tie payment to provision of coordinated care of all providers in the continuum. Physician leaders are drawn from an organization's anesthesiologists, surgeons, and hospitalists to achieve the goal of consistent application of evidence-informed and leading practices across specialty lines. The early identification of patients at risk for perioperative complications and subsequent readmission is an important concept so that these patients may be optimized preoperatively in an attempt to mitigate postprocedural morbidity. Tracking of patients' progress through all of the stages of the episode of surgical care provides an overarching assessment that directs the clinical management and closes the loop to transition back to primary care and the medical home. This model considers a patient's

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

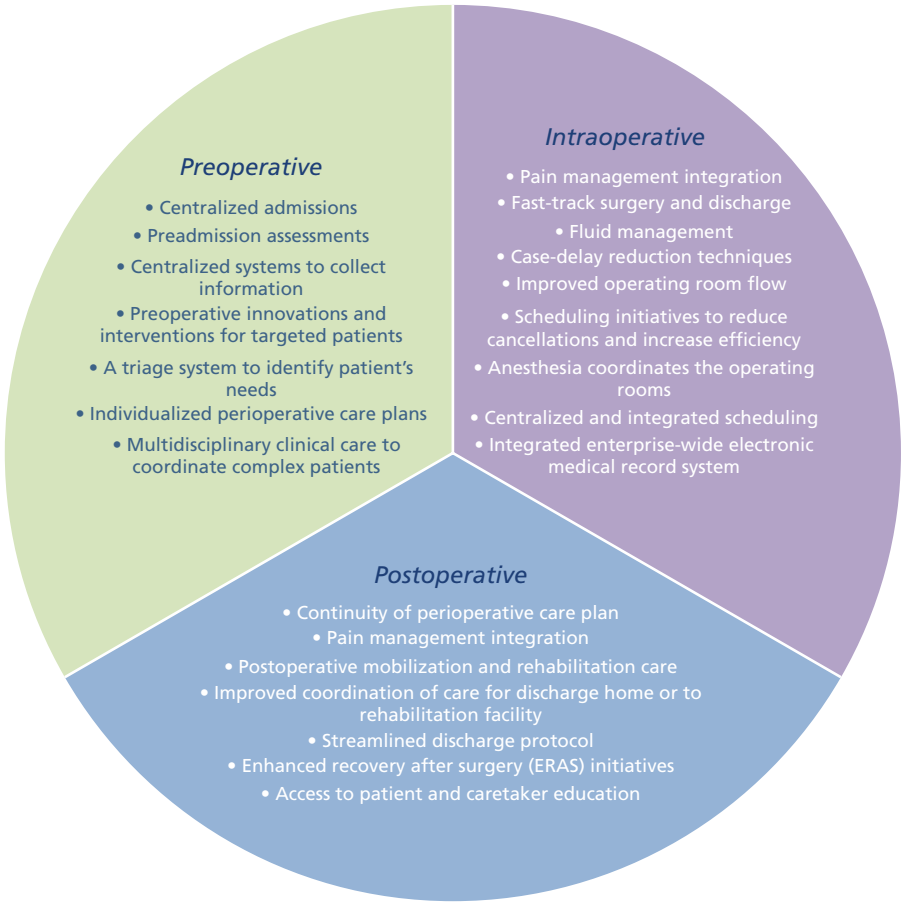


Figure 15.1 Elements of the pediatric perioperative surgical home.

Box 15.1: The goals of the perioperative surgical home

- Provide a portal of entry to perioperative care and ensure continuity
- Stratify and manage patient populations according to acuity, co-morbidities, and risk factors
- Deliver evidence-informed clinical care before, during, and after the procedure
- Manage, coordinate, and follow up on perioperative care across specialty lines
- Measure and improve performance and cost efficiency

preferences and values in all healthcare decisions, which has been associated with better outcomes and decreased postsurgical complications [8] (Box 15.1).

The PPSH is a team-based patient-centered model designed to improve the delivery of healthcare and reduce the cost of care overall. These goals are achieved through continuity of care for surgical patients, shared decision making with patients and family, and integration of care throughout the entire surgical episode of care. The components of this practice model include optimal preoperative testing and preparation together with the right care at the right place and at the right time utilizing evidence-based care principles to reduce unexplained variability, intraoperative inefficiency, complications, redundancy, and cost of care. Also included are efforts to standardize physician preference items, to reduce supply costs as well as to decrease the utilization of expensive tests and procedures.

$$\text{Value} = \frac{\text{Quality} + \text{Safety} + \text{Satisfaction}}{\text{Cost of surgical episode of care}}$$

Figure 15.2 Value equation for the surgical episode of perioperative care.

Postprocedural care initiatives include care coordination and transition planning which are defined prior to the procedure itself. This type of care coordination and integration within primary care pediatric practice is associated with a decrease in non-urgent emergency room visits, enhanced family satisfaction, reduced unplanned hospitalizations, lower out-of-pocket expenses, fewer school absences, and less impact on parental employment [9–11].

The value proposition

Fee for service rewards the quantity but not the quality or efficiency of medical care [12]. An alternative is an improved mechanism to pay for healthcare which rewards providers for delivering superior value to patients and achieving better health outcomes at lower cost. The move toward "value-based reimbursement" is accelerating. In healthcare, value is defined as the health outcomes achieved that matter to patients relative to the cost of achieving those outcomes

[13] (Fig. 15.2). It is essential for providers to have accurate cost information that includes understanding the cost of each component of care and how cost is related to the outcome achieved. To determine value, providers must measure the cost of each condition or procedure by tracking the expenses in treating the patient over the full cycle of care. This requires an understanding of the resources required, the capacity cost of supplying each resource, and the support costs associated with the care such as information technology and administration [14].

The broad phrase "value-based reimbursement" encompasses two radically different payment approaches: capitation and bundled payments. In capitation, the healthcare organization receives a fixed payment per year per covered life and must meet all the needs of a broad patient population. In a bundled payment system, by contrast, providers are paid for the care of a patient's medical condition across the entire care cycle including all the services, procedures, tests, drugs, and devices used to treat a patient with a specific disease or surgical procedure [15].

In healthcare the goal of efficiency includes elimination of waste. The three basic categories of waste are production-level waste, case-level waste, and population-level waste. The first category involves inefficiencies in producing "units of care" such as drugs, laboratory tests, radiographs, hours of nursing support, and any other item consumed in patient treatment. It accounts for about 5% of total healthcare waste. The second category, which comprises about half of all waste in care delivery, is unnecessary or suboptimal use of care during a hospital stay, an outpatient visit, or some other treatment episode, or "case." The third category, which accounts for about 45% of total waste, involves cases within a patient population that are unnecessary or preventable [16]. Failure of care coordination and integration contributes to the waste that ensues when patients receive fragmented care which may result in complications, hospital readmissions, and a decline in functional status of the patient [17] (Box 15.2).

Innovation and new care delivery methods are one solution to combating waste in medical care. Demonstrating the value of the PPSH to surgical colleagues, administrators, patients, policymakers, and payors will be needed to justify implementation of a new model which will require rigorous evaluation. In addition, it is likely that the type of PSH developed will vary based on institutional needs, payment structures, and discreet patient base. In all cases, however, the commonality of patient- and family-centered care and optimizing value are essential [18]. Specific elements inherent to the preoperative, intraoperative, and postoperative phases that reflect the added value should be identified. In addition to the development of outcome metrics and institutional assessment tools, health information technologies and methodologies for comparative effectiveness research will be needed to validate the impact of the PPSH on patient-centeredness, evidence-based practice, quality, safety, and value [19,20].

Integration with the medical home and primary care providers

As in the patient/family-centered medical home, the PPSH model must organize around each patient's condition rather than each physician's medical specialty and allow successful transition for the patient between outpatient care and episodes of procedural care. Care must be integrated across specialties and facilities, with the patient and family positioned at the center [21]. This is especially important in the population of children with chronic conditions, an important segment of the population for whom care delivery is often fragmented. The prevalence of children in the US with special healthcare needs, defined as physical, developmental, behavioral, or emotional conditions requiring health services beyond those of the general population, has increased by 18% between 2001 and 2010 and now represents 15.1% of the total population under 18 years of age [22,23].

It is well appreciated that preoperative risk reduction will result in reduction in the cost of care [23]. Especially in this patient population, integrated patient care should be coordinated across professionals, facilities, and support systems; continuous over time and between visits; tailored to the patients'/families' needs and preferences; and based on shared responsibility between the patient/family and caregivers for optimizing health [24]. Ideally the patient would transfer from a patient-centered medical home to the PPSH and back again in a continuum of care that provides seamless integration [6]. The National Quality Forum has endorsed care coordination as a "function that helps ensure that the patient's needs and preferences for health services and information sharing across people, functions, and sites are met over time" [8]. The conceptual framing for assessing care coordination includes five domains: a healthcare "home"; a proactive plan of care and follow-up; communication across team members; supportive information systems; and structured transitions of care (i.e. handoffs) [25,26]. The transfer of care using standard protocols ensures that essential information is communicated to primary care providers, subspecialists, and other providers.

KEY POINTS: GOALS AND OBJECTIVES OF THE PPSH

- Integration which is organized around each patient's condition rather than the physician's medical specialty
- Care which is integrated across specialties
- Patients transfer from a patient/family-centered medical home to the PPSH and back again in seamless integration
- Value is defined as the health outcomes achieved that matter to patients relative to the cost of achieving those outcomes

Box 15.2: Value-based transformation

Value-based care
- Patient-centered medical home
- Clinical integration
- Care management
- Post-acute care
- Electronic health record
- Data analytics

Value-based payment
- Care transformation costs
- Care management payment
- Shared savings
- Episode of care payment
- Global payment

Critical steps for implementation

Managing organizational transformation, in the words of Scott Keller and Colin Price in the *Harvard Business Review*, is like trying to change the wheels on a bike while you are riding it. The leaders of change bear the brunt of taking the organization apart and putting it together in a new way while keeping the process running [27]. Physician organizations are being asked to lead a cultural shift toward a lower-cost, higher-value healthcare delivery system. The modern physician organization must be large enough to manage population health, nimble enough to cultivate collaboration across multiple specialties, and small enough to create a "home" for each patient's healthcare needs [28]. Creating an environment of enthusiasm is one of the most important considerations in making the case for support. The problem and opportunity for improvement that will be the focus of the PPSH must be identified early with a clearly defined scope, a measurable outcome, and a surgeon champion collaborator. Examples might include identifying a discreet preoperative intervention to decrease cancellations in a specific patient population such as the preoperative insulin regime for diabetic adolescents. Another example would be proposing a decrease in length of stay for teenagers with idiopathic scoliosis undergoing spinal fusion or putting processes in place to decrease postoperative readmissions in tonsillectomy patients [29,30].

When gathering the implementation team the critical roles and stakeholders on the team should be identified. Front-line staff is critical and choosing high performers increases the potential for success. Stakeholders should be invited to identify the problem and outline a plan for improvement. The project should have a defined scope and a measurable outcome that matters to the institution. The team should include anesthesia providers, surgeons, nurses, information technology experts, an executive sponsor, staff from the institutional quality improvement division, and a parent/patient representative when feasible. The scope of the project should be established, timelines determined, and outcomes to be measured defined. (Fig. 15.3) Members of the team should be assigned specific tasks so that appropriate protocols are developed, data are collected in an efficient manner, and education is planned.

The desired changes should be fully developed, piloted, tested, and refined. One method is to begin with one part of the overall plan and measure the specific metrics as well as overall outcome. A detailed education plan should include building clinical pathways and order sets, nursing education, as well as patient and staff education. The initial project phase begins with data collection and establishing the current state. A small change should be implemented by means of one surgery, one protocol, with the goal of one small win. Results should be brought to the identified stakeholders, especially the executive sponsors, to demonstrate the success of the model and solicit ideas for the next focus. The cycle is then repeated with additional protocols and service lines [31].

Overcoming institutional barriers

Successful implementation of a PPSH requires sufficient institutional support and resources. There is a need for physician protected time to complete the administrative activities and explore other ongoing institutional efforts to partner with (neonatal/pediatric intensive care unit, etc.). The information technology role cannot be emphasized enough and dedicated

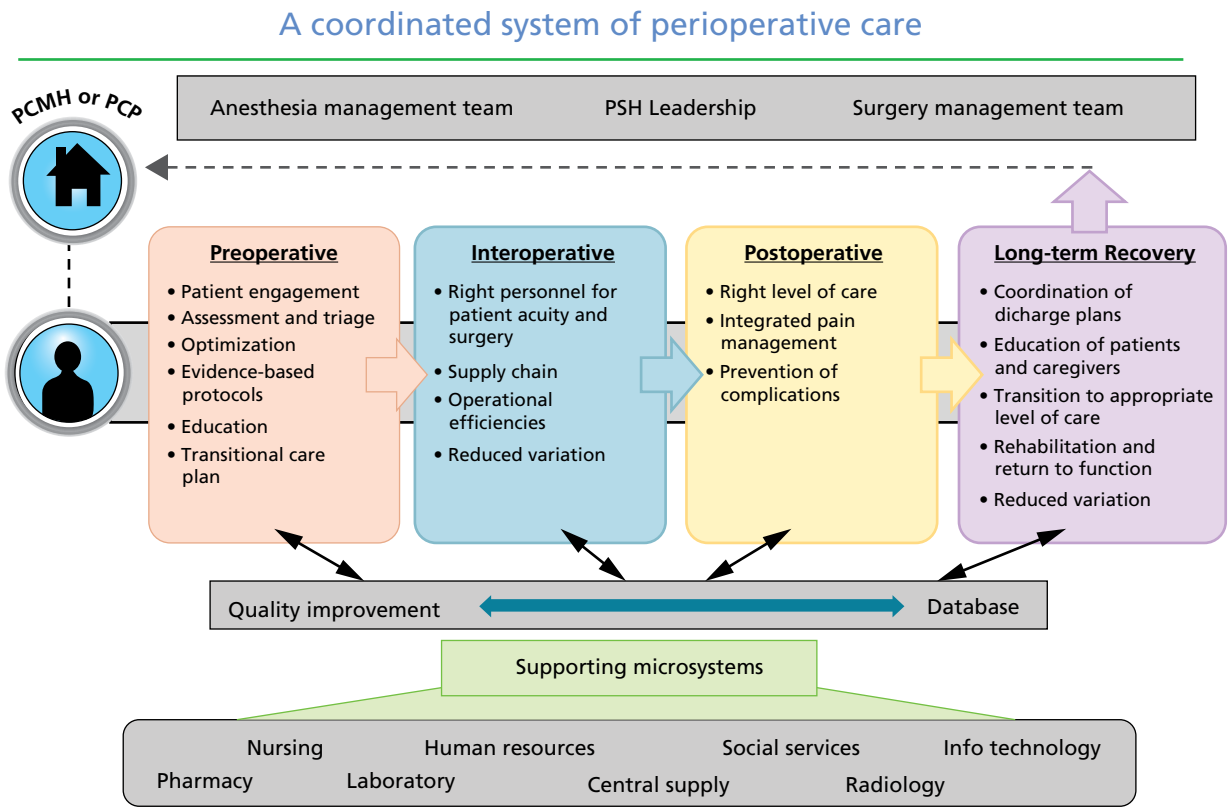


Figure 15.3 Structure of the perioperative surgical home (PSH). PCMH, patient-centered medical home; PCP, primary care physician.

teams must be created to build the tools for implementation, data analysis, and reporting of key metrics. Some of the most significant barriers might be within the anesthesia department itself as skeptical colleagues resist the adoption of innovation until much of the uncertainty has been removed and the value of change has been demonstrated [13,32,33]. Knowing the driving forces (e.g. quality, patient experience, and cost for a given institution) may be helpful in targeting the areas for change. Engagement of surgical colleagues and institutional leadership should be considered so that change may be facilitated throughout the institution. For each PPSH population a surgical champion is an important partner. It is helpful to have an "elevator speech" which is a short description of the PPSH and its advantage and value that can be communicated in its entirety during an elevator ride. This is especially useful in communicating with the institutional "C" suite consisting of the Chief Medical Officer, Chief Operating Officer, and Chief Nursing Officer. Finally, there is a need to have access to financial metrics which include both costs and charges.

Care coordination

Care coordination and integration is a complex set of functions that facilitates the provision of comprehensive health promotion, planned activities, and effective communication strategies [34]. The integration and coordination of care begins prior to the scheduling of a surgical procedure as soon as the decision for surgery is made. Involvement in the decision for surgery during the prescheduling phase in collaboration with surgical colleagues permits a multidisciplinary discussion regarding the right patient, right procedure, right place, and right provider which is especially valuable when considering children with complex or chronic health issues [5,35]. The preoperative evaluation phase provides a portal of entry to the perioperative care pathway and cost-effective preprocedure testing and consultation including "prehabilitation" interventions to optimize preoperative condition. A subtle but effective component of the preprocedural process is risk stratification to predict complications and prospective planning for length of stay and discharge so that discharge and transition planning occurs before the acute episode of care. Standardization of perioperative practice reduces variability and improves quality, and the coordination of multimodal therapy preoperatively and plan for intraoperative care may all be initiated during the preprocedural phase. Optimization of organ function to reduce the effect of co-morbidities is an important component of the preprocedural phase, as is the coordination of regional anesthesia adjuncts when appropriate. Team-based and evidence-driven care during and after surgery is an essential component of the PPSH.

Metrics, measurements, quality, and safety

The majority of pediatric readmissions are due to progression of chronic disease rather than surgical procedure and the readmission rates for infants and children are lower than in the adult population so determining the appropriate metrics for the PPSH is a challenge [36]. The demonstrated outcomes may be divided into several categories as noted in Table 15.1. Providers participating in the PPSH will be required to monitor the quality of care delivered using both internal measures and external reporting.

Types of procedures for pediatrics

The factors that distinguish pediatric heath issues from those of adult patients are referred to as the "Five Ds": *d*evelopmental trajectory, *d*ependency on adults, *d*ifferential epidemiology of chronic disease, *d*emographic patterns of poverty, and *d*iversity and overall healthcare dollars spent on the healthcare needs of children [37,38]. Additionally, the family/parent is the driver of healthcare for pediatric patients rather than the individual adult patient. The PPSH as it applies to infants and children will encompass many but not all of the competencies and functions included in overall pediatric care coordination. Overlapping functions relevant to surgery include the completion and analysis of assessments, development of care plans, management and tracking of tests, referrals, and outcomes, integration of critical care information, facilitation of care transitions, use of health information technology to manage continuous communications, and engagement of patients and families [39,40]. High-yield case types that are most suited to the PPSH model should be prioritized by determining those procedures with the greatest relative burden of preventable complications and cost variation (Fig. 15.4).

The highest-cost surgical procedures in pediatric patients according to a recent Pediatric Health Information Systems (PHIS) analysis include adenotonsillectomy, appendectomy, and spinal fusion. Other procedures that are well suited to the PPSH process are pectus excavatum repair, placement of gastrostomy tube, ventriculoperitoneal shunt insertion, laryngeal cleft repair, other otolaryngology procedures, and correction of bladder extrophy.

To understand the distribution of healthcare cost it is important to note that 75% of the pediatric population is generally healthy and incurs approximately 5% of healthcare expense, whereas 25% of the pediatric population has chronic disease consuming 70% of healthcare expense and the remaining 0.5% of the pediatric population has complex disease and requires 25% of healthcare expense [40] (Fig. 15.5). It then follows that children with medical complexity have a substantial impact

Table 15.1 Outcomes of the pediatric perioperative surgical home

Domain	Metric
Patient-centered outcomes	• Patient/family satisfaction • Success of the planned procedure • Return to prior or improved functional status
Internal operational efficiency outcomes	• Appropriateness of preoperative testing • Case delays • Case cancellations • Inpatient length of stay • Timeliness of discharge
Clinical and safety outcomes	• Unanticipated upgrade of care • Complications, morbidity, mortality • Readmissions within 30 days • Post-acute functional status
Economic outcomes	• Total cost of the episode of care • Utilization of hospital resources

on the healthcare system [41]. These children have lifelong chronic conditions with associated medical co-morbidities related to impairment of multiple organ systems and experience frequent costly hospitalizations which include surgery to improve their quality of life. Surgery in these children may be complicated and have a high likelihood of perioperative adverse events and suboptimal outcomes. Identification of those co-morbidities that have the strongest association with health outcomes and use of expensive hospital resources is an important consideration in creating a plan for a PPSH.

The adult community has fully implemented the Perioperative Surgical Home for total joint replacement surgery whereas spinal surgery is the first procedure to be an appropriate platform for pediatric patients [42]. For example, children with neuromuscular disease undergoing spinal fusion surgery exhibit an array of chronic conditions which include co-morbidities in the digestive, neurological, respiratory, and renal systems. As each patient's number of chronic conditions increases, the length of hospital stay, cost of surgical episode of care, and likelihood of readmission with 30 days increase. The most significant increase in postoperative length of stay due to a chronic condition has been noted in children with chronic respiratory insufficiency, bladder dysfunction, and epilepsy. Acute illnesses associated with increased length of stay, hospital cost, and readmission include the presence of decubitus ulcer, hypertension, and respiratory arrest. For example, urinary tract infection adds approximately $14,000 to the cost of the surgical episode of care and 3.5 days to the length of stay [41]. Adolescent idiopathic scoliosis is a condition that is associated with one of the highest annual cumulative costs in pediatric inpatient care and the implementation of a PPSH for this patient population has been shown to decrease the median length of stay from 5.2 days to 3.4 days ($p < 0.001$) as well as decreasing the rate of readmission within 30 days [29,43]. Other chronic diseases that affect a significant portion of the surgical population include cerebral palsy, myelodysplasia, congenital facial abnormalities, trisomy 21, neoplastic disease, congenital heart disease, and hydrocephalus.

Many of the metrics that define value in the domains of quality, safety, and patient/family satisfaction in adult surgical patients may apply to pediatric practice as well. These include hospital cost, length of stay, readmission, same-day cancellations, postoperative pain, nausea and vomiting, unplanned upgrade of care, actual discharge disposition, and mortality. Although inpatient length of stay and 30-day readmission are metrics that may be applied to both populations, the use of home health aides, skilled nursing, or post-acute transfer to rehabilitation facilities is not widely applicable to the pediatric population. Readmission rates are being used as an indicator of the quality of care by hospitals, clinicians, and payors. The Center for Medicare and Medicaid Services has proposed to reduce payments to hospitals with excessively high readmission rates [44]. The Pediatric Quality Measures Program, established by the Children's Health Insurance Program Reauthorization Act, has identified pediatric readmissions as an important measure and children with medical complexity have the highest rates of readmission [45,46]. The overall rate for unplanned readmissions within 30 days of discharge is approximately 6.5% with 2% occurring in children following ambulatory surgery [47]. As opposed to adults, pediatric postoperative care involves home care with family as the primary provider and in recent studies up to 29.5% of readmissions were potentially preventable [30]. Compared to adults, the reasons for readmission of pediatric patients within 30 days of discharge are significantly different and include dehydration, electrolyte imbalance, gastritis, constipation, seizures, pneumonia, anemia, upper respiratory infection, appendicitis,

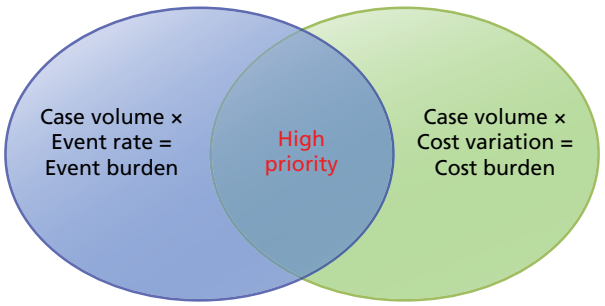


Figure 15.4 Determination of case types with the greatest yield from a pediatric perioperative surgical home model.

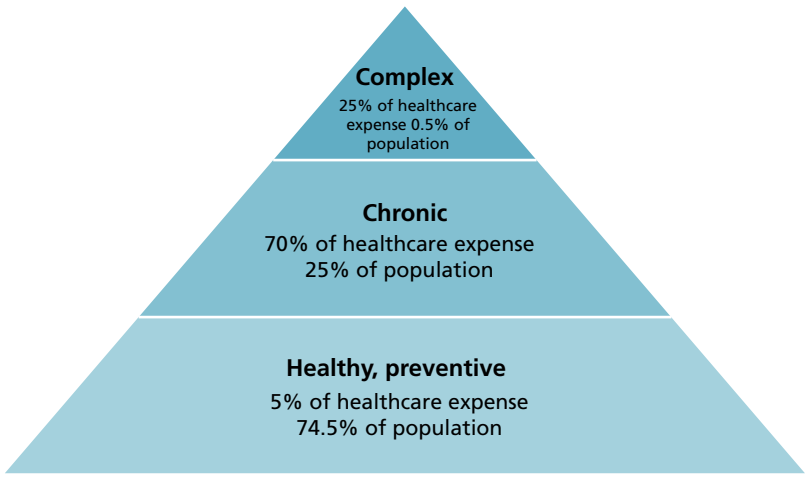


Figure 15.5 Distribution of medical expense in pediatric practice. *Source:* Courtesy of R. Antonelli, MD Director, Integrated Care, Boston Children's Hospital, Boston, MA, USA.

sickle cell crisis, and ventriculoperitoneal shunt malfunction [36,48] (Box 15.3).

Box 15.3: Most prevalent diagnoses for readmission

- Seizures
- Pneumonia related to asthma
- Bronchiolitis
- Anemia/neutropenia
- Sickle cell crisis
- Upper respiratory infection
- Acute asthma
- Diarrhea/dehydration
- Gastroenteritis/electrolyte disturbance
- Abdominal pain after appendectomy
- Neurological abnormalities after ventriculoperitoneal shunt surgery

KEY POINTS: CRITICAL STEPS FOR IMPLEMENTATION OF THE PPSH

- Pediatric health issues differ from those of adult patients
- Greatest cost variation and complication rate define the group to study
- Subsets of the highest-cost surgical procedures performed in children are defined
- Children with complex and chronic medical co-morbidities incur substantial healthcare cost

Enhanced recovery after surgery

Both the PSH and enhanced recovery after surgery (ERAS) initiatives share the goal of reducing cost while providing improvement in clinical outcomes, however the approach between the two modalities is different. ERAS is a multimodal perioperative care pathway designed to achieve early recovery for patients undergoing major surgery. ERAS represents a paradigm shift in perioperative care and is a defined clinical protocol that relies on specific elements which are implemented in every patient in a specific service line. The key areas of focus in ERAS protocols include the need for parenteral analgesia, the need for intravenous fluids secondary to gastrointestinal dysfunction, complications due to bed rest caused by lack of mobility, and carbohydrate loading preoperatively to reduce the stress of surgery during the immediate preoperative period [49]. Limited routine mechanical bowel preparation, use of multimodal analgesia and regional anesthesia to minimize narcotic administration, goal-directed restriction of balanced crystalloid intravenous fluids, early enteral feeding, early mobilization, and early removal of urinary catheters are specific components of the ERAS process.

The utilization of ERAS protocols is usually limited to the immediate pre- and postsurgery period whereas the PPSH has a larger conceptual framework that is focused on coordination and integration of care among providers for the duration of the entire episode of surgical care. This extends from the time that surgery is scheduled to 30 days post discharge [50]. The ERAS model of care may be considered a component of a PPSH process.

KEY POINTS: ENHANCED RECOVERY AFTER SURGERY

- ERAS and the PPSH are not the same
- ERAS protocols are focused on the immediate pre- and postoperative/postprocedural care
- The PPSH spans the entire continuum of the perioperative episode of care

Education and training

The specific skills required for anesthesiologists to be successful in the perioperative care model are evolving as perioperative medicine advances. Leadership and managerial skills as well as education in evidence-informed perioperative care expand the role that anesthesiologists assume outside of the operating room. Managing and directing the perioperative care of pediatric patients in partnership with surgical colleagues involves a new collaborative paradigm, and pediatric anesthesiologists are well trained and positioned to implement these changes [51]. Replacing traditional practices by integrating and reformatting existing systems will be the innovation that should result in increased access to perioperative services, value-added processes, and ultimately improved outcomes. Meeting the real needs and the true value of the pediatric PPSH requires an individual to coordinate and integrate each patient's care [2,4]. Given the vital need to restructure the perioperative experience and environment for pediatric patients and their families, the pediatric anesthesiologist should lead the implementation of the PPSH.

This new model provides an opportunity for residents and fellows to broaden their scope of care and take ownership of patients beyond the operating room and intensive care unit [52,53]. To advance this new model of care, consideration must be given to incorporating the competencies which are fundamental to the PPSH. There is a precedent for successful implementation of PSH training within the standard residency training programs in which traditional residency modules have been replaced with more PSH-specific training. For instance, in the first clinical year an introduction to the foundation in the PSH may be offered followed by the Clinical Anesthesia (CA)-1 year training in perioperative risk reduction and optimization in lieu of the standard preoperative clinic rotation. The postanesthesia care unit module is expanded to include recovery after surgery principles and pathways, and finally a design, implementation, and PSH management pathway elective is offered in the CA-3 year [53]. Should all anesthesiologists be trained in perioperative care outside of the operating room? Does this require lengthening the residency by an additional year? Should there be a specific fellowship in perioperative care? There is a major educational hurdle within anesthesiology to define the training of future generations of anesthesiologists as perioperative physicians.

The Accreditation Council for Graduate Medical Education (ACGME) approved subspecialty fellowship programs to provide rigorous training environments for the current generation of pediatric anesthesiologists [54]. In 2013 the American Board of Anesthesiology established the first certification examination in pediatric anesthesiology. These demographic and

oversight changes coupled with the ongoing restructuring of traditional models of healthcare delivery provide a unique opportunity for pediatric anesthesiologists to integrate their specific expertise and contribute to the care of the pediatric surgical patient [55,56]. The American Board of Pediatrics together with the American Board of Anesthesiology launched a combined training program in 2009 that enables physicians to fulfill training requirements for board certification in both specialties in 5 years. The goal of this innovative program is for newly trained physicians to develop careers focused on caring for children with complex medical and surgical conditions who require perioperative or periprocedural management. The educational experience provided by the complementary strengths of training in both pediatrics and anesthesiology should enable these physicians to become leaders in this expanding field.

KEY POINTS: EDUCATION AND TRAINING

- Managing perioperative care in collaboration with surgical colleagues represents a new paradigm
- Broaden the scope for anesthesiologists in training
- There is precedent for the successful implementation of PPSH inclusion in standard residency training

Payment models

Designed in the 1960s, the Medicare fee-for-service system created a healthcare payment model organized around healthcare providers rather than patients, rewarding the volume rather than the value of services, and focusing on sickness rather than preventative care. In order to define appropriate value-based payment models for children's healthcare, it is necessary first to define the value sought through the purchase of healthcare services for children. The experts believe society's goal for children is to maximize each child's opportunity to develop physically and emotionally such that he or she can productively contribute to society throughout his or her life, and a mix of process-of-care and outcomes should define the value of care for children including access to coordinated specialty care when indicated [40]. Although the dominant value-based payment models including supplemental payments, pay-for-performance, episode-based payments, and shared savings on total cost of care have been implemented within the context of pediatric practices across the US, pediatric practice lags behind in reimbursement reform.

The transition toward value-based care includes the movement toward alternative payment models (APMs). The APM is one of the few broadly supported ideas for moving healthcare forward. APMs such as accountable care organizations (ACOs), patient-centered medical homes and bundled payments, align reimbursement around the patient, focusing on coordinated, team-based care and improved outcomes. With increasing evidence and momentum building, APMs are one solution to the current cost and quality conundrum in healthcare. They hold the promise to alter the healthcare cost trajectory to create a sustainable, long-term future for government-supported and affordable private coverage. ACOs are not a payment method and the growth of ACOs in pediatric care has lagged behind adult models in part due to the uncertainty of the effectiveness of this model in pediatrics [57–59]. Each ACO is an arrangement among providers who are organized to receive bundled payments on behalf of participating providers [26,28]. There are specific areas where the PPSH model may contribute to payment enhancement. These include attention to cost management focusing on acute inpatient length of stay, post-acute care disposition, utilization cost, service line cost, physician preference items in supply chain, and reduction in variation analysis and strategies. Claims analysis and reconciliation, monthly reporting, dashboards, benchmarking, and monitoring to support process improvement are important analytics within the scope of the PPSH model. Gap assessment and redesign, quality improvement practices, collaborative sharing, care coordination and integration, and post-acute care partner designation all may positively influence reimbursement.

"Monetizing" the PSH refers to the process of valuing the coordination of services that are provided to patients during the perioperative episode of care and ensuring that each provider receives appropriate payment consistent with their contribution to the optimization of comprehensive surgical care and reduction of healthcare inefficiencies. The challenge is to show that the PPSH provides greater value to the institution than the cost of supporting the PPSH. Hospitals may pay PPSH participants based on achieving decreased overall costs of the perioperative episode of care. This may be achieved by decreasing hospital resources, standardization of implants and equipment, reducing laboratory and imaging studies, decreasing blood utilization, reducing intensive care utilization, and a reduction in the overall length of stay. Alternatively payors may directly compensate PSH providers based on a reduction in the use of hospital services resulting from earlier discharge or shifting care from inpatient to outpatient.

Once a PPSH is established within a specific institution and the services provided are defined, a method of payment must be designed. There are different options depending on the structure of each institution. Several potential models have been suggested, however the proportional split of professional fees must be determined prior to the delivery of care [60] (Box 15.4).

Box 15.4: Perioperative surgical home (PSH) payment models

- A fee for service payment for specific services provided or a discounted fee for service arrangement plus an opportunity to share in PSH-generated savings
- A percentage of bundled payments to the hospital (commercial or Medicaid)
- A portion of shared savings paid to the hospital as a result of the PSH
- Co-management agreements that define specific services provided by the PSH and compensation determined by tracking quality improvements
- Bonus payments for meeting quality and cost-saving metrics such as Hospital Quality Efficiency Programs (HQEP)
- Shadow bundles in accountable care organizations

Source: Reproduced from Leib and Dunbar [60].

CASE STUDY

Implementation of a pediatric perioperative surgical home care pathway for anterior cruciate ligament (ACL) repair at Boston Children's Hospital.

PPSH team

Anesthesiologist, surgeon champion, perioperative care coordination nurse, postanesthesia care unit (PACU) nurse, information technology group leader, executive sponsor, case manager.

Hypothesis

Anesthesia management varies across providers. The wide variability of anesthesia management can impact cost by impacting surgical end to transport out of OR (SET) time, PACU length of stay, patient outcomes, and readmissions.

Goals

- Reduce SET time and PACU length of stay.
- Reduce pain score variability by 20%.
- Maintain patient satisfaction.

Opportunity statement

- Anesthesia management that reliably produces shorter SET and PACU times while maintaining a positive recovery experience for patient and family.
- Present the identified anesthesia management as a departmental benchmark goal.
- Reduce the cost of the ACL repair episode of perioperative care.

PPSH population

ASA I and ASA II patients undergoing elective surgical repair of ACL.

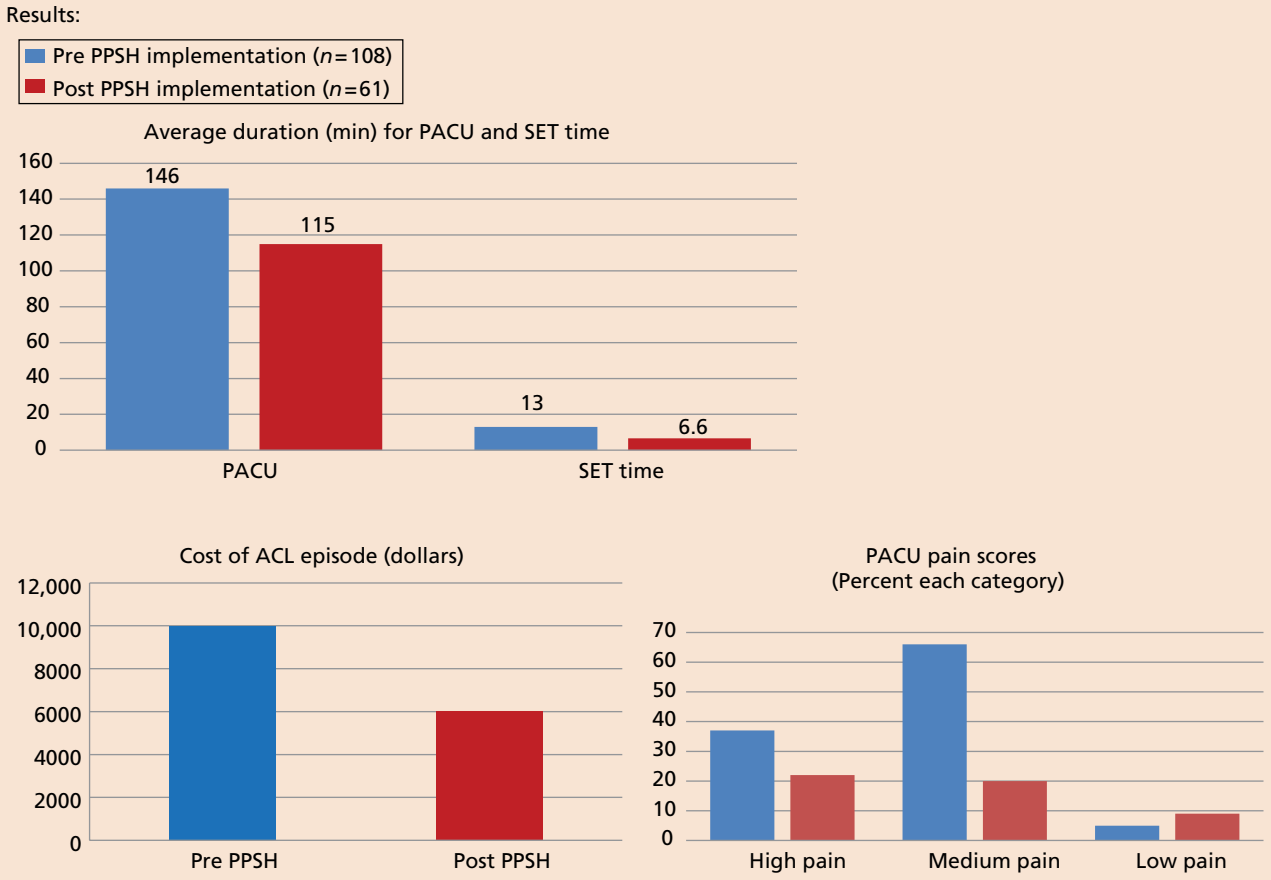
Measurements/outcomes

- Surgical time: surgery start to surgery end
- SET time: surgical end to transport out of OR
- PACU length of stay: PACU admission to PACU discharge
- Cost of surgical episode of care
- PACU pain scores:
  - 0–3, low pain scores
  - 4–6, medium pain scores
  - >7, high pain scores.

Phase	Element of care	PPSH	Standard care
Before surgery	*Surgical Office* • ACL education • Postsurgical expectations • Discharge planning • Post-discharge follow-up planned • PT scheduled	*PPSH Team* Chart review and communication with subspecialists Phone call within 5 days prior to scheduled surgery Phone screen: • Medication reconciliation • NPO guidelines • Arrival time • Education of periprocedural plan • Identify postoperative caretaker • Getting ready for discharge on day of surgery Consider regional anesthesia adjunct Education sheets and teaching	Surgeon schedules case without communication with perioperative team
Preoperative	Patient education	Written education materials Standardized electronic order sets Initiation of multimodal pain regimen	Written education optional
	Standardized preoperative discharge planning	Patient and family education, including post-discharge caretaker and follow-up appointments	Lack of standardized discharge planning
Postoperative	Pain management Protocols for escalation of care	Oral medication and avoidance of opioids Decision tree for rapid escalation of care in case of medical deterioration or complications	Use of opioids
Discharge	*Surgical Teaching* Verbal and written education material post ACL repair	*PPSH Team* Verbal and written education material: • airway care • pain management with opioid sparing • diet • active crutch teaching	

Phase	Element of care	PPSH	Standard care
Data extraction and monitoring	Monitoring plan	PPSH dashboard outcomes tracking of perioperative management and care coordination Adherence to PPSH care guidelines Cost Patient and family experience Complications Unplanned upgrade of care 30-day post-discharge readmissions	Lack of regular audits Data scattered across many systems and databases Before PPSH dashboard unable to monitor in real time

ACL, anterior cruciate ligament; NOP, nil per os; PPSH, pediatric perioperative surgical home; PT, physical therapy.



Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 16
Pediatric Airway Management

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Introduction

Expertise in airway management in infants and young children is the cornerstone of pediatric anesthesia. This expertise consists of two major facets: a comprehensive knowledge and understanding of the developmental anatomy and physiology of the human upper airway from birth through adolescence, and the physical skills of airway management. This chapter will provide the basis upon which knowledge of pediatric airway management is gained. The chapter is divided into three major sections: (1) developmental anatomy and physiology of the upper airway; (2) procedures and techniques for management of the normal pediatric airway, and (3) specialized techniques with which to manage the child with an abnormal upper airway that presents challenges in ventilation or tracheal intubation.

The human upper airway is loosely defined as the air-conducting passages from the nose to the carina [1]. Anatomically, the upper airway of the developing fetus, infant, and child is a moving target. Its developmental course during fetal life is relatively less known compared with other organ systems, since much of this understanding is gained from descriptive animal and human postmortem studies. The structures of the upper airway continue to change their shape and properties until the latter part of the first decade of life. Furthermore, up to 3% of children may have congenital or acquired upper airway abnormalities [1].

From an evolutionary perspective, the human upper airway is relatively smaller than other related species, and is oriented in a more vertical position in the body. In humans, the facial bones and accompanying oral airway structures assume a more vertical position beneath the cranium (this mirrors the changes seen during human growth; see section "Developmental anatomy"). These changes were likely due to the acquisition of language for survival [2,3]. Diamond called this adaptation "The Great Leap Forward" and postulated that it occurred approximately 40,000 years ago [4].

Many other species are able to produce sounds that are analogous to vowels, but only humans are able to produce

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

consonants, the basis of the spoken language. The ability to form consonants, according to Shprintzen, is the result of the relatively smaller supralaryngeal tract that evolved in humans. This adaptation included the ability of humans to close off and separate the communication between the nasal or oral pharynx to facilitate production of consonants. The unique human property of having large adenoid tissue facilitates this separation. It is notable that the peak age of adenoidal growth (i.e. 3–5 years) is the same approximate age of the refinement of consonant sounds [3].

This anatomical adaptation necessarily confers a disadvantageous human property: the predisposition to upper airway collapse during sleep (i.e. obstructive sleep apnea syndrome, OSAS) or during artificially induced unconsciousness (i.e. sedation or general anesthesia). Other than brachycephalic dogs, such as the peculiar English bulldog [5], OSAS appears to occur only in humans.

Developmental anatomy

In embryological life, the upper airway develops within the structural framework of the development of the cranium and the most cephalad ends of the digestive and respiratory systems. The following description of the embryological development of the human is based on writings and descriptions from a number of references [6–10]. On the lateral surface of the 5-week-old, 4.0 mm embryo, one can observe five or six pairs of narrow masses called *branchial arches* (Fig. 16.1). Each branchial arch contains characteristic types of ectoderm and mesoderm, the primordial precursors of epithelial (e.g. skin) and mesothelial structures (e.g. muscle, bone), respectively. The areas between the arches are called *branchial clefts*. The tissue underlying the branchial clefts contains outpouchings of the foregut region, the *pharyngeal pouches*. These consist of endoderm and will develop into corresponding endothelial structures of the upper digestive and respiratory systems. The developing structures of each branchial arch receive motor or sensory innervation from an adjacent cranial nerve. Regardless of where the primordial muscle cell migrates, it will retain its original embryonic innervation.

The branchial arches

The first branchial arch will ultimately develop into the ramus of the mandible and the muscles of mastication. It also contributes to development of the middle ear bones and muscles between the ear and mandible, such as the tensor tympani, tensor veli palatini, and anterior belly of the digastric muscle. Motor and sensory innervation to the structures derived from the first arch is supplied by the trigeminal nerve.

The second branchial arch forms bony and muscular structures from the ear (proximally) to the hyoid bone (distally), including the muscles of facial expression that are innervated by the facial nerve (cranial nerve (CN) VII). In the developed human, the path of second branchial arch development can be traced from the styloid process, to the stylohyoid ligament, to the lesser cornu of the hyoid bone. Embryological abnormalities in the growth of the first and second branchial arches result in any one of a number of congenital airway syndromes involving the ear and jaw, such as Goldenhar syndrome.

The third branchial arch develops into the body and greater cornu of the hyoid bone and the stylopharyngeus muscle, which aids in elevating the pharynx during swallowing, and is innervated by the glossopharyngeal nerve (CN IX).

The fourth through sixth branchial arches contribute to the formation of the thyroid, cricoid, arytenoid, corniculate, and cuneiform laryngeal cartilages, as well as the muscles that form the pharynx, larynx, and upper half of the esophagus. These structures are innervated by the vagus (CN X) and accessory (CN XI) nerves. The earliest appearance of the future larynx is seen as a bud growing out from the ventral part of the foregut at approximately 4 weeks' gestation. The laryngeal and esophageal tracts are initially seen as one common tube that eventually separates into two adjacent functionally different conduits. By 16 weeks' gestation, the larynx contains all its definitive elements in their proper proportions.

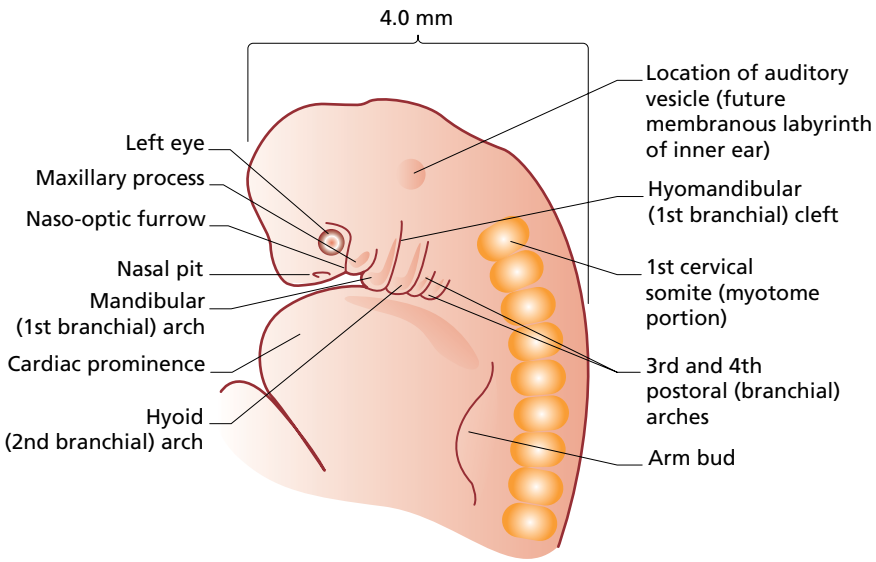


Figure 16.1 On the lateral surface of the 5-week-old, 4.0 mm embryo, one can observe five or six pairs of narrow masses called branchial arches.

During fetal and postnatal growth, the development of the size of the larynx closely parallels the size of the surrounding bony and cartilaginous structures [11].

The pharyngeal pouches

The pharyngeal pouches are outpouchings of the lateral wall of the foregut that develop into the pharyngeal structures. Each pouch, at its lateral-most aspect, contacts the ectodermal epithelium of a branchial cleft. The first branchial cleft becomes part of the external auditory canal, but the remaining branchial clefts are remodeled and do not correspond to recognizable structures in the mature human. Nevertheless, abnormal formation of this area can lead to cysts or more significant malformations.

The first pharyngeal pouch becomes incorporated into the future temporal bone and forms the epithelial lining of the middle ear and the tympanic membrane. Adjacent to the first pharyngeal pouch, the first branchial cleft develops into the external auditory canal.

The second pharyngeal pouch develops into the tonsil.

The superior portion of the third pharyngeal pouch differentiates into the inferior parathyroid and the inferior portion migrates caudally to become the thymus.

The fourth pharyngeal pouch forms the superior parathyroid gland; the area roughly corresponding to the fifth and sixth pharyngeal pouches is incorporated into the thyroid gland.

Anatomical structures of the upper airway and their relation to the practice of pediatric anesthesia

The approach to airway management of infants and young children is influenced by developmental differences in head and neck anatomy. These differences are modified by two major growth spurts during childhood, the first at the time of the acquisition of permanent dentition (i.e. age 7–10 years), and the second during puberty in the teenage years, both of which contribute to the vertical growth of the facial structures. Thus, it is no coincidence that these two general age ranges are the approximate points in life in which certain persons without obvious anatomical deformities will become difficult to intubate.

Skull

When compared to the older child, the infant's skull (especially the occipital region) is relatively larger, such that neck flexion may not be required to attain the classical "sniffing" position that optimizes visualization of the glottic structures during laryngoscopy. At birth, the neurocranium to face size ratio is 8:1, and declines to 6:1 at 2 years of age, 4:1 at 5 years of age, and approximately 2:1 by adulthood [12,13]. The growth of the lower facial bones is proportionately linear from ages 1 to 11 years [11].

The mandibular arch of the infant is U-shaped and becomes more V-shaped during childhood until adolescence when it is completely developed. The angle between the ramus and the body of the mandible is more obtuse in infants than in adults. This largely accounts for the relatively low incidence of difficult intubations in infants and young children compared with adults.

Nose

Overall, the most important difference in nasal anatomy between young children and adults is merely the smaller size. Small nasal passages are more likely to become obstructed with blood or secretions as a result of manipulations during general anesthesia. Young children are less likely to have occult nasal polyps or septal deviations when compared with adults [14]. The anatomical dimensions of the nasopharynx increase linearly between 1 and 11 years of age [11].

In the past, small infants were considered to be obligate nasal breathers and therefore predisposed to breathing difficulties during periods of nasal obstruction. However, this has largely been disproven [15], although infants with choanal atresia will often develop upper airway obstruction that results in varying degrees of hypoxemia [16].

Oral cavity

The infant tongue is relatively larger in proportion to the oral cavity when compared with the adult. Tongue volume increases linearly between ages 1 and 11 years [11]. Magnetic resonance imaging (MRI) studies of the upper airway during general anesthesia have demonstrated that, as in adults [17], upper airway obstruction occurs primarily at the levels of the soft palate and epiglottis, and not at the level of the tongue [18].

The 20 primary teeth are identified by a lettering system (Fig. 16.2A) They begin to erupt during the first year of life, and are shed at between 6 and 12 years of age. The 32 permanent teeth begin to appear at the same time as the primary teeth are shed and are identified by a numbering system (Fig. 16.2B).

Oropharynx

In newborns, the uvula and epiglottis are in close proximity, which makes possible the simultaneous acts of nasal breathing and oral ingestion of liquids. This anatomical relationship is maintained throughout most of the first year of life, but during the second year, the larynx begins to descend as it adapts to its greater role in phonation.

Although mechanisms have not been elucidated, the pharynx of premature newborns is susceptible to passive collapse, especially during apnea, but may also collapse as a result of cervical flexion or nasal obstruction [19]. These effects are exacerbated by the administration of general anesthesia or sedatives, which decrease pharyngeal muscle tone. Furthermore, pharyngeal collapse often occurs in premature infants during application of cricoid pressure.

Of interest, the upper airway of a normal infant is smaller in both inspiration and expiration at 6 weeks of age compared to the neonatal period. This relative narrowing may be caused by postnatal growth of adenoid tissue, or thickening of the mucous membrane lining in response to infection or second-hand smoke exposure. The linear dimensions of the soft palate and oropharynx increase linearly between 1 and 11 years of age [11,20].

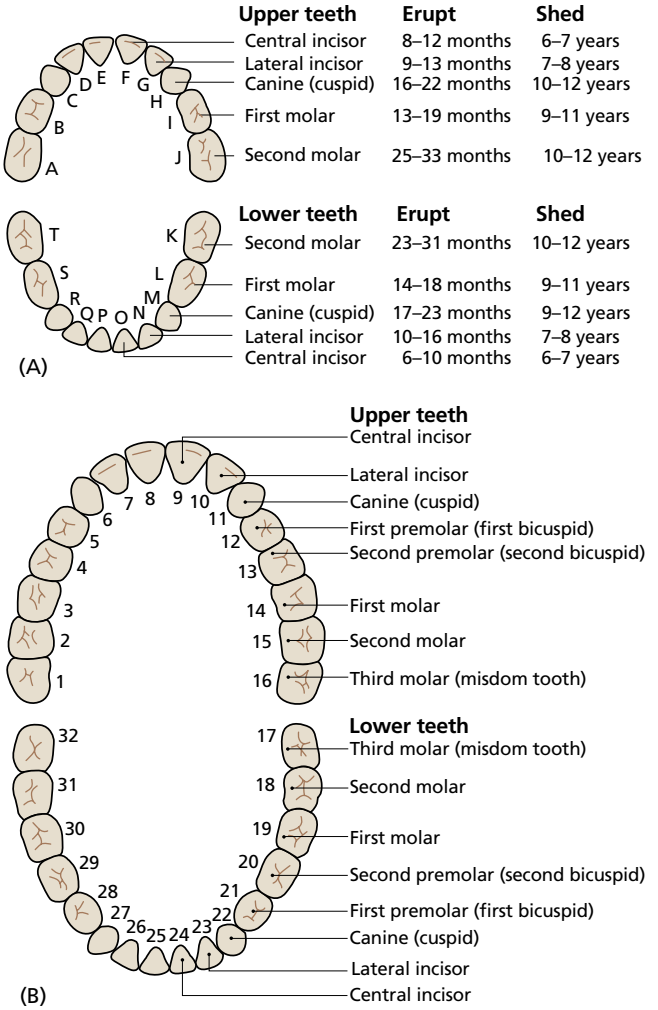


Figure 16.2 The picture is viewed as if the patient is facing the examiner with their mouth open. (A) The 20 primary teeth are lettered A through T, beginning with the right upper molar and ending at the right lower molar. (B) The 32 permanent adult teeth are identified by a numbering system that begins at the right upper third molar and ends at the right lower third molar. *Source:* Reproduced from The American Dental Association [421].

Adenoidal and tonsillar tissue are minimal at birth, and then grow rapidly between 4 and 7 years of age. The growth of airway lymphoid tissue parallels the growth of the facial and cervical bony structures [11]. Hypertrophied tonsil and adenoid tissue is likely the most common cause of upper airway obstruction after administration of general anesthesia in children in this age group.

The epiglottis of infants is relatively narrow and short, and angled into the lumen of the airway. The lower portion of the oropharynx at the level of the epiglottis is particularly compliant and prone to collapse during anesthetic- or sedative-induced upper airway obstruction [21]. Therefore, obstruction at the epiglottic level can be significantly lessened by placing the patient in the lateral position [21].

The effect of gender on oropharyngeal length has been studied, with particular reference to an association between relatively longer airway length and the predisposition to obstructive sleep apnea [22]. Prior to the onset of puberty, boys and girls have relatively similar oropharyngeal length but after the onset of puberty, the oropharyngeal lengths in boys are greater than that of girls, even after correcting for

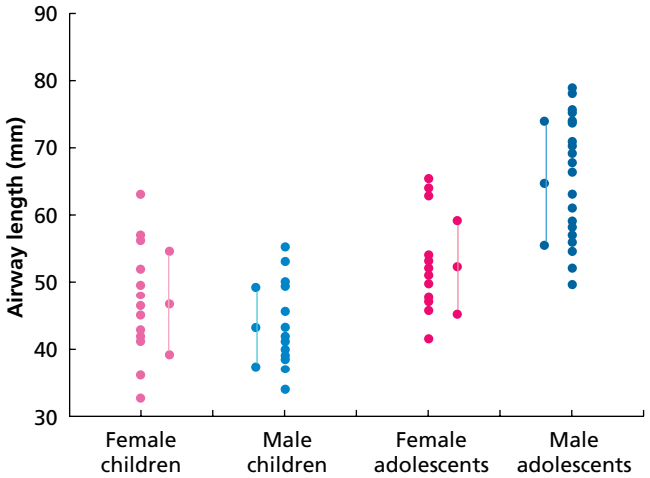


Figure 16.3 Prior to the onset of puberty, boys and girls have relatively similar oropharyngeal length but after the onset of puberty, the oropharyngeal lengths in boys are greater than those in girls, even after correcting for height and weight. *Source:* Reproduced from Ronen et al [22] with permission of the American Academy of Pediatrics.

height and weight (Fig. 16.3). The relatively longer upper airway length in males has been implicated as a possible etiological factor in the greater disposition in males toward OSAS [23]. Thus, postpubertal males may have a greater disposition toward upper airway collapse in response to administration of pharmacological agents that depress consciousness.

Larynx

During infancy, the relative position of the larynx is slightly higher in the neck than in older children and adults. Although its position relative to the cervical spine is complete by the age of 3 years (it descends from C2–C3 to C4–C5), it continues to descend relative to other facial structures such as the mandible [24]. The tip of the epiglottis proceeds in a gradual and linear descent from C2 to C3 from birth to 18 years of age [25]. This relative movement is unique to humans because of the shifting functionality from sucking and swallowing while breathing to the development of speech later in life. Early in life, a relatively high larynx facilitates simultaneous sucking and respiration due to the apposition of the epiglottis (as high as C1) and the soft palate. Additional differences in early life that protect against aspiration during feeding include relatively thicker aryepiglottic folds and larger arytenoids.

The chest wall of neonates and small infants is highly compliant and tends to collapse inward, thus reducing functional residual capacity (FRC) and promoting atelectasis. To preserve FRC, the adductor muscles of the larynx act as an expiratory "valve," and restrict exhalation in order to maintain positive end-expiratory pressure. This is referred to as "laryngeal braking" [26,27].

The higher position of the larynx during infancy influences airway management to the extent that the glottic opening is more easily visualized using a straight, rather than a curved laryngoscope, and in infants less than 1 year of age, elevation of the base of the skull is usually not necessary [28].

In children with pharmacologically induced neuromuscular blockade, the cricoid cartilage is the narrowest portion of the upper airway because of its inability to distend in a similar

manner as the vocal cords [29–31]. A tracheal tube that easily passes through the relatively compliant vocal cords may compress surface mucosa at the level of the cricoid cartilage and predispose to inflammation, edema, and subsequent scarring and stenosis [32–34]. Tracheal edema is more likely to increase airway resistance in smaller diameter airways since the resistance to flow through a tube is related to the fifth power of the radius of the tube (since this flow is largely turbulent). In non-intubated, sedated children without neuromuscular blockade, the adductor muscles of the vocal cords are active, and are the basis for the narrowest portion of the upper airway to occur at this level [35–37]. The relationship between the sizes of the structures along the upper airway remains relatively stable throughout growth and development [37]. Therefore, there appears to be no specific age during childhood at which the form or structure of the most appropriate tracheal tube (i.e. cuffed versus uncuffed) would require a change for the benefit of the child.

Some congenital conditions, notably trisomy 21, are associated with smaller than normal subglottic and tracheal diameters [38–42]. Therefore, appropriate tracheal tube sizes may be smaller than usual for age in these patients. Ultrasound examination of the subglottic region may be used to guide tracheal tube size selection [43].

Tracheal lengths (distance between glottis and carina) increase linearly during childhood [30,44]. A familiarity with these distances in infants will facilitate proper placement of the tracheal tube midway between the glottis and carina (Fig. 16.4). A shortened tracheal length (i.e. higher bifurcation) caused by a reduced number of tracheal cartilage rings is noted in certain conditions such as trisomy 21 [40] and myelomeningocele [39,45]. Therefore, in these patients, special attention is warranted to ensure proper tracheal tube position and avoidance of right bronchial intubation.

Developmental physiology of the upper airway

The human upper airway serves a concomitant function as a conduit for breathing and for the passage of food. This property, which is only found in higher evolved species, presents a unique problem, the basis of which is that the upper airway is integrally involved in the processes of breathing, speech, and eating, without the benefit of rigid cartilaginous support. In the conscious state, this requires rigorous neurological coordination between competing structures. Although relatively little is known about the development of neural control in the upper airway [1], it is this characteristic that renders the upper airway vulnerable to collapse during administration of sedatives or anesthetics.

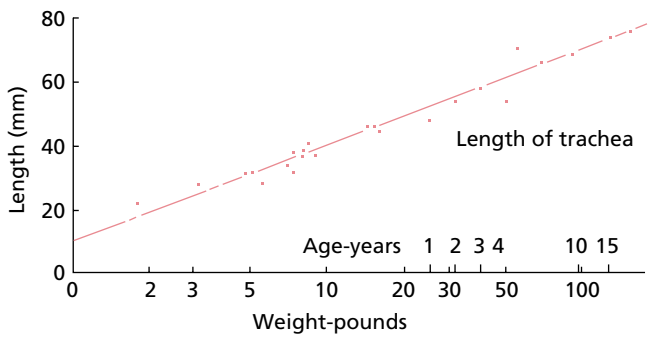


Figure 16.4 Distance between vocal cords and carina as a function of weight in pounds. *Source:* Reproduced from Butz [30] with permission of the American Academy of Pediatrics.

The pharyngeal and laryngeal muscles that normally contract to maintain upper airway patency are activated in parallel with the diaphragm. Activation of pharyngeal abductor muscles prevents upper airway collapse in response to the brief challenge of negative pressure created by diaphragmatic contraction. Contraction of pharyngeal adductor muscles maintains lung volume during the exhalation portion of a breath [46].

Development of airway protective mechanisms

The term "airway protective mechanisms" encompasses two separate but interrelated functions of the upper airway: (1) protection against aspiration of foreign material into the respiratory tree; and (2) protection against airway collapse during sleep or states of pharmacologically impaired consciousness.

The mechanisms that protect against aspiration of liquid or solid contents into the respiratory tree include a series of unconsciously controlled reflexes that include swallowing and cough (to transport substances away from the laryngeal inlet), and apnea and airway obstruction, which are attempts at prevention of substances from entering the respiratory tree [47]. Additional reflexes consist of laryngospasm and arousal [48]. Collectively, these have been termed the laryngeal chemoreflexes (LCR), and they mature throughout development [49]. The perinatal period represents a time of relatively high vulnerability to aspiration, as is clinically seen in the meconium aspiration syndrome, which occurs in nearly 2% of all livebirths [50].

In the newborn, introduction of water into the larynx results in a characteristic set of responses that include swallowing, apnea, bradycardia, and peripheral vasoconstriction with shunting to the central vascular bed. These adaptive responses are prominent in preterm infants and lessen with advanced gestational age [47,51–56]. The apneic reflexes have been implicated in the etiology of sudden infant death syndrome (SIDS) [57]. Administration of sedatives and anesthetic agents is associated with prolongation of the apneic reflex [58–60]. The apneic reflex is also prolonged (and bradycardia worsened) during baseline hypoxemia [61,62], anemia [63], and respiratory syncytial virus (RSV) infection [64,65]. Conversely, the apneic reflex is shortened by administration of central stimulants such as theophylline [59]. Soon after the newborn period, the apneic portion of the LCR response disappears [66]. Cough is more prominent, and continues for the remainder of life when foreign substances enter the laryngeal area.

The effects of anesthetics and sedatives on the efficacy and potency of airway protective reflexes are clinically important to establish the safety of pharmacological agents administered to non-tracheally intubated children. The body of knowledge concerning these effects is beginning to develop. At predefined depths of general anesthesia, propofol appears to be a more potent inhibitor of the laryngospasm reflex than sevoflurane [67], and fentanyl does not appear to reduce the propensity toward laryngospasm in sevoflurane-anesthetized children [68]. Data are also emerging on the effects of anesthetics on

upper airway patency. In adults, at similar depths of sedation or general anesthesia, propofol appears equal to isoflurane in promoting upper airway collapse [69,70], and both are more potent than equivalent levels of deep sedation attained with midazolam [71]. In children, the addition of 50% nitrous oxide promotes upper airway closure in those with enlarged tonsils who received oral midazolam [72], and halothane appears to preserve upper airway patency better than equipotent levels of sevoflurane [73].

KEY POINTS: DEVELOPMENTAL ANATOMY AND PHYSIOLOGY OF THE PEDIATRIC AIRWAY

- All six branchial arches and all four pharyngeal pouches contribute to formation of the airway
- The infant's occiput is relatively larger than the older child's, rendering neck flexion unnecessary to attain the sniffing position
- Primary teeth are shed between 6 and 12 years of age; attention to loose teeth is important in this age group
- Tonsil and adenoid tissue size is maximal between 4 and 7 years of age
- The larynx is at the C2–C3 level at birth, and descends with growth to the C4–C5 level at age 3 years
- With neuromuscular blockade, the cricoid cartilage is the narrowest portion of the pediatric airway; without neuromuscular blockade the vocal cords are the narrowest location

Management of the normal pediatric airway

Preoperative airway assessment

Preoperative airway assessment will identify nearly all children who, when anesthetized, are likely to develop difficult mask ventilation or difficult tracheal intubation. Information gained from the preoperative history and physical examination will determine the method of anesthetic induction and the approach for maintaining a patent upper airway following loss of consciousness. Similarly, risk factors for postoperative respiratory complications are identified at this time, allowing for appropriate preparation or delay of anesthesia and surgery when appropriate. Common airway assessment techniques used in adults have not been validated for use in infants and children; however, modifications of these methods may yield valuable information.

History

In almost all cases, a review of the child's previous anesthetic records as well as discussion with parents will reveal potential airway management problems. A history of previous uneventful anesthetics is encouraging, but changes in growth and development may affect airway anatomy. A reliable history of unobstructed breathing during sleep, especially while supine, often predicts the ability to mask ventilate without difficulty. Conversely, loud snoring and/or obstructive apnea are excellent predictors of upper airway obstruction following anesthetic- or sedative-induced unconsciousness.

During the preoperative interview, children and parents should be asked about the presence of loose deciduous teeth. Chipped or missing teeth should be documented. Very loose teeth should be electively removed after induction of general anesthesia to avoid accidental dislodgement (and pulmonary aspiration) during airway manipulations. A loose tooth is removed by grasping the tooth with a dry piece of gauze and pulling while rocking the tooth gently back and forth. Some bleeding is expected. Tooth removal is performed immediately following induction of anesthesia or after tracheal intubation, depending on the location of the tooth and risk of dislodgment during direct laryngoscopy. If elective tooth removal is contemplated, it should be discussed with parents and caregivers during the preoperative visit to avoid an unpleasant surprise when they are reunited with their child in the recovery room.

Children with non-permanent orthodontic hardware that may be dislodged during airway management should have such devices removed whenever possible. Occasionally, preoperative orthodontic consultation may be required.

Coexisting diseases and airway management

A number of coexisting diseases may influence airway management. For example, children with tumors of the head or neck may have distorted airway anatomy. Previous radiation therapy which results in scarring of the tongue and submandibular tissues is often associated with difficult tracheal intubation secondary to poor mandibular soft tissue compliance. Radiation therapy may also cause mucosal tissues to be friable and prone to bleeding.

If a child presents with an unfamiliar syndrome or diagnosis, the anesthesiologist should obtain a comprehensive understanding of the condition as it relates to airway management. The anesthetic implications of a number of common congenital syndromes and conditions are presented in Chapter 43.

The presence, type, and severity of pulmonary disease impact the advantages and disadvantages of different airway management techniques. For example, the child with limited pulmonary reserve may not tolerate anesthetic-induced hypoventilation and may require tracheal intubation and controlled ventilation for a procedure that would be performed with spontaneous ventilation and a natural airway in an otherwise healthy child. On the other hand, the child with highly reactive lower airways may benefit from a technique that is less stimulating to the airway.

In children with asthma, the severity, triggers, and current medication status should be assessed. Medical management should be optimized prior to surgery. This may include inhaled β-agonist therapy, inhaled corticosteroids, or a course of systemic corticosteroids, depending on the severity of disease and the procedure being performed. Adequate preoperative preparation of asthmatic children results in decreased intraoperative bronchospasm [74]. Uncontrolled asthma may warrant postponement of elective surgery. Some children may have persistent lower airway obstruction despite maximal medical management. In such cases, the anesthetic plan should include provisions for limiting triggers that exacerbate bronchoconstriction.

Bronchopulmonary dysplasia is a chronic lung disease associated with prematurity. Currently, most cases occur in

infants born at less than 30 weeks' gestational age and weighing less than 1200 g at birth [75]. Various factors contribute to the genesis of bronchopulmonary dysplasia, including mechanical ventilation-induced barotrauma and volutrauma, hyperoxia, infection, and genetic factors [75,76]. Although one study did not demonstrate an increased risk of postoperative respiratory complications [77], former preterm infants with pulmonary sequelae of prematurity may have a reduced tolerance of apnea and heightened airway reactivity, which can manifest as bronchospasm, oxyhemoglobin desaturation, or laryngospasm.

Children with significant pulmonary disease may benefit from preoperative consultation with a pulmonologist. Conditions meriting such consultation include cystic fibrosis, severe asthma, or pulmonary hypoplasia associated with congenital conditions such as congenital diaphragmatic hernia. Preoperative optimization of medical management and development of a postoperative care plan may decrease the incidence of postoperative complications.

Preoperative fasting and risk of aspiration

The adequacy of preoperative fasting and the risk of pulmonary aspiration of gastric contents should be assessed in every child. Current guidelines and recommendations for preoperative fasting in children are presented in Chapter 17. Children with high intestinal obstruction ideally should have gastric decompression prior to a rapid-sequence induction of general anesthesia. A history of gastroesophageal reflux disease warrants an assessment of its severity and response to therapy. Children with mild reflux disease or disease that has been effectively treated are candidates for inhaled induction of anesthesia. Children with esophageal motility disorders such as achalasia should be regarded as being at risk for pulmonary aspiration and managed accordingly.

Physical examination

Preoperative airway examination focuses on identification of physical features that suggest a difficult facemask ventilation or tracheal intubation. In adults, there are validated assessments that identify predictors of airway management difficulty [78–82]. Although seemingly useful (Fig. 16.5), similar validated assessments have not been published for infants and young children. Nonetheless, there are certain anatomical features that are consistently associated with airway difficulty in the pediatric population. These include limited mouth opening, limited neck mobility, maxillary hypoplasia, mandibular hypoplasia, and diseases associated with decreased compliance of the submandibular space. School-aged children and adolescents will cooperate with physical examination maneuvers to assess the airway, but in toddlers and infants, the airway exam is limited to an assessment of external physical features. In infants, neck mobility can be assessed by watching the infant track a colorful object, and mouth opening is assessed during crying.

Ultrasound examination has been used to examine the child's airway in an attempt to delineate the internal anatomical characteristics, predict optimal endotracheal tube size, and determine the presence of subglottic stenosis [83].

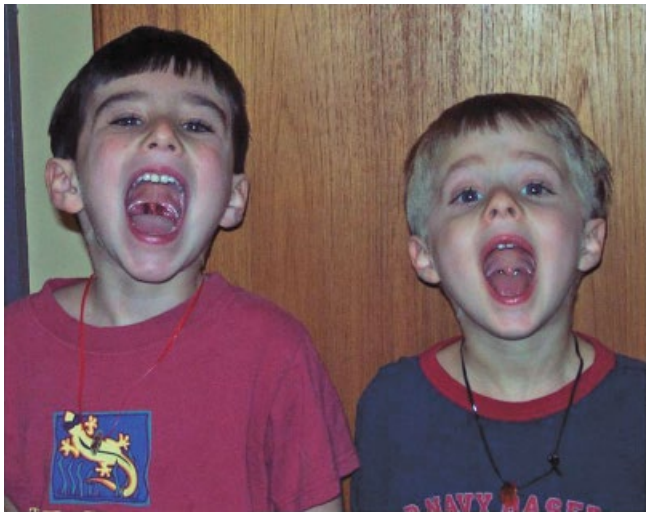


Figure 16.5 Although visualization of pharyngeal structures correlates with ease of intubation in adults, similar validation studies in pediatric patients have not been performed.

Routine airway management

Preoperative preparation of airway equipment

Airway-related equipment that should be prepared in the operating room prior to the arrival of the patient include the appropriate sized facemask, laryngoscope handle and blade, tracheal tube, oral airway, laryngeal mask airway, and working suction catheter. If use of a laryngeal mask is planned, it should be prepared with lubricant and ready for insertion.

A syringe of succinylcholine, 4–5 mg/kg, for intramuscular injection should be within reach in the event that laryngospasm or other type of upper airway obstruction occurs and immediate paralysis is required when intravenous access is absent. This dose should be calculated prior to the induction of general anesthesia.

Facemask ventilation

Proper positioning of the child during induction of general anesthesia is important in promoting upper airway patency and facilitating facemask ventilation and direct laryngoscopy. Because of the wide range of patient sizes encountered in pediatric practice, the adequacy of mask size and fit should be assessed prior to anesthetic induction. A properly fitting mask will cover the nose and mouth without covering the eyes or extending beyond the chin. A common mistake among trainees is to press the cephalad end of the mask onto the middle of the nose and unknowingly obstruct the airway. The cephalad end of the mask should be properly positioned on the bridge of the nose without pressing into the orbits. Introducing the mask to the child before it is connected to the anesthesia circuit provides a non-threatening opportunity for the child to acclimatize to it while giving the anesthesiologist an opportunity to assess fit.

Various types of pediatric facemasks are commercially available. While some have been designed to minimize dead space (attractive in the smallest patients), there are no data supporting the superiority of one mask type over another. Reusable black facemasks have largely been supplanted by transparent disposable facemasks. These disposable masks are advantageous in that the anesthesiologist can look through

them during ventilation and see the mist that accompanies airflow, assess the position of an oral or nasopharyngeal airway, or identify regurgitated fluid or vomitus. Application of a fruit- or candy-scented lip balm to the interior of the unscented mask may improve the child's acceptance.

During inhaled induction of general anesthesia, the facemask is initially applied gently to the face. The hand holding the mask should be held in such a way that the child's field of view is not obstructed. The other hand may be placed on the child's head and kept ready to hold the head still during the excitement stage of anesthetic induction. As consciousness is lost, the position of the hand holding the mask is adjusted so that the third and possibly the fourth and fifth fingers are over the bony mandible. Special care must be taken in smaller children not to exert pressure on the submandibular tissues, which can create upper airway obstruction by posterior displacement of the tongue. Following loss of consciousness, 5–10 cmH_2O of continuous positive airway pressure (CPAP) is applied by partial closure of the adjustable pressure limiting (APL) valve, and a head tilt or chin lift maneuver is performed with the left hand holding the mask while the right hand holds the breathing bag to assess breath-to-breath adequacy of air movement. Adequacy of ventilation is also continuously assessed by visual inspection of chest rise and breathing bag movement, auscultation with a precordial stethoscope, and the presence of a capnographic waveform.

Difficulty or inability to effectively perform manual ventilation through a facemask is uncommon in pediatric patients in the hands of experienced practitioners. Common causes for the inability to ventilate adequately through a facemask in children include enlarged tonsils or adenoids, and soft tissue (tongue, pharynx, etc.) obstruction in very small infants. A prospective, observational study found the incidence of difficult bag-mask ventilation in children up to 8 years of age to be 6.6%, using two or more of the following findings: application of CPAP of 5 cmH_2O, required use of an oral or nasal airway, need for two-person ventilation, oxygen desaturation <95%, or unanticipated need to increase inspired fraction of oxygen (FiO_2) [84].

Chin lift, jaw thrust, and continuous positive airway pressure

Simple maneuvers such as performing a chin lift or mandibular protrusion (jaw thrust) can restore upper airway patency and relieve obstruction by increasing pharyngeal diameter at several levels [85–89]. The combination of either of these two techniques with the application of approximately 10 cmH_2O of CPAP is the initial treatment of airway obstruction in the spontaneously breathing child [90]. These combined maneuvers (jaw thrust with CPAP or chin lift with CPAP) increase the diameter and patency of the upper airway and glottic opening [86]. While chin lift and jaw thrust have effects on tongue and epiglottis position, CPAP acts as a pneumatic splint to increase airway dimensions. Because jaw thrust combined with CPAP has not been shown to be superior to chin lift combined with CPAP, it has been suggested that chin lift with CPAP is preferable to a forceful jaw thrust, since this can result in postoperative discomfort [87]. In children with suspected cervical spine injuries, neck extension should be avoided; jaw thrust may be preferable in these cases.

Oral airway

After optimization of positioning, facemask application, and application of CPAP, the oral airway is usually the next intervention to restore patency of an obstructed upper airway in the anesthetized child. A variety of oral airways with subtle differences in design are commercially available for pediatric patients, with no literature supporting the superiority of one type or brand over another. However, those with hollow channels offer the advantage of being able to insert a suction catheter into the oropharynx with the oral airway inserted.

When inserting an oral airway, care must be taken to select the appropriate size. A properly sized airway should have its pharyngeal tip project just beyond the angle of the mandible when held next to the child's head with the opposite end at the mouth (Fig. 16.6). Insertion of an undersized airway can push the tongue posteriorly and worsen obstruction, while an oversized airway can impinge on the epiglottis or glottis and worsen obstruction or trigger coughing and laryngospasm.

Oral airways are generally reserved for use in anesthetized children and are poorly tolerated by awake or lightly anesthetized children as they can stimulate gagging, coughing, or laryngospasm. However, as a child emerges from anesthesia, it is best to leave an oral airway in place to prevent the child from biting on the tracheal tube and to maintain airway patency following extubation. Children will typically expel the device as they regain full consciousness.

Nasopharyngeal airway

A nasopharyngeal airway may be inserted to restore patency of the obstructed upper airway when the obstruction is suspected to be at the level of the upper pharynx or higher. Unlike an oral airway, a nasopharyngeal airway can be tolerated in the sedated or lightly anesthetized child and can be left in place postoperatively to maintain airway patency in selected circumstances such as following tonsillectomy for obstructive sleep apnea.

A disadvantage of nasopharyngeal airway insertion is occurrence of epistaxis. This can be minimized by using a soft airway and adequate lubrication. If time allows, topical administration of a vasoconstrictor to the nasal mucosa is helpful. Hypertrophic adenoid tissue can impede passage and may result in bleeding. The proper size nasopharyngeal

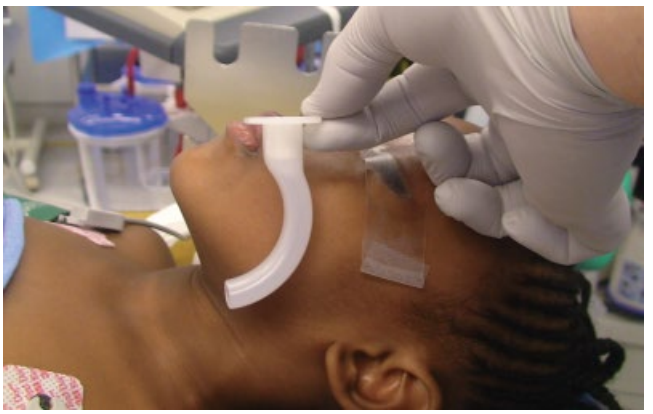


Figure 16.6 Sizing the oral airway, showing the pharyngeal tip projecting just beyond the angle of the mandible.

airway can be selected by holding it next to the face before insertion. With the flared external end at the position of the nasal opening, a properly sized airway will have the pharyngeal tip extending a finger breadth beyond the space between the angle of the mandible and the tragus (Fig. 16.7). A nasopharyngeal airway that is too short may not bypass upper airway obstruction, while one that is too long can impinge on the epiglottis and trigger coughing or laryngospasm.

Two-person, two-handed mask ventilation

When it is difficult to maintain a patent airway with the above techniques, having one provider apply the facemask using two hands and simultaneously perform a chin lift and jaw thrust while another provider delivers breaths with the breathing bag is more effective than a single-handed mask ventilation technique (Fig. 16.8). Patients requiring a two-person technique should be considered difficult to ventilate by facemask [91,92].

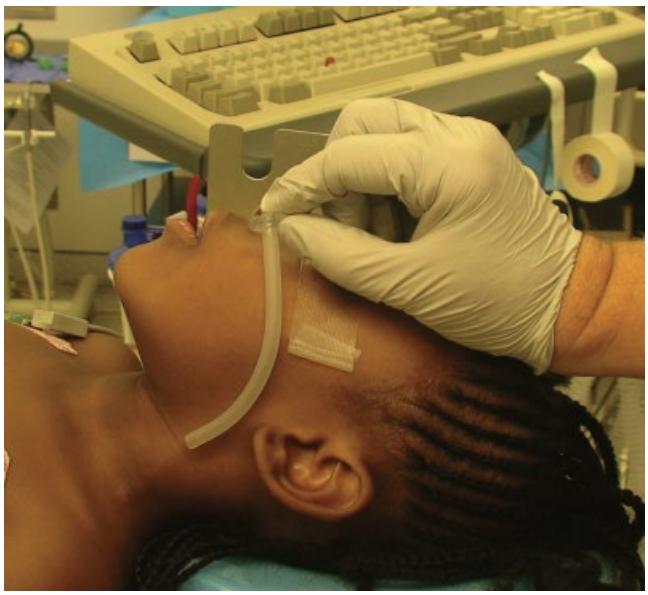


Figure 16.7 Sizing the nasopharyngeal airway, showing the pharyngeal tip projecting just beyond the space between the angle of the mandible and the tragus.

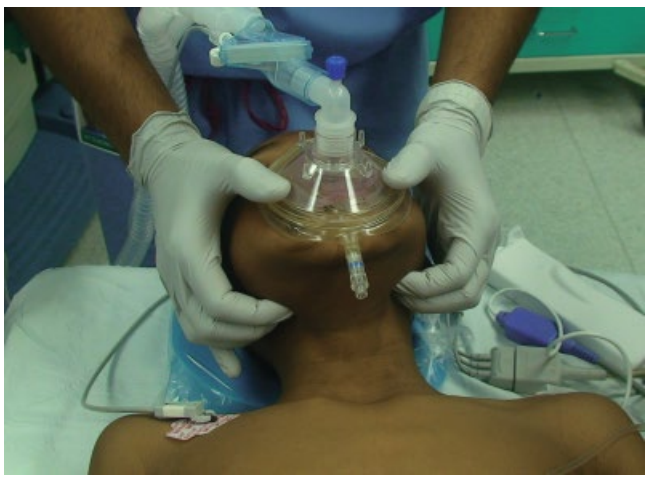


Figure 16.8 Two-handed mask technique.

Modified oral or nasal airway

The functionality of a standard oral or nasopharyngeal airway can be increased by inserting a 15 mm tracheal tube adaptor into the opening of the oral airway or the flared end of a nasopharyngeal airway (Fig. 16.9). The resulting modified airway can then be connected to the anesthesia circuit, and positive pressure can be delivered if the leaks around the airway are manually sealed. Positive pressure ventilation can be delivered by holding closed the mouth and opposite nasal passage [93]. This assembly with a nasopharyngeal airway is particularly useful in patients with limited mouth opening in whom oral airway or laryngeal mask insertion is not possible. The modified nasal airway is also a valuable adjunct to pediatric difficult airway management as a means to provide oxygen and inhaled anesthetic during oral intubation while maintaining spontaneous respiration [94]. Similarly, a cut tracheal tube can also be used for the same purposes [95], but because it is made of stiffer material it is more likely to cause trauma and bleeding during insertion.

Airway management with a facemask or natural airway

Maintenance of general anesthesia with a facemask is possible if a patent airway is easily achieved with or without an oral or nasal airway. Generally, use of a facemask is preferred for cases of shorter duration, and when the head of the operating room table is not turned away from the anesthesia machine. A natural airway that does not require the assistance of the anesthesiologist for patency is often used in conjunction with a nasal cannula for supplemental oxygen administration and the use of intravenous general anesthesia such as propofol. Special cannulae designed to monitor exhaled carbon dioxide are commercially available or a standard cannula can be modified for this purpose. This technique is commonly used during total intravenous anesthesia for radiological or gastrointestinal endoscopy procedures.

Figure 16.9 Oral and nasopharyngeal airways can be attached to a 15 mm tracheal tube adaptor to provide easy connection with an anesthesia machine circuit.

Laryngeal masks and supraglottic devices

The introduction of the laryngeal mask airway (laryngeal mask) into clinical practice marked the beginning of a new era of anesthesia care for adults [96] and children [97]. Since that time, the laryngeal mask has functioned as an alternative to the facemask and the tracheal tube, depending on the clinical situation. Of equal importance is its use as an airway rescue device in patients with life-threatening upper airway obstruction, or as an aid to difficult tracheal intubation.

The laryngeal mask consists of an airway tube with an elliptically shaped cuff at the distal end that is inflated after insertion. When properly positioned, its distal aperture lies opposite the laryngeal inlet while the tip of the cuff rests in the proximal esophagus. The inflated cuff creates a seal with the lateral walls of the hypopharynx, the esophageal inlet, and the tongue base.

The classic sniffing position is used for routine laryngeal mask insertion. The deflated or partially inflated laryngeal mask is held in the dominant hand like a pencil, with the tip of the index finger at the junction of the cuff and the airway tube on the side of the laryngeal aperture. The mouth is opened and the tip of the device is pressed cephalad along the hard palate and into the oropharynx until a resistance is felt as the tip engages the esophageal opening. Because of anatomical differences in children (e.g. large tongue, cephalad larynx, tonsillar hypertrophy), this technique may result in a lower success rate than in adults. Therefore, alternative approaches have been devised (i.e. lateral and rotational insertion techniques) and may be more successful in children [98–103]. These studies were performed using the classic laryngeal mask; therefore it is unknown whether these results can be extended to other commercially available laryngeal masks and supraglottic airways that may have more favorable insertion properties.

Airway management with the laryngeal mask is advantageous in a number of ways. Insertion of the device is simple and easily learned, and there is a high success rate with insertion even by inexperienced operators. Laryngeal mask insertion does not require muscle relaxation, can be performed at a lighter level of anesthesia as compared to tracheal intubation, and is associated with fewer hemodynamic changes when compared to tracheal intubation [104,105]. Use of a laryngeal mask is associated with less airway reflex activation than an endotracheal tube and has been shown to be associated with a nearly threefold reduction in the risk of perioperative respiratory adverse events (e.g. laryngospasm, bronchospasm, coughing, desaturation) in infants [106]. A meta-analysis of 19 studies comparing supraglottic airway devices to tracheal intubation in children found that during recovery from anesthesia the incidence of desaturation (odds ratio (OR) = 0.34 (0.19–0.62)), laryngospasm (OR = 0.34 (0.2–0.6)), cough (OR = 0.18 (0.11–0.27)), and breath holding (0.19 (0.05–0.68)) was lower when a laryngeal mask airway was used. Postoperative incidences of sore throat (OR = 0.87 (0.53–1.44)), bronchospasm (OR = 0.56 (0.25–1.25)), aspiration (1.33 (0.46–3.91)), and blood staining on the device (OR = 0.62 (0.21–1.82)) did not differ between laryngeal mask airway and tracheal intubation [107]. However, when compared to adults, optimal positioning of the laryngeal mask becomes progressively more difficult in direct relation to decreasing age of the child. Improper positioning of the laryngeal mask may lead to inadequate ventilation, airway trauma, mask dislodgement, and gastric insufflation. Fiberoptic assessment of laryngeal mask position is often useful to ascertain that the laryngeal mask is properly positioned. A jaw thrust maneuver while inserting the smaller sized laryngeal masks may facilitate optimal positioning by lifting the epiglottis off the posterior pharyngeal wall and allowing the laryngeal mask tip to slide into the upper esophageal sphincter without causing downfolding of the epiglottis. In a large dataset of pediatric patients, retrospective analysis demonstrated that laryngeal mask failure was associated with use during head and neck procedures, non-outpatient admission status, prolonged surgical duration, congenital or acquired airway abnormality, and patient transport [108,109]. The laryngeal mask may be difficult to place in conditions where mouth opening is limited, such as temporomandibular joint ankylosis. Thermally softening the laryngeal mask before placement may allow the mask to fit through the limited opening [110].

The laryngeal mask is not usually associated with mechanical trauma to the tracheal mucosa and vocal cords. This is particularly relevant in children undergoing multiple anesthetics over a relatively short time interval (e.g. daily radiation treatment). In one study the incidence of postoperative sore throat was equally as common compared with a tracheal tube [111]. The occurrence of postoperative sore throat in children appears to be correlated with laryngeal mask intracuff pressures above 40 cmH_2O [112]. The incidence of other less commonly reported complications from laryngeal mask use, such as lingual, hypoglossal, or recurrent laryngeal nerve injury [113–116], may also be decreased by routine monitoring of laryngeal mask cuff pressures.

In the years following the introduction of the originally designed laryngeal mask, a variety of different supraglottic devices have become available that have slightly different modifications. The ProSeal™ laryngeal mask (LMA North America) is similar to a classic laryngeal mask with the addition of a channel through which a gastric drainage tube can be passed. The ProSeal laryngeal mask is available in sizes appropriate for use in infants and children. Some practitioners avoid positive pressure ventilation with laryngeal mask use because of the possibility of gastric insufflation. Thus, the ProSeal may be preferred in patients who require positive pressure ventilation [117,118]. However, there is no evidence that any specific type or model of supraglottic airway (SGA) device is superior in clinical pediatric anesthesia practice. The choice of SGA is therefore left to practitioner preference.

The i-gel® SGA (Intersurgical, Liverpool, NY, USA) is another type of SGA that has been useful in pediatric anesthesia. It has a built-in bite block and contains a gastric access channel. An observational study in 50 children reported easy insertion and gastric access in all patients [119]. When compared to the Ambu® AuraOnce™ laryngeal mask (Ambu, Glen Burnie, MD, USA), the i-gel demonstrated higher leak pressures, longer insertion times, and a tendency to slide out of the oral cavity after insertion [120]. A larger comparative study (n = 170) in children demonstrated that the i-gel was equally as efficacious as the LMA® Supreme™ but the i-gel required relatively more manipulations [121]. A meta-analysis of nine prospective randomized controlled trials comparing the i-gel to other laryngeal masks found no differences in first

insertion success rates and ease of insertion when compared to the Proseal and classic laryngeal mask airways [122].

The air-Q intubating laryngeal airway (Cookgas LLC, Mercury Medical, Clearwater, FL, USA) is an SGA designed to facilitate tracheal intubation. It is unique because it easily accommodates a cuffed tracheal tube through the airway tube of its smaller sizes (<3) and has a custom stabilizer bar that allows its removal after tracheal intubation. Its efficacy as a conduit for tracheal intubation was assessed in an audit of 34 difficult intubations that found 97% tracheal intubations on the first attempt through the air-Q using fiberoptic bronchoscopy (n = 25), Shikani Optical Stylet (n = 7), or blindly (n = 2) [123]. However, blind insertion is not preferred and may result in severe airway trauma.

Like an oral airway, laryngeal masks and other SGAs are poorly tolerated in awake or lightly anesthetized patients (except infants with severe airway obstruction). Insertion at an inadequate plane of anesthesia can result in coughing, laryngospasm, gagging, and emesis. A number of studies have been conducted to determine optimal drug dosages to achieve adequate conditions for laryngeal mask insertion. Sevoflurane alone can be used to facilitate laryngeal mask insertion in children [124]: an effective concentration of 2.2 vol% provides satisfactory conditions in 95% of patients when 10 min are allowed to elapse for equilibration of brain and alveolar sevoflurane concentrations prior to insertion [104].

At approximately equipotent dose levels, propofol is a more potent suppressor of upper airway reflexes compared to thiopental [125] and is a superior induction agent for laryngeal mask insertion in terms of adverse respiratory events such as coughing or laryngospasm [126]. Propofol alone can be administered to facilitate laryngeal mask insertion. Doses exceeding 5 mg/kg are required to achieve satisfactory conditions in 90% of unpremedicated children [127]; however, such doses may result in undesirable hemodynamic effects and apnea. The combination of propofol with other drugs to facilitate laryngeal mask insertion is advantageous. For example, co-administration of lidocaine will result in less pain on injection of propofol [128–130] and may contribute to decreasing airway reflexes [131]. Opioids such as fentanyl [132], alfentanil [129], and remifentanil [133] may also aid in ease of laryngeal mask insertion when co-administered with propofol.

In adults, the laryngeal mask was originally designed for removal as the patient awakens [96]. In children, there has been controversy over whether it is better to remove the laryngeal mask under deep general anesthesia or after awakening. Some studies show a higher incidence of respiratory complications (coughing, laryngospasm, or oxyhemoglobin desaturation) when the laryngeal mask is removed when the child has largely regained consciousness [134,135], but others found a decreased incidence of such complications with awake removal [136,137], and some report no difference in complications based on removal technique [138,139]. One of the principal advantages of laryngeal mask removal under deep anesthesia is time efficiency – following laryngeal mask removal and assurance of a patent airway, the child can be transferred to the recovery room and allowed to emerge from anesthesia. If laryngeal mask removal under deep anesthesia is planned, the end-tidal sevoflurane concentration at which this can be safely performed in 95% of children without coughing, movement, laryngospasm or other airway complication is 2.2% [140,141].

Laryngeal mask insertion may be tolerated in conscious newborns with severe upper airway obstruction, as occurs with the Pierre Robin sequence, Treacher Collins syndrome, or Goldenhar syndrome [142–144]. This may facilitate management of the difficult airway by establishing a conduit through which fiberoptic intubation can be accomplished.

Pressure support ventilation decreases the work of breathing in spontaneously breathing children [145]. The advent of anesthesia machines with more sophisticated ventilators that can deliver pressure support ventilation has also made use of laryngeal masks more feasible as an alternative to tracheal intubation [146]. While work of breathing is improved with the application of CPAP [147], work of breathing is less and respiratory rate and end-tidal carbon dioxide are lower with pressure support ventilation compared to CPAP in children breathing with a laryngeal mask [148,149].

KEY POINTS: MANAGEMENT OF THE NORMAL PEDIATRIC AIRWAY

- Preoperative airway assessment includes a history of difficult airway management, assessment of dentition, and evaluation for craniofacial syndrome or anomaly
- Anatomical features consistently associated with difficult airway management include limited mouth opening and neck mobility, maxillary or mandibular hypoplasia, and decreased compliance of the submandibular space
- A properly fitting facemask covers the nose and mouth without covering the eyes or extending beyond the chin
- CPAP of 5–10 cmH_2O, chin lift, and jaw thrust by positioning fingers over the mandible (not subglottic soft tissue) are common maneuvers during routine airway management
- An oral airway of proper size can be placed if these maneuvers do not restore upper airway patency; placing an airway during light anesthesia can stimulate gagging, coughing, and laryngospasm
- Two-handed mask ventilation with jaw thrust, with a second person delivering manual breaths, is often useful for significant upper airway obstruction
- Supraglottic airway devices such as the laryngeal mask airway are very commonly used for shorter cases without airway anomalies or aspiration risk

Tracheal intubation

Indications for tracheal intubation are determined by the surgical procedure and the potential risk of aspiration of gastric contents. As a general rule, tracheal intubation is indicated for open cavity procedures of the abdomen or chest, intracranial procedures, and in cases where control of arterial PCO_2 is required. It is also indicated in cases where the anesthesiologist has limited access to the airway, such as procedures involving the head and neck or patients in the prone or lateral position.

Positioning for mask ventilation and tracheal intubation

In adults, the "sniffing position" (i.e. neck flexion and head extension) is classically described as the optimal head and neck position to facilitate direct laryngoscopy and tracheal intubation. The recommendation for this position is based on texts published between 1852 and 1944 [150]. However a number of more recent publications have suggested that the sniffing position in adults may offer no advantage over simple extension of the head for successful direct laryngoscopy [151–153]. In a study of the alignment of the oral, pharyngeal, and tracheal axes in children anesthetized for MRI scans of the head and neck, better alignment was achieved with simple extension of the head as compared to the sniffing position [154]. However, comparative trials examining the optimal position for laryngoscopy and intubation in children have not been carried out. The large occiput of an infant, when placed on a pillow, can flex the head and result in airway obstruction. Eliminating the pillow or placing a soft roll beneath the shoulders may improve upper airway patency.

Direct laryngoscopy

Direct laryngoscopy remains the most common method of tracheal intubation in children. Direct laryngoscopy using a straight Miller blade has traditionally been emphasized in infants and young children. This practice is largely based on anatomical studies [28] but comparative studies have not been performed [150,155,156]. The straight Miller blade may allow for greater control and displacement of the base of the tongue. The smaller size and lower profile of the straight blade may give the operator more room to pass the tracheal tube through the mouth and pharynx. When laryngoscopy is performed using a straight blade, the blade is advanced and used to directly lift the epiglottis to expose the larynx. The straight blade can also be directed into the vallecula and used to indirectly lift the epiglottis as is done with the standard curved blade. In Miller's 1946 original description of the infant version of the blade, it states "…the epiglottis is visualized and raised slightly to expose the cords or, if the operator desires, the tip of the blade may be placed in front of the epiglottis and raised sufficiently to visualize the cords after the method of Macintosh" [157]. While direct laryngoscopy with the Miller blade may be more difficult to learn [158], there is evidence in adults that a superior view of the larynx can be achieved compared to the Macintosh blade [158,159]. A comparison of laryngoscopic views between size 1 Miller and Macintosh laryngoscope blades in children age less than 2 years found similar views. The authors also noted that the view with the Miller blade lifting the epiglottis was similar to the view obtained when it was placed in the vallecula. The view with the Macintosh blade was improved when it was used to lift the tongue base when compared to lifting the epiglottis [160].

If visualization of the glottis is suboptimal during direct laryngoscopy, the laryngoscopist can improve it by external manipulation of the thyroid cartilage. This practice was described by Benumof and Cooper as optimal external laryngeal manipulation (OELM) [161]. The application of backward, upward, and rightward pressure on the thyroid cartilage (known as the BURP maneuver) is an example of a specific type of OELM that many laryngoscopists employ as a first-line attempt at achieving optimal glottic exposure [162]. In newborns and small infants, OELM can be performed using the fifth finger of the left hand (Fig. 16.10).

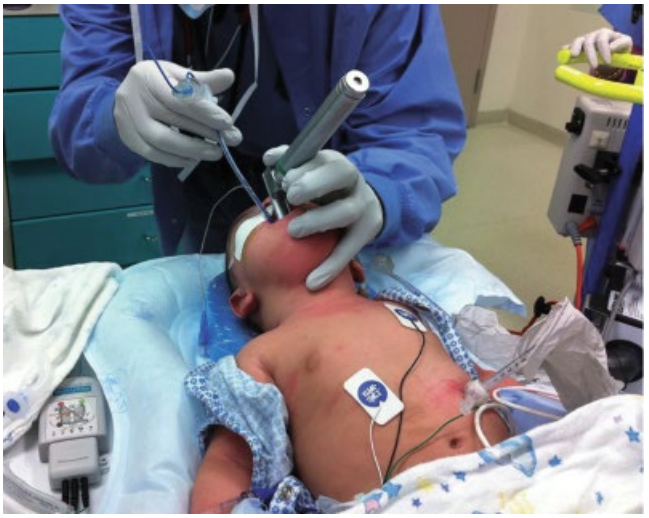


Figure 16.10 The glottis can be externally manipulated by using the fifth finger of the left hand that holds the laryngoscope.

Maintaining arterial hemoglobin saturation during laryngoscopy and tracheal intubation

The administration of high-flow oxygen via a nasal cannula (transnasal humidified rapid insufflation exchange or THRIVE) has been shown to be an effective technique for prolonging the time from apnea to oxyhemoglobin desaturation in adults [163]. This approach to achieving apneic oxygenation has been demonstrated to be effective in children under controlled conditions during apnea with jaw thrust to maintain airway patency [164]. Subsequent studies may demonstrate whether this technique is effective in preventing oxyhemoglobin desaturation during intubation attempts and airway management in children.

Hemodynamic response to laryngoscopy and tracheal intubation

Tracheal intubation in infants and children is an intensely stimulating procedure and can provoke tachycardia, hypertension, increased intracranial pressure, and bradycardia [165–169]. Tracheal intubation with flexible bronchoscopy does not result in a decreased pressor response compared to direct laryngoscopy [165]. Performance of intubation under deep anesthesia attenuates the pressor response to intubation; however, many of the agents used to achieve this can cause cardiovascular depression. The opiates fentanyl, remifentanil, and sufentanil have each been used for this purpose with success [170–172], while lidocaine does not appear to be effective [173].

Movement of the tracheal tube tip with neck movement

Flexion or extension of the neck results in predictable changes in location of the tracheal tube tip. In children, with both orotracheal and nasotracheal tubes, neck flexion results in caudal migration of the tube tip, while extension causes cephalad migration of the tube tip [174–176]. Therefore, bronchial

intubation or extubation may result with neck movement after securing the tracheal tube.

Tracheal intubation without neuromuscular blockade

With the introduction into clinical practice of sevoflurane, propofol, and remifentanil, there has been increased interest in achieving tracheal intubation without neuromuscular blockade. Successful intubation can be accomplished with sevoflurane alone [177], although other drugs are commonly co-administered. Intubating conditions can be improved when sevoflurane is combined with propofol [178,179], lidocaine [131], and remifentanil [180,181]. Topically administered lidocaine delivered to the larynx and trachea during laryngoscopy is commonly performed, however it has been associated with a greater likelihood of airway reflex activation, desaturation, and perioperative respiratory adverse events in observational studies [182,183]. If tracheal intubation without neuromuscular blockade is performed following intravenous induction with propofol, a systematic review identified remifentanil (4 μg/kg) as the only single-agent adjuvant to yield an acceptable incidence of excellent intubating conditions [184]. Dexmedetomidine (1 μg/kg) combined with remifentanil (2 μg/kg) following intravenous propofol induction (3 mg/kg) has also been demonstrated to be an effective technique [185].

"Awake" tracheal intubation

In select circumstances outside of the obstetric delivery room, tracheal intubation may be performed in unpremedicated newborn infants who might not tolerate the cardiovascular depressant effects of anesthetic or sedative drugs. However, infants and neonates do experience the pain and discomfort from laryngoscopy; its performance without sedative premedication or general anesthesia has untoward cardiovascular (and behavioral) effects and should be avoided whenever possible. Furthermore, the administration of anesthetic, sedative, and neuromuscular blocking drugs improves conditions for intubation and decreases the likelihood of airway trauma [186–189]. A consensus statement published by the International Evidence Based Group for Neonatal Pain states "tracheal intubation without the use of analgesia or sedation should be performed only for urgent resuscitations in the delivery room or for life-threatening situations associated with the unavailability of intravenous access" [190].

Nasotracheal intubation

Before the advent of muscle relaxants, nasotracheal intubation was the preferred route for tracheal intubation; the technique was perfected by pioneering anesthesiologists such as Dr Ivan Magill (now memorialized for the forceps used for this purpose that bear his name) [191]. Following the introduction of muscle relaxants into anesthesia practice, orotracheal intubation became the favored technique. In current anesthesia practice, nasotracheal intubation is required for certain procedures (e.g. Lefort I osteotomy), while it is preferable for other procedures but not essential (e.g. oral rehabilitation). In other situations, such as in infants in the prone position, many anesthesiologists prefer a nasotracheal tube because of the possibility that it is more stable and secure than an oral tube. For children undergoing cardiac surgery, a nasotracheal tube may leave more room in the mouth for transesophageal echocardiography probe insertion. Nasotracheal intubation may be more comfortable than orotracheal intubation if postoperative tracheal intubation is expected.

Nasotracheal intubation is more challenging to perform than orotracheal intubation. The most common complication is epistaxis, especially in children with adenoidal hypertrophy. Other less common complications include retropharyngeal perforation [192,193], sinusitis [194], bacteremia [195–197], turbinate avulsion [198,199], and necrosis of the skin of the alae nasae with excessive pressure from the endotracheal tube. Nasotracheal intubation is contraindicated in the setting of facial or skull fractures; intracranial tube placement has been reported following attempted nasotracheal intubation in this setting [200]. Oxymetazoline 0.05% can be applied to the nasal mucosa for vasoconstriction and to decrease the risk and severity of epistaxis. Cocaine (4–10%) and lidocaine with epinephrine have also been used for this purpose. Oxymetazoline is as effective as 10% cocaine and more effective than lidocaine with epinephrine for the prevention of epistaxis from nasotracheal intubation [201]. In a related study assessing vasoconstriction for endoscopic sinus surgery, oxymetazoline was preferable over both 0.25% phenylephrine and 4% cocaine [202]. To avoid triggering laryngospasm, topical vasoconstrictors should be sprayed after a deep plane of anesthesia has been reached or following administration of a neuromuscular blocking drug.

Topical vasoconstrictors used for nasal mucosal vasoconstriction are potent α-agonists that can be absorbed and exert systemic effects; these agents should be used judiciously. Life-threatening hypertension and pulmonary edema following the use of topical 0.5% phenylephrine has been described [202–204]. Severe hypertension and reflex bradycardia progressing to sinus arrest has also been reported following oxymetazoline administration [205,206].

The occurrence of nasal bleeding may also be reduced by softening the tracheal tube, which is achieved by soaking the tip in warm water or saline [207]. The use of a red rubber catheter to guide the tracheal tube through the nose into the pharynx is a more effective method to decrease epistaxis compared to softening the tube tip in warm water [208–210].

Once inserted through the nose, the tube should be advanced so that its tip lies in the pharynx. Direct laryngoscopy is then performed, and the tip of the tracheal tube located in the pharynx. Once laryngeal exposure is optimized, the tube is gently grasped and guided into the trachea using Magill forceps as the tube is advanced. Care must be taken not to damage the cuff of a cuffed tube with the forceps.

Occasionally, it is difficult to advance the nasotracheal tube into the trachea despite an excellent view of the glottic inlet. This may occur because the natural curvature of the nasotracheal tube directs the tip anteriorly as it is advanced rather than in a direction parallel to the long axis of the trachea. Techniques to overcome this problem include neck flexion, directing the tube posteriorly with the Magill forceps, rotating the tube so the narrowest part of the beveled tip is aligned parallel with the glottic opening, turning the head to the side,

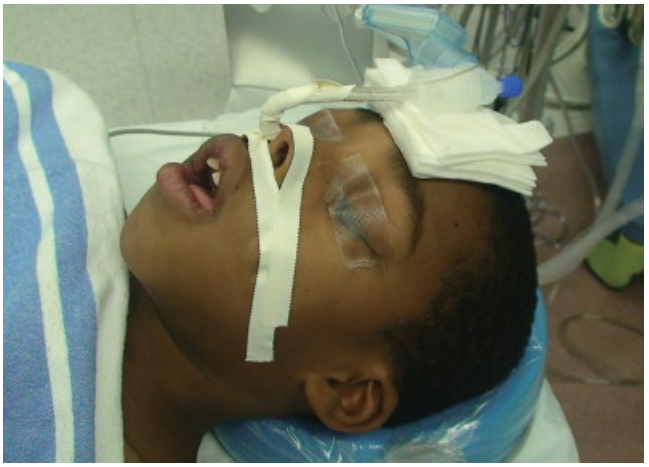


Figure 16.11 Proper taping of the nasal RAE tracheal tube to avoid pressure on the skin of the nasal alae.

and rotation of the tube 180° as it is advanced to direct the natural curvature of the tube more posteriorly.

When securing a nasotracheal tube, it is important to tape the tube in a way that avoids excess pressure between the tube and the ala, as this can result in ischemia and subsequent ulceration (Fig. 16.11).

Tracheal tube selection

A variety of methods exist for determining the expected tracheal tube size in children, including formulas based on age, height–length ratio, ultrasound measurement [43], and qualitative methods such as comparison of tube size with the size of the fifth finger nail [211]. Although height is often used in the emergency department setting [212,213], age-based formulas are more commonly used by anesthesiologists. Similarly, although ultrasound measurement of the transverse diameter of the subglottic trachea accurately predicts proper tracheal tube size [214], the practicality of routinely performing ultrasound measurements to select tube size may limit the widespread application of this technique.

Uncuffed tube size is often determined by a modified Cole's formula: internal tube diameter (mm) = 4 + age/4 [211,215]. If a cuffed tube will be used, a one-size smaller diameter tube should be selected to account for the small increase in external diameter created by the deflated cuff: internal tube diameter (mm) = 3+ age/4 [215].

RAE tubes

Oral and nasal tracheal tubes with a preformed bend (RAE tubes, named from the initials of the inventors Ring, Adair, and Elwyn) may be desirable in surgical procedures involving the eyes, oral cavity, or face [216]. These tubes allow the anesthesia circuit to be directed away from the surgical field without kinking. The length of the preformed bend is fixed and varies with tube size. Sometimes the RAE tube that is the proper size for the child's tracheal diameter is too short or too long due to the fixed location of the bend. In cases where it is too long, a smaller size cuffed RAE can be used. In cases where it is too short, a standard straight tube may need to be substituted. For oral and nasal RAE tubes, a useful way of choosing the proper size based on length is to hold the tube next to the child's face and assess the location of the cuff or tube tip. For cuffed tubes, the cuff should lie at the level of the suprasternal notch; the tip of an uncuffed tube should lie at the level of the sternoclavicular junction.

Cuffed versus uncuffed tracheal tubes

Historically, uncuffed tracheal tubes were preferred in children up to the approximate age of 8–10 years. The lack of a cuff allowed for a greater internal diameter, which translated into lower resistance and decreased work of breathing during spontaneous ventilation, and greater ease of suctioning secretions. There was also concern that the use of cuffed tubes might be associated with a higher risk of subglottic injury. However, the use of modern tracheal tubes with high-volume, low-pressure cuffs has not been associated with an increased incidence of subglottic airway injury or an increased incidence of postextubation croup in anesthetized children [217].

In 1951, Eckenhoff published a seminal article describing the anatomy of the infant and pediatric larynx [29]. The widespread teaching based on this article was that the infant larynx is funnel shaped with the widest portion at the glottic inlet and the narrowest portion at the cricoid ring. This has been disproven in a purely static anatomical measurement model using MRI [35,37]; however, the cricoid ring remains *functionally* the narrowest portion of the airway because it is a complete ring and is non-distensible. These latter studies found the pediatric larynx to be slightly elliptical in cross-section, with a smaller transverse diameter and a larger anteroposterior diameter. Given this elliptical shape, an uncuffed tube of a size that effectively ablates an air leak would be expected to exert more pressure on the lateral walls of the larynx and trachea [218]. The cuff of a properly sized cuffed tracheal tube would conform to the shape of the trachea as it is inflated and pressure would be evenly distributed. The use of cuffed tubes in children is associated with a decreased incidence of postintubation stridor [219]. In addition to the anatomical factors described here, this may also be related to decreased need for repeat laryngoscopy and tube changes in cases where an uncuffed tube that is too small or too large is initially inserted.

Cuffed tracheal tubes provide a better seal to protect the trachea from macroaspiration, while simultaneously allowing for lower fresh gas flows (with associated economic advantages) and decreased operating room pollution. In cases such as tonsillectomy, use of a cuffed tube can limit escape of oxygen-enriched inspired gases and decrease the risk of intraoperative fires, although this does not obviate the importance of limiting inspired oxygen concentration in these cases. However, there is some evidence that the presence of a cuff may contribute to bronchoscopically proven airway injury [220].

In our clinical practice, uncuffed tracheal tubes are rarely used [221]. However, they remain useful in certain situations where maximizing the internal diameter of the tube is important. Because resistance to airflow is inversely proportional to the fourth power of the radius of the tube (or fifth power with turbulent flow), the ability to ventilate can be impaired by selecting a cuffed tube that is a size smaller than the appropriate uncuffed tube. This effect is most clinically significant with smaller tube sizes used in preterm and very low birthweight

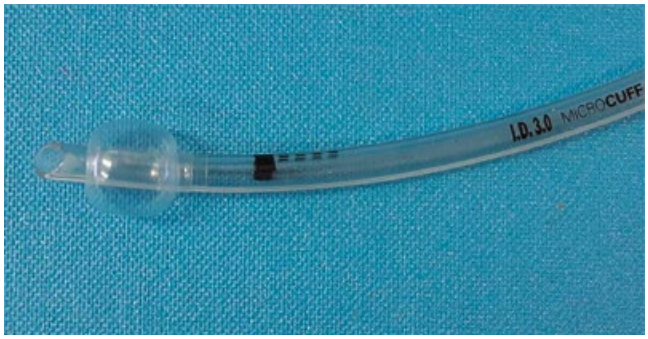


Figure 16.12 The Microcuff endotracheal tube. There is no Murphy eye, enabling location of the cuff more distally and allowing shorter cuff length. Note also the depth markings with the thick black line intended to be placed at the vocal cords. *Source:* Reproduced from Thomas et al [422] with permission of BMJ.

infants. Moreover, suctioning and pulmonary toilet are more difficult with the smallest tubes. An uncuffed tube is also advantageous when used as a bronchial blocker to achieve single lung ventilation. Because the bronchial blocker occupies a portion of the lumen, a larger lumen will help limit resultant increased resistance to airflow through the tube.

In 1994, a newly designed endotracheal tube called the Microcuff® was introduced for use in small pediatric patients (Halyard Health, Alpharetta, GA, USA) (Fig. 16.12). The Microcuff tube contains an ultrathin (10 μm) polyurethane-based inflatable cuff with a low-pressure high-volume profile to prevent tracheal mucosal trauma. In addition, the traditional Murphy eye was sacrificed to make room for the cuff to be located more distally than normal endotracheal tubes, situating it below the vulnerable subglottic area. Although numerous publications have demonstrated its usefulness [219,222], there is no proven advantage to its use over standard endotracheal tubes, and some anecdotal reports implicate the Microcuff in causing tracheal damage in neonates [223]. The absence of the Murphy eye may also have disadvantages. Rarely the distal end of the endotracheal tube can be obstructed with secretions or blood and the Murphy eye allows some ongoing ventilation; also, in the case of unrecognized right mainstem bronchus intubation, the Murphy eye may allow some ventilation of the left lung.

Determining proper endotracheal tube length

As in tracheal tube diameter selection, a variety of formulas have been created to predict the proper depth of orotracheal tube insertion. In infants and neonates, a commonly used rule of thumb is the "1,2,3,4–7,8,9,10 rule," where a 1 kg infant will have the tube taped at 7 cm at the maxillary alveolar ridge, a 2 kg infant taped at 8 cm, a 3 kg infant taped at 9 cm, and a 4 kg infant taped at 10 cm. In infants, when an uncuffed tracheal tube is used, it is common practice to advance the tube to achieve a deliberate right main bronchial intubation while auscultating the left chest. The centimeter depth at which breath sounds disappear (or become greatly decreased) is identified as the carina. The tube is then withdrawn midway between the carina and the vocal cords. Prior to performing this maneuver, it is useful to identify the centimeter marking relative to the gum or incisors following intubation and advancement of the cuff just beyond the vocal cords (or, with an uncuffed tube, 1–2 cm beyond the vocal cords). Knowing the centimeter marking with this depth of insertion as well as the depth of the carina gives the anesthesiologist an idea of how much cephalad or caudal tube displacement can safely occur. One study compared auscultation after deliberate main stem intubation to cuff palpation in the suprasternal notch and using the depth markings on the endotracheal tube. Auscultation after deliberate main stem intubation and cuff palpation resulted in a tube tip above the carina that was shorter and more predictable than placement of the tube using depth markings [224].

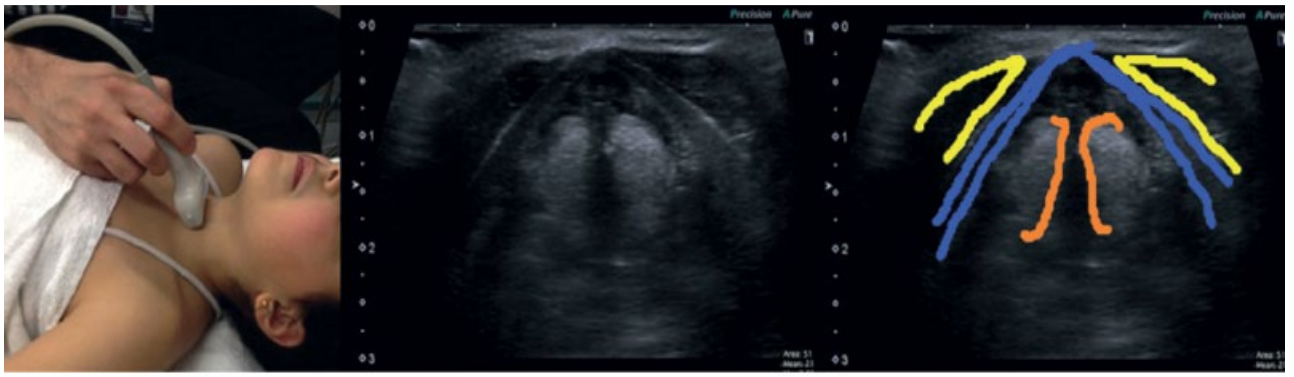
In older children, a good rule of thumb that is used to estimate the proper orotracheal tube depth in centimeters is to multiply the appropriate tube internal diameter (in millimeters) by 3. For nasotracheal intubation, multiplying the appropriate tube internal diameter by 4 is an effective method. When a cuffed tube is used, the "ballotte" technique can be used to place the cuff in its proper position at the level of the suprasternal notch. Identification of the depth of the tube relative to the maxillary alveolar ridge or maxillary incisors gives a more precise depth marking than identification relative to the lip.

A recent study suggested that the use of body surface area predicted proper tracheal tube length better than the use of age (in children older than 1 year of age) or weight (children less than 1 year of age) [225]. In recent years, the use of bedside point-of-care ultrasound has been described for confirmation of placement of the endotracheal tube in the trachea and to determine proper depth of insertion [83,226] (Figs 16.13, 16.14). This approach can be useful for additional confirmation of endotracheal tube placement in the case of difficult airway visualization.

Assessing tube size following endotracheal intubation

The appropriateness of the tracheal tube size selected must be verified in every child. A tube that is too large may exert excessive pressure on the tracheal mucosa, resulting in mucosal ischemia. In the short term, this can lead to mucosal edema and stridor following extubation, while in the long term it may contribute to the development of subglottic stenosis.

In some children, an oversized tube is identified by an inability to advance the tube into the trachea during the intubation attempt. The most common method to assess tube size after placement of the tube is the air leak test. After midtracheal positioning of the tube tip, the APL valve is closed and the circuit pressure is allowed to increase while a stethoscope is placed over the thyroid cartilage. The leak pressure occurs when air is heard escaping around the tube. The ideal leak pressure is between 15 and 25 cmH_2O. It is important to avoid a slow and prolonged leak test as this will have the hemodynamic consequences of a prolonged Valsalva maneuver. When a cuffed tube is used, the cuff inflation volume can be adjusted to achieve the desired leak pressure. For short cases, if the initial leak test is above 40 cmH_2O, some anesthesiologists will not exchange the tube for a smaller one in the interest of avoiding the trauma of repeated laryngoscopy. For longer cases, if the leak pressure is greater than 30–35 cmH_2O, exchange with a smaller tracheal tube may be preferred.



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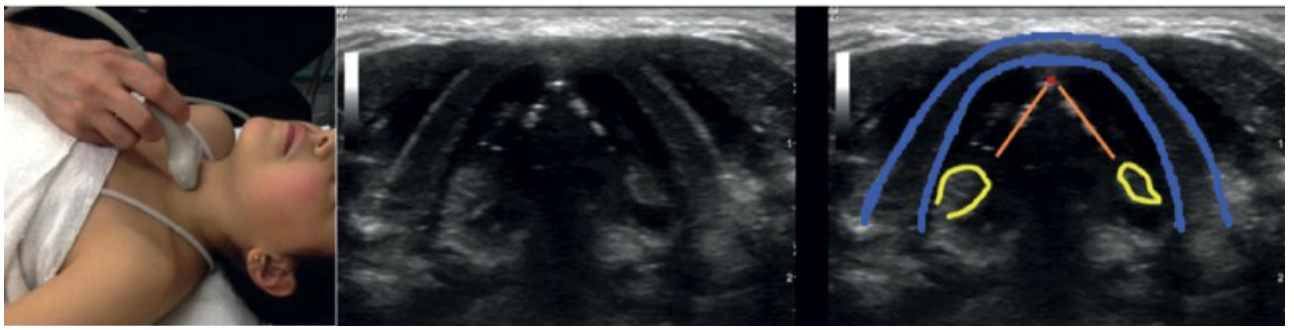
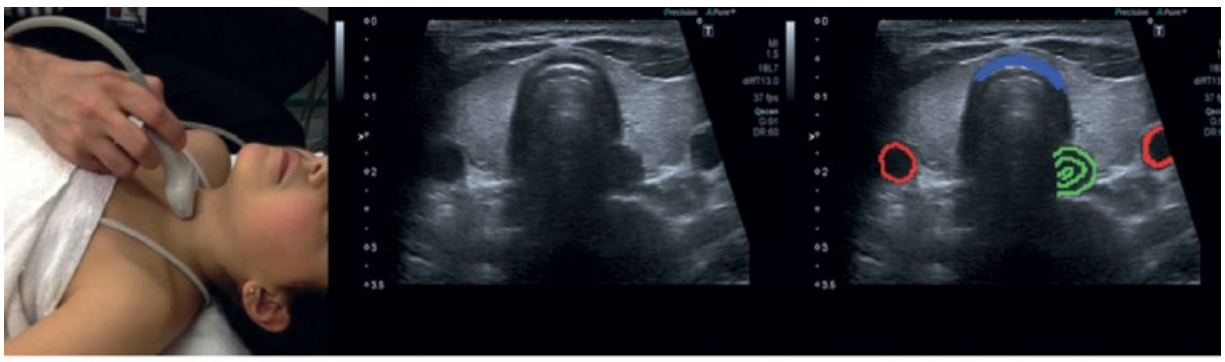
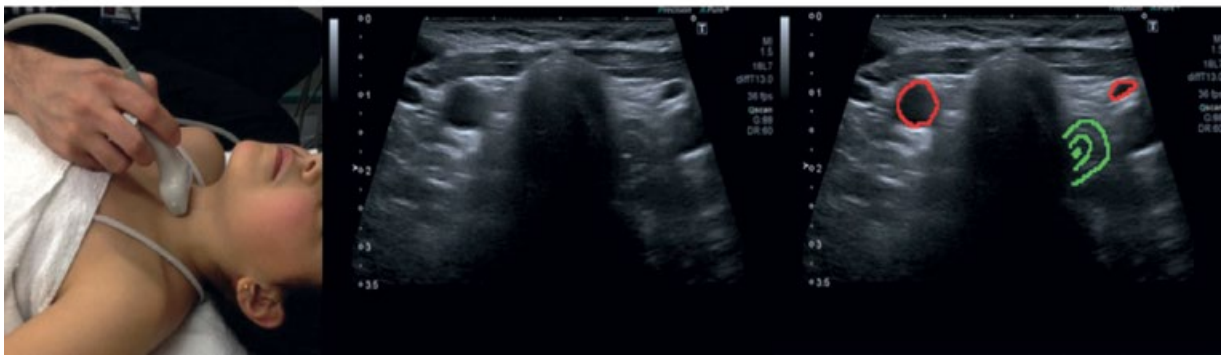


(B)

Figure 16.13 Ultrasound of the larynx. (A) Transverse image at the level of the upper larynx. The strap muscles are identified as hypoechoic (yellow), the thyroid cartilage (blue), and the echogenic false vocal cords (orange). (B) Sliding the probe minimally further caudally, the level of the true vocal cords is reached. The thyroid cartilage appears mildly echogenic (blue). The margin (the free edge) of the true cords appears hyperechoic (orange). The tiny area of echogenicity at the anterior margin represents the anterior commissure (red). The areas of echogenicity deep and lateral to the cords represent the arytenoid cartilages (yellow). *Source:* Reproduced from Stafrace et al [83] with permission of John Wiley and Sons.



(A)



(B)

Figure 16.14 Ultrasound of the trachea. (A) This structure comes into sight as the probe is oriented slowly inferiorly from the lower larynx. The thyroid gland surrounding the trachea is easily identified. The hypoechoic (=dark) anterior part of each tracheal ring (blue) is easily identified, but the walls of the trachea are not well identified on the transverse plane – ring down artifact from air is seen centrally. The esophagus is well seen posteromedial to the trachea on the left, often as a multilayered structure (green). The carotid arteries (red) are seen postero-lateral to the thyroid lobes. (B) As the probe is further oriented inferiorly, the thyroid gland is no longer visualized, but the remainder of the structures listed above remain clearly visible. The carotid vessels (red) are now seen to lie slightly more anteriorly and medially. Echogenic connective tissue now also fills in the space below the thyroid gland. The appearances of the trachea are unchanged. The multilayered structure of the esophagus (green) is easily appreciated. *Source:* Reproduced from Stafrace et al [83] with permission of John Wiley and Sons.

Rapid-sequence induction and intubation in pediatric patients

Rapid-sequence induction and intubation (RSII) is used to minimize the time from anesthetic-induced loss of consciousness and endotracheal intubation, to decrease the risk of pulmonary aspiration of gastric contents. RSII is often more challenging in pediatric patients when compared to adults because infants and small children have relatively higher oxygen consumption rates, reduced functional residual capacity (FRC), and elevated closing volumes, and thus will develop oxyhemoglobin desaturation more quickly during periods of apnea. Because of this propensity toward hypoxemia during RSII in children, and the lack of any feasible period of preoxygenation, many pediatric anesthesiologists perform a "modified" rapid-sequence induction [227]. In this modified technique, gentle facemask ventilation is performed using low inflation pressures (<10–15 cmH_2O) while cricoid pressure is applied until enough time has elapsed for complete neuromuscular blockade to be established. In support of this practice, appropriately applied cricoid pressure has been shown to be effective in preventing gastric inflation during gentle bag-mask ventilation in anesthetized infants and children [228,229]. In older children and adolescents who can cooperate with adequate preoxygenation, a classic RSII may be performed. If the initial attempt at intubation fails, gentle facemask ventilation through cricoid pressure should be performed. If ventilation is difficult with cricoid pressure despite the use of adjunctive devices (e.g. oral or nasopharyngeal airway, laryngeal mask) cricoid pressure should be lessened or released [230,231]. Regurgitation of gastric contents is more likely caused by performing laryngoscopy prior to the complete onset of neuromuscular blockade, rather than any other aspect of the induction technique.

Cricoid pressure is contraindicated in the presence of active vomiting, suspected laryngeal or tracheal injury, and unstable cervical spine injuries [230,232]. In children, cricoid pressure applied below the cricoid ring can result in significant distortion of the larynx and trachea and increase the difficulty of ventilation or intubation [233]. A report of the complications of RSII in a large children's hospital population revealed an incidence of difficult intubation of 1.7%; however it is unclear if these difficulties were related to presence of cricoid pressure [234]. The application of cricoid pressure can cause relaxation of the lower esophageal sphincter, paradoxically promoting the potential for regurgitation of gastric contents [235].

There is a lack of high-quality evidence supporting the efficacy of a "classic" RSII (induction followed by cricoid pressure and apnea) in children. Furthermore, in infants and young children, oxyhemoglobin desaturation will predictably occur with the duration of apnea required for the onset of complete neuromuscular blockade. These factors, together with the undesirable effects of cricoid pressure, have resulted in a "modified" RSII approach (gentle/low-pressure ventilation and ensuring complete neuromuscular blockade prior to laryngoscopy) being preferred to the "classic" RSII approach in pediatric anesthesia practice [236].

KEY POINTS: TRACHEAL INTUBATION

- Simple extension of the head, as opposed to "sniffing position"(neck flexion and head extension), may better align oral, pharyngeal, and tracheal axes in children
- Direct laryngoscopy with a straight (Miller) blade can be accomplished directly by lifting the epiglottis, or indirectly by placing the tip behind the epiglottis
- The curved (Macintosh) laryngoscope blade is best utilized by placing the tip behind the epiglottis into the vallecula
- Optimal external laryngeal manipulation using the BURP maneuver can often improve laryngeal visualization
- Tracheal intubation can be accomplished with neuromuscular blockade, or without blockade if deep anesthesia is achieved, often with propofol
- Nasotracheal intubation with Magill forceps and topical vasoconstriction is utilized for dental or craniofacial cases, some cardiac cases, and some cases in prone position
- Cuffed endotracheal tubes are preferred for use even in infants; exceptions may be premature or full-term neonates where larger internal diameter is important
- Assessment of proper depth of ETT placement can be achieved using formulae based on ETT diameter, depth markings on the tube during direct laryngoscopy, deliberate right mainstem intubation, or palpation of the cuff in the sternal notch
- An airleak at 15–25 cmH_2O with cuff deflated indicates an appropriate ETT size
- A "modified" rapid-sequence induction approach (gentle/low-pressure ventilation and ensuring complete neuromuscular blockade prior to laryngoscopy) is preferred to the "classic" approach (induction followed by cricoid pressure and apnea) anesthesia practice

Postoperative airway management

The first priority in the postoperative care of the child is ensuring a patent airway. Assessment should focus on residual effects of anesthetic agents, opioids, and sedatives in the context of the preoperative condition of the child, the course of intraoperative airway management, the surgical procedure, anticipated fluid shifts, and the expected postoperative course. During recovery, proper head and neck positioning promotes airway patency. In the supine position, a soft roll placed under the shoulders will extend the head and neck and help open the upper airway. Placing the child in the "recovery (lateral) position" increases upper airway size [21] and allows secretions to drain out of the mouth rather than backward into the pharynx. If airway obstruction fails to improve with positioning, and the child is semi-conscious, a soft nasopharyngeal airway can be inserted; if the child is still anesthetized, an oral airway may be preferred. If airway obstruction is incompletely relieved with a nasopharyngeal airway, a 15 mm tracheal tube adaptor can be placed into the external

flared end of a nasopharyngeal airway for the delivery of CPAP [93]. If one suspects that postoperative upper airway obstruction is caused by the residual effect of opioids, naloxone can be cautiously administered to test and treat this possibility. Incremental doses of 0.5–1 μg/kg can be carefully titrated to reverse respiratory depressant effects without reversal of analgesic effects. Children who fail these measures to restore airway patency may require tracheal reintubation.

Non-invasive respiratory support

In selected cases, non-invasive ventilatory support, such as CPAP or bi-level positive airway pressure (BiPAP) may be a useful option and can allow some patients to avoid tracheal intubation and mechanical ventilation in the postoperative period. Non-invasive support in older children is most often delivered by facemask or nasal mask, while nasal prongs are used in neonates and infants. Children and adolescents who use such devices preoperatively should receive respiratory support from these devices in the postoperative period. CPAP delivered by nasal prongs to neonates and infants is an effective way to improve respiratory function and prevent reintubation following extubation in the neonatal intensive care unit [237], as well as for treatment of apnea of prematurity [238,239].

Postoperative mechanical ventilation

If postoperative mechanical ventilation is required, a plan must be developed for transfer of the child's care from the operating room to the intensive care unit. Clear communication regarding the course of airway management should include discussion of the ease of facemask ventilation and direct laryngoscopy, tracheal tube size and insertion depth, current ventilator settings, and the reason for the need for postoperative mechanical ventilation. The child will need to be transitioned from general anesthesia to an appropriate sedation regimen. If airway management was difficult, a plan should be in place in the event of accidental extubation. Keeping an appropriately sized laryngeal mask at the bedside is essential in such cases. If an oral RAE tube was used, this should be changed to a standard tracheal tube as protrusion of the tongue can easily result in extubation, and pulmonary toilet is more difficult with RAE tubes.

KEY POINTS: POSTOPERATIVE AIRWAY MANAGEMENT

- After tracheal extubation, lateral positioning or an oral or nasal airway can improve airway patency in the anesthetized child
- Non-invasive respiratory support, such as nasal CPAP, bilevel positive airway pressure, or high-flow oxygen via nasal cannula, may be useful in selected patients
- If postoperative mechanical ventilation is necessary, a secure ETT, adequate postoperative sedation, clear communication to the ICU staff about airway management difficulties, and extubation plans are essential

Upper airway complications and management

Laryngospasm

Laryngospasm is a prolonged glottic closure maintained beyond the initiating stimulus and is a protective reflex that causes complete closure of the vocal cords to protect the trachea from aspiration of foreign material [240]. Prolonged laryngospasm can result in hypoxemia, bradycardia, postobstructive negative-pressure pulmonary edema, regurgitation and aspiration of gastric contents, and cardiac arrest. Laryngospasm is more common in children than adults; it has been estimated to occur at a frequency from 1 per 1000 anesthetics to 17 per 1000 anesthetics [241–243]. While one belief has been that hypoxemia itself will result in abolition of this reflex, data from the Pediatric Perioperative Cardiac Arrest Registry reveal that laryngospasm continues to be a cause of cardiac arrest in children [244].

The incidence of laryngospasm appears to be increased in children with a history of active or recent upper respiratory tract infection, especially within 2 weeks of anesthesia [245–249]. In addition to upper respiratory tract infection, a history of eczema, exercise-induced wheezing, nocturnal dry cough, and wheezing more than three times in the prior year have been observed to be strongly associated with bronchospasm, laryngospasm, and other perioperative adverse respiratory events. Likewise, having parents that smoke or a strong family history of asthma or atopy is associated with perioperative adverse airway events [249]. In a matched cohort study, the occurrence of perioperative adverse airway events was associated with a greater likelihood of hospital stay after surgery, longer hospitalization, and higher costs [250].

Anesthetic management choices also affect the risk for acute adverse airway events: intravenous induction (versus inhaled), inhaled maintenance (versus intravenous), and airway management with a laryngeal mask (versus endotracheal tube) are each associated with reduced likelihood of adverse airway events (laryngospasm, bronchospasm, desaturation, coughing) [106,249].

Initial treatment of laryngospasm consists of CPAP delivered by facemask with 100% oxygen. Deepening the anesthetic may relieve the obstruction and can be achieved with intravenous propofol, 1–3 mg/kg. If hypoxemia is occurring, the treatment of choice is immediate neuromuscular blockade with succinylcholine. In adults, low-dose succinylcholine (e.g. 0.1 mg/kg) is effective in treating laryngospasm [251]. However, larger doses may be preferred if reintubation is planned. When administering succinylcholine in children, some pediatric anesthesiologists prefer to co-administer an anticholinergic agent (i.e. atropine or glycopyrrolate) to prevent succinylcholine-induced bradycardia.

If laryngospasm develops prior to establishment of intravenous access, succinylcholine (4–5 mg/kg) may be administered via the intramuscular route [252]. Maximal twitch depression at the abductor pollicis following intramuscular injection of succinylcholine will develop in 3–4 min; however, clinical relief of airway obstruction occurs much sooner [253,254]. Succinylcholine-induced bradycardia is less likely with intramuscular administration [252,255]. Intralingual or submental administration of succinylcholine

has been recommended because of its rapid onset of action [256,257]; however, many avoid this route because of concerns about intraoral bleeding. Intramuscular administration of 4–5 mg/kg of succinylcholine may result in a phase II block, and more than 20 min may elapse before neuromuscular blockade resolves [252].

Additional treatments for laryngospasm, such as pressure in the "laryngospasm notch" [258], digital elevation of the tongue [259], nitroglycerine [260], and doxapram [261] have been proposed but their efficacy in children has not been evaluated.

Laryngospasm accompanied by a strong inspiratory effort and hypoxemia may lead to negative pressure pulmonary edema with or without pulmonary hemorrhage [262–265]. The treatment depends on the severity of symptoms and includes supplemental oxygen, furosemide, and positive pressure respiratory support.

Pulmonary aspiration of gastric contents

Pulmonary aspiration of gastric contents is a relatively uncommon event, although its incidence in children appears equal to or higher than that in adults [266–268]. The incidence in the pediatric population ranges from 1 in 2632 anesthetics [268] to 1 in 1000 anesthetics [266]. Death from anesthetic-related pulmonary aspiration is rare. Children with clinically apparent pulmonary aspiration who did not develop symptoms within 2 h were unlikely to develop subsequent respiratory complications [268].

Factors associated with increased risk of pulmonary aspiration include emergency surgery, presence of bowel obstruction or ileus, younger age, and ASA physical status 3 or 4 [266,268]. Obesity is not associated with an increased gastric fluid volume or increased risk of pulmonary aspiration [269].

Postintubation croup

Postintubation croup presents as inspiratory stridor, hoarseness, a "barky" cough, and in severe cases, intercostal retractions and respiratory distress. Postintubation croup is thought to result from airflow restriction due to tracheal edema from mechanical trauma or mucosal ischemia related to endotracheal intubation. The site of greatest restriction is at the level of the cricoid ring. The incidence in children was reported to be 1% in 1977 [270]; however, more recent data suggest a lower incidence [271]. Postintubation stridor may develop shortly following tracheal extubation or several hours later. Upper airway obstruction from other causes must be investigated before the diagnosis is made. Physical examination findings determine the need for treatment. Nasal flaring, subcostal or intercostal retractions, or other features indicative of increased work of breathing are indications for pharmacological therapy. Dexamethasone, 0.5 mg/kg up to 10 mg, may be effective, albeit not immediately. Nebulized racemic epinephrine may also be effective in the short term but should be reserved for severe cases. Because of the potential for rebound edema following racemic epinephrine, children should be observed for at least several hours to ensure that symptoms do not recur.

KEY POINTS: UPPER AIRWAY COMPLICATIONS AND MANAGEMENT

- Laryngospasm is treated first with positive pressure ventilation with jaw thrust; intramuscular succinylcholine or intravenous propofol or succinylcholine is used for significant airway obstruction
- Factors associated with pulmonary aspiration include emergency surgery, presence of bowel obstruction or ileus, younger age, and ASA physical status 3 or 4
- Significant postextubation croup is treated with nebulized racemic epinephrine and intravenous dexamethasone

Airway management for tracheostomy insertion

Infants and children who require chronic ventilatory therapy will likely benefit from insertion of a tracheostomy tube. Diagnoses associated with the need for tracheostomy include neuromuscular impairment, chronic lung disease, trauma, upper airway anomalies, congenital heart disease, and prematurity [272]. Infants who have had long-term tracheal intubation and mechanical ventilation may develop subglottic stenosis and require tracheostomy to provide long-term ventilatory support. The in-hospital mortality in pediatric patients who undergo tracheostomy during their hospitalization is as high as 8.5% [272]. Most of these children present to the operating room with a secured airway (tracheal tube). In these cases the ease of previous mask ventilation and tracheal intubation must be assessed preoperatively. Those children in whom direct laryngoscopy was difficult should have a plan developed in case accidental extubation occurs before tracheostomy completion. Such a plan might include leaving an airway exchange catheter in the trachea during completion of the tracheostomy and withdrawal of the tracheal tube to a position just above the tracheostomy incision, with the tip still between the vocal cords, that can be easily advanced for reintubation should this be required. These cases require close vigilance and communication with the surgeon throughout the procedure. The risk of a surgical fire can be reduced by minimizing the inspired oxygen concentration and avoiding the use of nitrous oxide. The choice of tracheostomy tube size and length depends on the indications for tracheostomy. Patients requiring chronic mechanical ventilation often benefit from low-pressure, high-volume cuffed tubes, often made with silicone or other soft material to minimize airway trauma. Patients with upper airway obstruction without significant lung disease often benefit from small uncuffed tracheostomy tubes, which are large enough to provide a patent airway yet permit sufficient air leak to allow vocalization. Consultation with the surgeon and pulmonologist is important to understand all the goals of the procedure and select the correct tracheostomy tube.

Certain children with upper airway congenital anomalies may not have an existing tracheal tube immediately prior to surgical tracheostomy. Airway management for tracheostomy may entail tracheal intubation with subsequent management

as described earlier. Alternatively, a laryngeal mask may be used as an anesthetic airway conduit during tracheostomy insertion.

A newly placed tracheostomy requires 7–10 days for the stoma to be well formed; prior to this period, if a tube change is needed, it should be performed by an otolaryngologist. After healing, tracheostomy tubes should be changed every 1–2 weeks to reduce the formation of granulation tissue or mucous plugs of the tube. A tracheostomy bypasses the humidification and warming function of the nose and upper airway; thus, an artificial humidification device is necessary. Heat and moisture exchangers (HMEs) are generally used to facilitate this function. They should be selected to minimize resistance to airflow, and minimize work of breathing [273].

Management of the child with a pre-existing tracheostomy

Tracheostomized children who present for general anesthesia and surgery require a different approach to airway management. During the preoperative visit, the anesthesiologist should determine the type, size, and presence of a cuff on the tracheostomy tube. Parents and caregivers should be asked about the frequency of suctioning, as well as the suction catheter size and the depth to which it is inserted. The presence or absence of a leak around the tracheostomy tube as well as the amount of ventilator support the child requires should also be determined during the preoperative assessment. These children should come with emergency replacement supplies for their tracheostomy, which should be kept with them throughout their perioperative course.

Inhaled anesthetic induction is the most common induction technique in these children. It is often necessary to connect a flexible "accordion" extension from the end of the anesthetic circuit to the tracheostomy tube to increase the limited clearance between the clavicles and mandible, especially in infants. In those with a significant leak around the tracheostomy tube, inhaled induction may be prolonged due to mixing of air inspired from the upper airway with gases inspired through the tracheostomy tube. Following the loss of consciousness, holding the mouth and nose closed or applying a sealed facemask will help decrease mixing and facilitate ventilation through the tracheostomy.

For short procedures, it is often unnecessary to change the tracheostomy tube. For intracavitary or long procedures, if there is a significant leak around the tracheostomy tube, a standard cuffed tracheal tube will enable effective positive pressure ventilation. This can be achieved by exchange of the existing tracheostomy tube with the same-sized cuffed tracheal tube. With an established tracheal stoma, this is easily accomplished; however, consultation with an otolaryngologist may be useful in selecting the most appropriate tube and for performing the exchange, if necessary. Another option is replacement of the tracheostomy tube with a wire-reinforced tube. This lower profile alternative can be useful in cases where a standard tracheostomy tube would encroach on the surgical field. This tube can be secured to the chest with tape or sutured in place in select circumstances. In cases where the tracheostomy site encroaches on the surgical field, the child's airway can be secured with an oral or nasal tracheal tube, and the tracheostomy site can be sealed with gauze and nonocclusive tape and dressing.

Tracheostomy tubes are available in a variety of sizes and lengths for pediatric use. They can be constructed from metal or plastic. Plastic tubes are most frequently used and are made from silicone or polyvinyl chloride. Some tracheostomy tubes are supplied with a tracheostomy disconnection wedge, which facilitates separation of connections to the tracheostomy. The internal and external diameters are usually marked on the flange of the tracheostomy tube. Several manufactured tubes have wire-reinforced designs allowing flexibility without kinking, and some have a long flexible proximal ends (e.g. FlexTend™), which place connections to the tube away from the child's neck, thus reducing the chance of tube obstruction in small patients.

Tracheostomy tubes are available in cuffed and uncuffed versions [274]. The cuff helps to protect the airway from secretions and facilitates positive pressure ventilation in children with poor lung compliance. Cuffed tracheostomy tubes have either a high-volume, low-pressure cuff, low-volume, high-pressure cuff, or a foam cuff, which is useful in patients with chronic aspiration. The Tight-To-Shaft tube (TTS™) has a low-volume, high-pressure cuff used for patients who need intermittent inflation such as during meals and at night. When deflated, the cuff assumes the profile of the tube and enables phonation and use of the upper airway. The cuff should be inflated with sterile water because it is gas permeable and will slowly deflate over time.

The Montgomery tube is a T-shaped silicone tube that has a short lumen projecting from its side at a 75° or 90° angle. It is typically used after tracheal reconstruction to stent the airway and can be left in place for months. The upper limb extends above the glottis and the short limb is brought out through the tracheostomy stoma.

KEY POINTS: AIRWAY MANAGEMENT FOR TRACHEOSTOMY

- Preoperative assessment of difficulty of standard tracheal intubation is important; leaving an airway exchange catheter or withdrawing the ETT to just above the tracheostomy but below the larynx may be necessary
- A tracheostomy tube is usually changed in 7–10 days by an otolaryngologist; provision for adequate sedation until that time is important
- Patients with an existing tracheostomy may need larger or cuffed tracheostomy, or standard ETT in the stoma or inserted translaryngeally, to mimize leak and allow airway access for longer surgeries

The difficult pediatric airway

There are two broad categories of pediatric patients with a "difficult" airway: those who are difficult to mask ventilate, and those who are difficult to tracheally intubate. Each category assumes that the attempts have been made by an experienced practitioner using standard methods of mask ventilation or direct laryngoscopy. Definitions for each of these categories

have been proposed but are inconsistent throughout the literature. Therefore, in this chapter we focus on airway management techniques once a practitioner is faced with the expected or unexpected situation of inability to adequately perform mask ventilation or tracheal intubation despite the use of standard equipment, as described previously in the section on management of normal pediatric airways.

There have been few systematic and validated studies that define predictors of difficult mask ventilation or tracheal intubation in the pediatric population. In adults, limited head extension, reduced mandibular space, and large tongue are predictive of difficult intubation [275]. These are also features in children with difficult intubations [276]. The mandibular space represents the area available to displace the tongue and soft tissue, which is required for an easy direct laryngoscopic view of the glottis. Reduction of this space by anatomical anomalies (e.g. micrognathia) limits the room available for soft tissue displacement by direct laryngoscopy. The mentum–hyoid distance provides an estimate of the mandibular space. In infants, the minimal mentum–hyoid distance for a "normal" airway in an infant should be 1.5 cm [276]. In one cohort study, difficult direct laryngoscopy in children was associated with age below 1 year, underweight patients, and ASA physical status 3 and 4 [277]. Another study of 511 children developed an equation to predict the probability of difficult laryngoscopy based on multivariate regression analysis of distances. The equation

$$Y = (0.015 \times L) + (0.007 \times T) - (0.015 \times E) + 0.179$$

(where L = lower lip border to mentum, T = ear tragus to the corner of the mouth, and E = ear lobe to corner of the mouth) predicts a greater probability of a difficult laryngoscopy if Y tends toward 1 and lower if it tends toward 0 [278].

The most information about characteristics of intubation attempts in children with difficult airways comes from the multicenter Pediatric Difficult Intubation (PeDI) registry [279]. This analysis contained over 1000 intubations in children with difficult airways and demonstrated that complications were associated with multiple intubation attempts, weight less than 10 kg, short thyromental distance, and three direct laryngoscopy attempts before the use of an indirect technique. This analysis, as well as two additional recently published studies, has indicated that the addition of supplemental oxygen during the intubation attempts will decrease the incidence of hypoxemia during intubation attempts [280–283].

Airway management in children with craniofacial anomalies

The diversity and complexity of craniofacial anomalies in children is vast; thus, an exhaustive review is not possible. Nevertheless, children with craniofacial anomalies can be defined according to the anatomical compartment that relates to the airway difficulty. Craniofacial dysmorphism may be defined as primary abnormalities of the maxilla, abnormalities of mandibular size, abnormalities of mandibular hinge and sliding function, and anatomical anomalies of the tongue and cervical spine. Classifying patients in this manner allows the selection of the most appropriate equipment for addressing the airway anomaly.

There is no device that represents a panacea for airway management; each device has unique strengths and weaknesses that need to be matched with the patient's condition and anatomical details. For example, a patient with limited mouth opening would be best managed with a flexible bronchoscope or optical/lighted stylet rather than a rigid video laryngoscope, whereas a patient with Pierre Robin sequence who presents with a potentially difficult mask ventilation may be best managed with a laryngeal mask followed by tracheal intubation through the mask, thus permitting ventilation during intubation. We use a simple acronym (AVAD: Anesthesia, Ventilation, Adjuncts, Devices) to guide the approach to airway management in these known difficult airway patients (Fig. 16.15). Thinking about the patient in terms of these components facilitates the formulation of a plan as well as a backup plan, and dictates the necessary equipment for the chosen

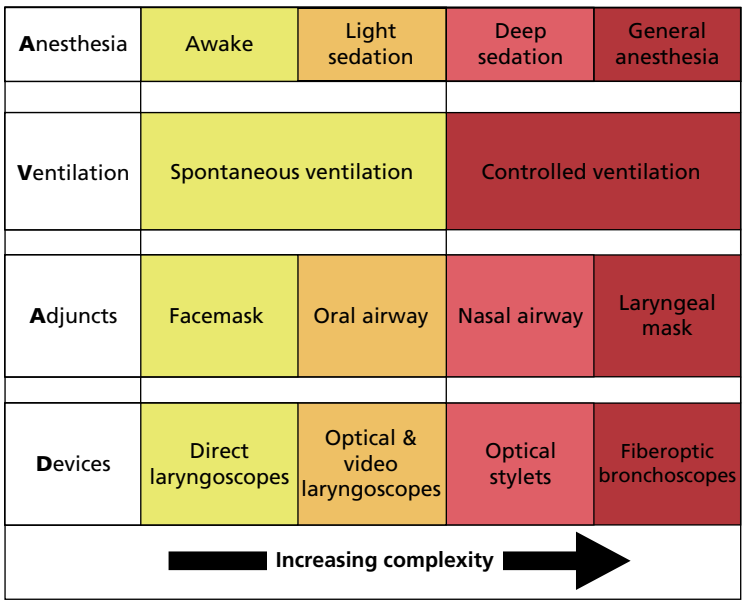


Figure 16.15 A simple acronym (AVAD: Anesthesia, Ventilation, Adjuncts, Devices) guides the approach to airway management in known difficult airway patients.

approach. The care provider should select an approach and device for each of the four components of the acronym. As an example, let us consider a neonate with Pierre Robin sequence. The Anesthesia plan may include deep sedation with a secondary plan for general anesthesia. The Ventilation plan may be spontaneous ventilation and the Adjunct a modified nasal airway, with a secondary plan of controlled ventilation using a laryngeal mask. The Device may be a video laryngoscope with the fiberoptic bronchoscope as a backup device. The chart ensures that all the critical aspects of the care plan are addressed, and horizontally represents increasing anesthetic and technical complexity. Nevertheless, practitioners should adopt a standard and consistent set of airway-related equipment and drugs for all anticipated difficult airway patients (Fig. 16.16). The most recent version of the American Society of Anesthesiologists Task Force on Management of the Difficult Airway was published in 2013 [284]. Although the general principles of difficult airway management are similar between adults and children, these guidelines did not specifically address management of pediatric patients.

When approaching the child with a known cause for a difficult airway, one of the first *a priori* decisions to be made is the anticipated level of consciousness during the airway management process. This largely depends on the anesthesiologist's confidence in their ability to avoid life-threatening hypoxemia in an anesthetized or sedated child using a facemask or a laryngeal mask.

"Awake" intubation

Tracheal intubation of an uncooperative child at a nearly conscious level is difficult and associated with complications [169,285]. Since the advent of the laryngeal mask, this approach has been largely abandoned for sedated or anesthetized techniques, with rare exceptions. For example, neonates with Pierre Robin sequence are expected to have difficulty with mask ventilation; therefore, awake insertion of a laryngeal mask and confirmation of adequate ventilation can precede induction of general anesthesia [142,144].

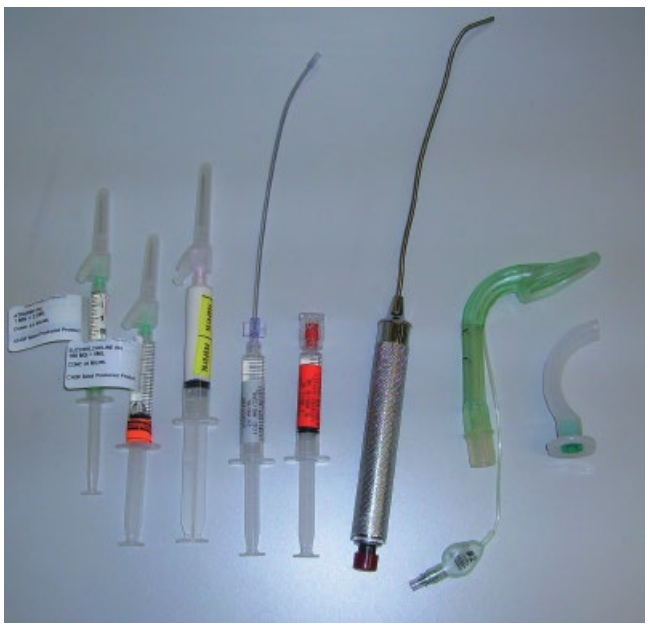


Figure 16.16 One example of a standard equipment and medication set-up for anticipated pediatric difficult airway. *From left to right*: atropine, succinylcholine, propofol, 2% lidocaine with mucosal atomizer attachment, vecuronium, lighted stylet, laryngeal mask, and oral airway.

Sedated intubation

Many children with anticipated difficult airways can be sedated to provide comfort and amnesia, yet retain spontaneous ventilation and upper airway patency during tracheal intubation attempts. A sedated technique is useful when there is the anticipation of life-threatening upper airway obstruction during induction of general anesthesia, such as may be seen in children with a large cystic hygroma [286]. Although light sedation has been described for intubation of infants using opioids, amnestic agents, and incremental doses of induction agents, most children will require deeper levels of sedation to ensure optimal intubating conditions. This can also be accomplished using dexmedetomidine, by itself or in combination with other agents [287]. Dexmedetomidine allows arousal with strong stimulation and maintenance of spontaneous ventilation, using a bolus dose of 1 μg/kg over 10 min followed by a continuous infusion of 0.7 μg/kg/h. Dexmedetomidine can be combined with incremental doses of ketamine (0.25 mg/kg) or midazolam (up to 0.1 mg/kg) to facilitate intubation without clinically significant respiratory depression [286,288]. Further studies are necessary to determine the optimal methods for preserving airway patency while minimizing reactivity during airway manipulations.

Intubation under general anesthesia

The majority of children with a known or expected difficult intubation can receive general anesthesia during the intubation process. Many pediatric anesthesiologists will require an indwelling intravenous catheter prior to administration of general anesthesia but this is practitioner dependent. Upper airway patency may be facilitated by insertion of an oral or nasal airway. A nasal airway may be attached to a 15 mm tracheal tube adapter, which allows connection to the anesthesia circuit for provision of anesthesia, oxygen, and CPAP during intubation attempts (see Fig. 16.9) [94].

Ventilation of the patient with a difficult airway

The ultimate goal of any airway management strategy is to maintain adequate oxygenation and avoid any level of life-threatening hypoxemia. It is critical that this overarching principle is not lost during attempts to secure the airway. Facemask ventilation represents the first step in maintaining oxygenation between intubation attempts. The optimal ventilation strategy for the management of the difficult pediatric airway remains unknown. Traditional teaching advocates the maintenance of spontaneous ventilation during airway management because of the fear of loss of the ability to ventilate with multiple traumatic attempts and to preserve the ability to quickly awaken the patient if necessary. In children, this concern is weighed against the possibility of coughing and other movements if the level of anesthetic is too light. There is no plausible research

that can examine this issue directly; much of the rationale for this strategy comes from case reports and clinical observations. Maintenance of spontaneous ventilation is advantageous because it facilitates oxygenation during airway manipulation [289], it provides clues to the glottic location by way of the bubbling of secretions that can be observed during fiberoptic intubation, and it provides the anesthesiologist with increased uninterrupted time to ventilate the child and accomplish the intubation. In addition, there may be greater upper airway patency and better visualization resulting from less soft tissue collapse when airway tone is preserved [290]. Although maintenance of spontaneous ventilation is preferred, some practitioners will attempt positive pressure ventilation and, if successful, will administer neuromuscular blockade to facilitate the intubation process. However, in adults, the addition of neuromuscular blockade in itself has been reported to change the anatomical characteristics of the upper airway and worsen ventilation or intubation conditions [291,292].

If paralytics are to be avoided, topical anesthesia should be applied to the glottic structures to minimize airway reactivity and should be performed when an adequate depth of anesthesia is confirmed. Lack of a physical response to a jaw thrust for 5 s usually indicates a satisfactory anesthetic depth for airway manipulation.

A total intravenous technique during intubation attempts will minimize operating room pollution from anesthetic gases. Various combinations of easily titratable intravenous agents (e.g. propofol, remifentanil) can be used for this purpose[293,294].

Much has been published recently on the value of oxygenation during indirect intubation attempts in an attempt to limit the number of episodes of oxyhemoglobin desaturation. Each episode of desaturation causes the intubation attempt to be halted, and additional intubation attempts are associated with increasing patient morbidity [279]. The use of pharyngeal or deep laryngeal oxygenation during orotracheal or nasotracheal intubation slows desaturation when compared to direct laryngoscopy without oxygen supplementation [281,283]. The use of nasopharyngeal oxygen has also been shown to limit desaturation during intubation attempts, and has been named "transnasal humidified rapid-insufflation ventilatory exchange (THRIVE)" [164]. We have suggested that oxygenation during indirect intubation attempts should become the standard of care in pediatric difficult airway management [280].

Impossible mask ventilation is unusual in the pediatric population. It is difficult to determine the true incidence because children suspected of impossible mask ventilation due to altered anatomy will undergo tracheal intubation using deep sedation and spontaneous ventilation. In an observational review of 22,000 adult anesthetics, the reported incidence of impossible mask ventilation was one in every 690 cases [295]. One-quarter of these patients were also difficult to intubate. Neck radiation was found to be the most significant predictor of impossible ventilation.

Indirect methods of tracheal intubation

There are many approaches to tracheal intubation in the child with a known or suspected difficult airway. In certain circumstances, it may be appropriate to attempt direct laryngoscopy if a reasonably long amount of time has passed since the previous intubation attempt and the anesthesiologist feels that the growth of the child has altered their airway anatomy in a favorable direction. If a direct method is deemed impossible, a variety of options exist for indirect tracheal intubation.

Fiberoptic bronchoscopy

The first article describing the use of flexible fiberoptic bronchoscopy in children appeared in 1978 [296], and despite many modifications in design it remains the "gold standard" for accomplishing tracheal intubation in the pediatric difficult airway [94,285,288,289,297–328]. Limitations of fiberoptic intubation in children include the significant time necessary for skill acquisition, the processing and preparation time of the equipment, the fragility of the bronchoscope, and the high purchase and repair costs. Despite these limitations the skill necessary to consistently perform a smooth fiberoptic intubation can be acquired during routine cases in children with normal airways. The introduction of 2.2 mm and 2.7 mm ultrathin bronchoscopes allowed fiberoptic intubation of neonates and small children with tracheal tubes as small as 2.5 mm [329,330]. These small bronchoscopes did not have a working suction channel, and so functionality was limited if the airway was occluded with secretions; however, modern versions are available with functional suction channels. Many larger bronchoscopes now incorporate a video chip-coupled device camera, which transmits the image from the tip of the scope to a screen and replaces the fiberoptic bundles that transmitted the image in older scopes. This provides a high-clarity image without the honeycombing typically seen with standard fiberoptic bronchoscopes.

Adult bronchoscopes can facilitate fiberoptic intubation in children. One method requires two providers. One places the bronchoscope at the glottic opening, while the other manipulates the tracheal tube independently into the trachea. This technique has the advantage over standard fiberoptic intubation of visualizing the passage of the tracheal tube through the vocal cords. A stylet in the tracheal tube will assist in directing the tube into the trachea. One case series describes use of this technique in small preterm neonates and it is a technique to consider when an ultrathin bronchoscope is not available or the clinicians lack the skill to use such a small scope [314]. A second technique involves the placement of a guidewire (e.g. 0.0035 in cardiac catheter guidewire; Mallinckrodt, St. Louis, MO) or tracheal tube exchanger into the trachea via the working channel of the bronchoscope. The bronchoscope is then removed and the tracheal tube advanced over the guidewire into the trachea [299,331–333].

In small children, the nasal route provides the most direct approach to the glottic opening with the flexible bronchoscope. This advantage has to be weighed against surgical considerations and the risk of nasal bleeding. Application of a vasoconstrictor such as oxymetazoline decreases this risk and visualizing the nasal passage prior to placing the tube may provide information as to the presence of polyps, adenoid tissue, or narrowing that may impede advancement of the tracheal tube. The other advantage of placing the scope first, before the endotracheal tube, is that a clear view of the airway anatomy and scope position can be maintained from the tip of the nares, through to the view of the carina, before the tube is advanced. The tracheal tube size should be matched closely to the fiberoptic bronchoscope size to reduce the incidence of

impingement of the tracheal tube on glottic structures. Rotation of the tracheal tube 90° counterclockwise will orient the Murphy eye anteriorly, and may enhance placement through the glottic opening [334,335].

During fiberoptic intubation, ventilation can be enhanced using the Frei endoscopy mask, which incorporates a perforated silicone membrane that allows passage of the bronchoscope [336]. Alternatively, one may use the "mask mouth technique," in which the facemask is applied only to the mouth and one naris is occluded while the bronchoscope is advanced through the opposite nasal passage [337].

The laryngeal mask can serve as a conduit for intubation and an adjunct for ventilation in children with difficult airways who do not tolerate brief periods of apnea. There are several manufactured designs and shapes but ideally the mask should provide full glottic exposure without encroachment of the epiglottis into the mask bowl. The ideal design will have a short and wide airway tube to facilitate removal of the device and allow passage of cuffed tracheal tubes, and will permit easy and effective ventilation through the device. Prior to using a laryngeal mask as a conduit for intubation it is critical to confirm that all components of the selected tracheal tube pass easily through the selected mask. Some masks will not accommodate the pilot balloon, particularly in smaller sizes [338,339].

To facilitate bronchoscopy through the laryngeal mask, a bronchoscope adaptor is placed on the 15 mm connector of the tracheal tube; the tracheal tube is then placed in the airway tube of the laryngeal mask and the cuff inflated. The anesthesia circuit is then attached to the tracheal tube and ventilation is established. An occlusive adhesive (e.g. Tegaderm™) can be applied to the bronchoscope adaptor to maintain a seal around the bronchoscope. Fiberoptic bronchoscopy is then carried out through the tracheal tube. When the trachea is entered, the tracheal tube cuff is deflated and the entire tube–bronchoscope adaptor unit is advanced into the trachea (Fig. 16.17) [340]. Removal of the laryngeal mask is challenging in children because the length of the tracheal tube is often similar to the length of the laryngeal mask tube. Techniques that may assist in laryngeal mask removal include using two tubes joined together to extend the working length, using a long pair of laryngeal forceps, or using a tube stabilizer or exchanger. Fiberoptic intubation through a supraglottic airway has been compared to videolaryngoscopy in a prospective multicenter study of patients with difficult intubation. Fiberoptic intubation via supraglottic airway and videolaryngoscopy had similar first-attempt success rates (67 of 114, 59% versus 404 of 786, 51%; OR 1.35; 95% confidence interval (CI) 0.91–2.00; p = 0.16); however, in subjects less than 1 year old, fiberoptic intubation via supraglottic airway was more successful on the first attempt than videolaryngoscopy (19 of 35, 54% versus 79 of 220, 36%; OR 2.12; 95% CI 1.04–4.31; p = 0.042). Complication rates were similar in the two groups (20% versus 13%; p = 0.096). The authors found that the incidence of hypoxemia was lower when continuous ventilation through the supraglottic airway was used throughout the intubation [341]. See Video clips 16.1–16.4.

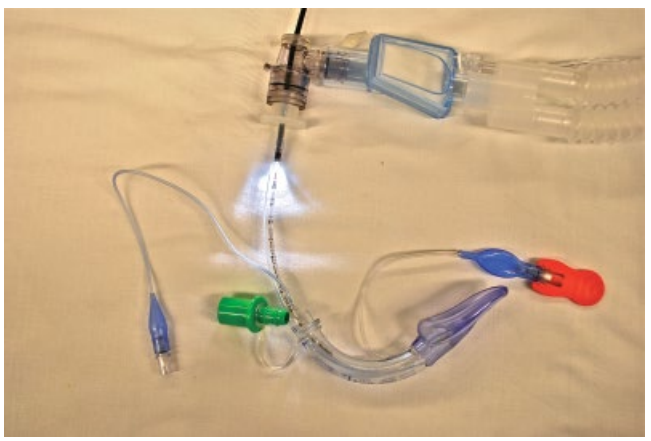


Figure 16.17 A bronchoscope adaptor is placed on the 15 mm connector of the tracheal tube, which is then placed in the airway tube of the laryngeal mask. This facilitates air exchange during bronchoscopic intubation.

Modified optical laryngoscopes

A variety of modified optical laryngoscopes have been developed to aid with direct visualization of the glottis in pediatric difficult airway patients. At the time of writing, there has not accumulated a sufficient body of knowledge with which to judge the comparative efficacy and complications of each of the devices. However, a number of case reports and case series have been published to date.

The Bullard laryngoscope (Circon ACMI, Stamford, CT) represents one of the earliest designs of an optical laryngoscope. It consists of a curved metal blade with an integrated fiberoptic light source attached to an eyepiece. It provides an indirect view of the glottic opening and requires minimal mouth opening (0.64 cm) for insertion. Like many optical laryngoscopes, visualization may be limited by secretions. In a series of 93 children aged 1 day to 10 years, intubation was successful in 90 patients (97%). Two failures were attributed to excess secretions [342].

The Airtraq® (King Systems, Noblesville, IN) is an intubating device that consists of a curved blade with two adjacent channels. It is designed to provide glottic exposure without alignment of the oral, pharyngeal, or laryngeal axes. One channel houses the optical system containing a series of prisms and lenses which end in a viewfinder (Fig. 16.18), while the second channel acts as a holder for the tracheal tube and a guide for advancing the tube into the trachea [343]. The infant Airtraq accepts tracheal tubes of internal diameter 2.5–3.5 mm, while the pediatric version accepts tubes of internal diameter 3.5–5.5 mm. The device is also available with the

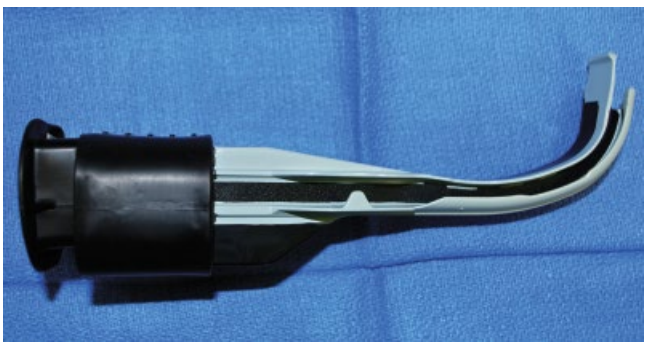


Figure 16.18 Pediatric Airtraq® intubating device.

posterior surface removed to facilitate nasal intubation. The Airtraq is inserted in the midline of the pharynx and the tip placed in the vallecula. The device is adjusted so that the glottis is located in the center of the viewfinder, after which the tracheal tube is advanced into the trachea. After confirmation of successful tracheal intubation, the tracheal tube is moved laterally away from the Airtraq, and the device slowly withdrawn. The Airtraq has been used successfully in patients with difficult direct laryngoscopy due to craniofacial anomalies such as Treacher Collins syndrome and Pierre Robin sequence [344]. In a series of 20 children managed with the Airtraq for elective surgery, one patient required the use of a malleable stylet to facilitate intubation because of difficulty aligning the glottis in the center of the view, and a second patient required two attempts to achieve successful intubation [345]. Other methods have been described to facilitate placement of the tracheal tube with an Airtraq® when there is difficulty aligning the glottis in the center of the image. These include the use of a gum elastic bougie, a flexible or malleable tracheal tube, and utilizing a fiberoptic bronchoscope while slightly withdrawing the Airtraq [346,347]. Like many indirect devices for tracheal intubation, the Airtraq may not be as useful for infants and neonates with difficult airways. Although it is possible to obtain an excellent view in this population, there is often difficulty with tracheal tube passage. This problem is also common with the non-channeled video and optical devices, and underscores the fact that the infant and neonatal airways are different from those of toddlers and older children [348]. The Airtraq improves the view in patients with difficult airways, and has the advantage of the preloaded tracheal tube which eliminates the maneuvers and injuries associated with non-channeled devices. However, its use may be limited to older children with ample mouth space in which to maneuver the device for an optimal glottic view and tube maneuverability.

The Truview EVO2 (Truphatek International, Netanya, Israel) is an indirect rigid laryngoscope with an angulated blade tip. The laryngoscope incorporates an optical lens that ends in an eyepiece that allows the operator to "see around the corner" and obtain an improved glottic view. It has an integrated oxygen port that allows oxygen administration during intubation. Tracheal intubation is achieved by placing the blade in the midline in the pharynx and following the curve of the tongue to the glottic opening. Once the glottis is visualized, the tracheal tube is advanced into the trachea. In a prospective comparison of intubation conditions between the Truview and the Miller laryngoscope in 60 neonates and infants, the Truview provided a statistically significant improvement in view with comparable intubation times [349]. In addition, since the Truview does not require neck extension for visualization and tracheal intubation, it can be used in patients with immobile cervical spines [350].

Video laryngoscopes

The miniaturization of video technology has fueled a revolution in laryngoscope design. There is a rapidly growing selection of video laryngoscopes available for pediatric use, such as the GlideScope®, the Storz® video laryngoscope, the McGrath Scope, and the Pentax Airway Scope. Video laryngoscopes can be categorized as angulated and non-angulated. Angulated video laryngoscopes provide improved views of the airway when compared to standard direct laryngoscopy but require a new skill to intubate the trachea indirectly. Non-angulated video laryngoscopes provide a magnified view which may not be adequate for an "anterior" airway, however inserting the breathing tube is usually not challenging. Sun et al performed a meta-analysis of 14 studies comparing video laryngoscopes to direct laryngoscopy in children. They showed that video laryngoscopy improved the glottic view in children with normal and difficult airways but took more time and failed more often. These results should be interpreted with caution since many of the studies included outdated early video laryngoscope designs such as the Bullard and GlideScope GVL 2, and the review did not distinguish between angulated and non-angulated devices [351]. A recent analysis of 1295 difficult intubations from the PeDI registry found that video laryngoscopy had a higher first-attempt success rate than direct laryngoscopy – 53% versus 4%; however, video laryngoscopy had lower success rates in patients who weighed less than 10 kg.

This section will focus on devices with specific pediatric designs.

GlideScope

The GlideScope (Verathon Medical, Bothell, WA) is a curved laryngoscope with an integrated miniature camera and a heated lens to minimize fogging during laryngoscopy. The device has evolved over the years from a bulky unit to a slim design (GlideScope Cobalt, Fig. 16.19). The Cobalt consists of a camera stick that is inserted into a disposable plastic sheath. A high-resolution image is displayed on a small portable video screen. The blade of the device is placed in the midline of the pharynx and the tip in the vallecula. A styletted tracheal tube is usually necessary, and although the manufacturer recommends a 50–60° degree angulation of the tube, others report higher success in placing the tube with a 90° hockey-stick configuration [352]. Passage of the tracheal tube should be observed on the video monitor to avoid injury to pharyngeal structures [353–359]. The Cobalt is available with a full complement of different-sized blades for use in premature neonates to adults. When compared with direct laryngoscopy in difficult airway patients, it has been shown to improve the glottic view without increasing the time to view [359–362]. In a study in infants, time to intubation was equivalent with the

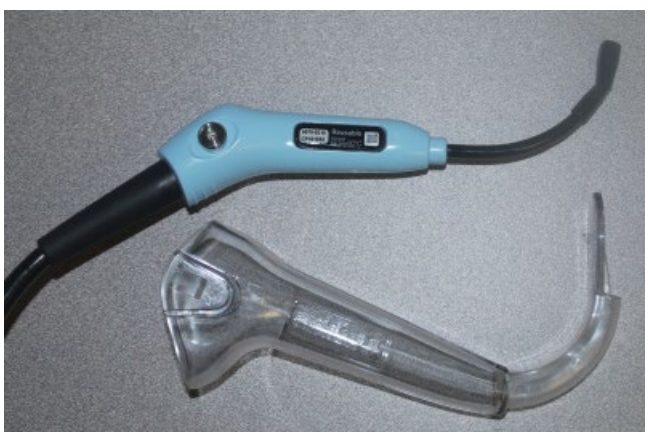


Figure 16.19 GlideScope® Cobalt and disposable plastic blade.

Cobalt compared to direct laryngoscopy. In this study, the time to achieving an optimal view of the larynx was shorter with the Cobalt, however this was offset by a longer time for tracheal tube insertion [363].

There remains a population of patients in whom significant difficulty is encountered with tracheal tube placement despite an adequate glottic view with the GlideScope. Difficulties can arise from a number of factors including the limited ability to manipulate the tube within the smaller pediatric pharynx, the acute angulation of the tracheal tube causing impingement on the anterior commissure or anterior trachea, and difficulty locating the tube in the pharynx after inserting the blade [364]. Some practitioners advocate placing the tracheal tube and GlideScope simultaneously as a single unit or placing the tracheal tube in the pharynx under direct vision prior to placing the GlideScope. If the tracheal tube impinges on the anterior trachea or anterior commissure, the GlideScope should be withdrawn slightly to decrease the anterior displacement of the glottis allowing the axis of the tube and the trachea to become better aligned, and the tube rotated so that its concavity is oriented more posteriorly ("reverse loading," Fig. 16.20). The gum elastic bougie has also been utilized as a guide when using the GlideScope for tracheal intubation in children [365]. There will always be certain patients in whom the GlideScope and other video laryngoscopes will fail; thus, alternatives need to be readily available in difficult airway patients. See Video clip 16.5.

Storz video laryngoscope

The Storz video laryngoscope (SVL; C-MAC®; Karl Storz Company,Tuttingen, Germany) (Fig. 16.21) incorporates a camera into various standard blades. The Storz C-MAC video laryngoscope is a rigid blade that integrates fiberoptics and a lens into the light source of Miller- and Macintosh-type blades [366]. The blades connect to a device-specific camera that transmits the image to a video monitor. The use of the SVL is similar to other video laryngoscopes in that the blade is placed in the midline followed by insertion of the tracheal tube. Advancing the tracheal tube along the shaft of the blade rather than from the right side of the pharynx as in traditional laryngoscopy facilitates quick visualization on the video monitor and avoids injury to the palatoglossal structures. The SVL has been successfully employed in intubating patients with normal airways and has been reported to be more efficacious in pediatric difficult airway patients when compared to direct laryngoscopy [366–372]. Use of the SVL requires adequate mouth opening and practiced hand–eye coordination. The view through the SVL may be limited by fogging, which can be decreased by use of an anti-fog solution or prewarming the device.

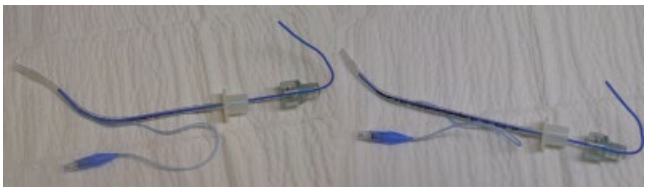


Figure 16.20 The tracheal tube on the left is "reverse loaded" by rotating the Murphy eye anteriorly on the stylet.

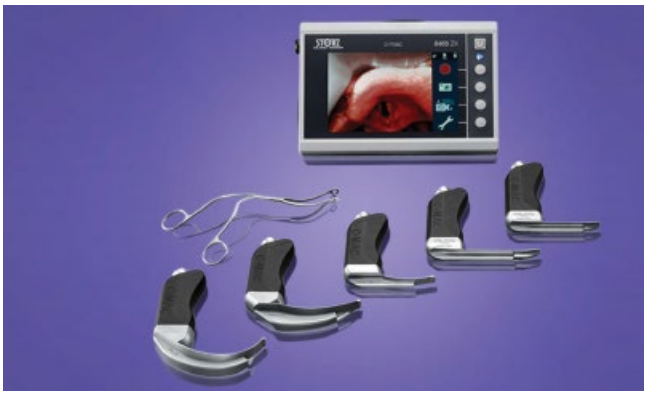


Figure 16.21 C-MAC® videolaryngoscope. Fiberoptics and a high-resolution video system are incorporated into standard laryngoscope blades, including Miller 0 and 1, and Macintosh 1, 2, 3. *Source:* Courtesy of Karl Storz Co., Tubingen, Germany.

Optical stylets

The optical stylets were first introduced into clinical practice in the 1970s and remain useful adjuncts in the management of the adult and pediatric difficult airway. The optical stylet consists of a fiberoptic bundle within a rigid or malleable J-shaped stylet that ends in an eyepiece. These stylets can displace pharyngeal soft tissue because of their rigid form and are more easily maneuvered than flexible scopes. They often incorporate a port for insufflating oxygen and minimize secretions and fogging. However, we do not recommend oxygen insufflation even at low flow rates as pneumothorax and subcutaneous emphysema remain an ever-present risk in infants [373–375]. Optical stylets are simple to assemble and their use involves a short learning curve. Furthermore, they are inexpensive when compared to fiberoptic bronchoscopes and video or optical laryngoscopes. The optical stylet allows visualization of the tracheal tube as it passes through the vocal cords because the stylet is recessed within the tracheal tube during intubation; however, this view may be compromised by secretions or fogging.

Bonfils fiberscope

The Bonfils fiberscope and very similar Brambrink fiberscope (Karl Storz Company,Tuttingen, Germany) are rigid fiberoptic stylets with a J-shaped 45° anterior-angulated tip (Fig. 16.22). They provide a 90° angle of view and are available in all pediatric sizes. They are designed to be used via the retromolar approach. This approach brings the glottis into view rapidly and avoids negotiating the stylet around the bulk of the tongue. Once at the glottic opening, the preloaded tracheal tube is advanced through the vocal cords under direct vision. Some practitioners recommend the use of a rigid laryngoscope to create space for placement of the scope; however, some authors recommend against the use of this device in neonates [347,376–379]. The small optic aperture and significant 40-fold magnification render the visualization vulnerable to secretions [377]. In a simulated difficult pediatric airway, the Bonfils was easier to use and associated with better views of the larynx than direct laryngoscopy; however, intubation success rate and intubation times were similar [380]. In a comparative study in normal children, use of the Bonfils resulted in better laryngeal visualization than use of direct laryngoscopy or the GlideScope [381]. The Bonfils was

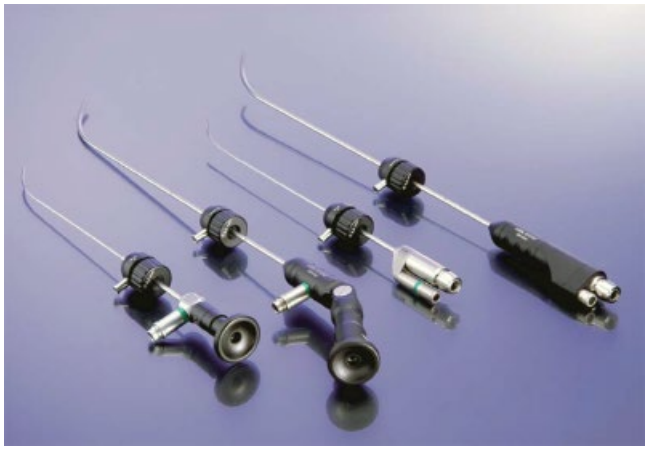


Figure 16.22 The Bonfils (two scopes on the left) and Brambrink (two scopes on the right) fiberscopes. See text for details. *Source:* Courtesy of Karl Storz Co.,Tuttlingen, Germany.

also successfully used in a 5-week-old infant with massive macroglossia and limited oral airway space due to multiple hemangiomata [382]. The Bonfils was compared to the fiberoptic bronchoscope in a small study of 26 children with known or suspected difficult intubation and found to be faster to use than the fiberoptic by two experienced investigators. The success rates were comparable and there were no differences in complications [383].

Shikani Optical Stylet

The Shikani Optical Stylet (SOS; Clarus Medical, Minneapolis, MN, USA) is a malleable, stainless steel, J-shaped stylet with an enclosed fiberoptic bundle [384] (Fig. 16.23). The pediatric SOS is 27 cm long and can accommodate tracheal tubes as small as 2.5 mm internal diameter. The SOS has been successfully used to intubate neonates and older children with a difficult airway. Extension of the head and application of jaw thrust facilitates elevation of the epiglottis off the posterior pharyngeal wall, which facilitates passage of the stylet [287,385–389]. The SOS is useful in patients who require maintenance of a neutral cervical spine during tracheal intubation [390]. As with the Bonfils, tracheal intubation can be accomplished efficiently and effectively with the assistance of the direct laryngoscope [391]. Use of the SOS is associated with minimal airway stimulation, permitting intubation in sedated children [144]. The SOS is lightweight, easily prepared and cleaned, and useful in managing the difficult airway in size ranges.

Lighted stylet

The lighted stylet allows tracheal intubation by observation of a transilluminated light in the neck. This often requires a darkened operating room to allow optimal visualization of the light. After the tracheal tube has been loaded onto the lighted stylet, it is inserted orally in the midline of the pharynx while performing jaw thrust, and the transilluminated light is located as a cone of light in the neck just above the suprasternal notch. It is critical that the light is located in the midline of the neck, as any deviation from the midline will direct the tube towards the esophagus. The centrally located light is then observed as the stylet is advanced caudally. Once the glottis is entered, the operator feels the stylet moving past the cords and observes an intensification of the light in the neck. Sometimes light is conducted down the trachea creating a characteristic "cone of light" effect. The tracheal tube is then advanced off the stylet and tracheal placement confirmed by the usual means. Resistance during the advancement of the stylet towards the glottis may suggest the device is off midline or the tip may be entrapped in the vallecula or on the aryepiglottic fold. This requires retraction of the device and reinsertion while improving jaw thrust to elevate the epiglottis off the posterior pharyngeal wall [392].

Lighted stylet-guided intubation utilizes tactile and visual cues to successfully place the tracheal tube. It is a low-cost technique that is easily learned and remains useful in cases where visualization of the glottis is difficult or impossible. It can be employed in awake patients with difficult airways and can be successfully utilized via the nasal route [393–399]. In a cohort of patients with normal airways, the lighted stylet was equally efficacious for tracheal intubation as the Airtraq [400].

In 1957, Sir Robert Macintosh was the first to describe the use of a lighted stylet to facilitate intubation [401]. Since the introduction of his 18 in illuminated tracheal tube introducer, there have been many stylet designs. The fiberoptic lighted intubation stylet (Anesthesia Medical Specialties, Santa Fe, CA) is available in pediatric sizes, accommodating tracheal tubes as small as 3.5 mm internal diameter. Lighted stylets for use with tube diameters less than 3.5 mm can be fashioned by inserting a single fiberoptic light pipe adjacent to an appropriately sized stylet for the selected tracheal tube. The light pipe is illuminated by a fiberoptic light source and in this manner a lightwand can be created for any sized patient (Fig. 16.24).

Digital intubation

Digital intubation is a rarely taught technique that should be learned by pediatric anesthesiologists [402]. It pre-dates direct laryngoscopy and may have been performed as early as the 1500s. It can be performed rapidly in patients who may be difficult to intubate by direct laryngoscopy or who may be in a position that does not allow easy access to the airway (e.g. extubation in the prone position). To perform a digital intubation, the anesthesiologist stands on the side of the patient facing the head of the operating room table. The gloved non-dominant index finger is placed along the surface of the tongue in the midline and is advanced to feel the epiglottis,

Figure 16.23 The Shikani Pediatric Optical Stylet. See text for details. *Source:* Courtesy of Clarus Medical, Minneapolis, MN.

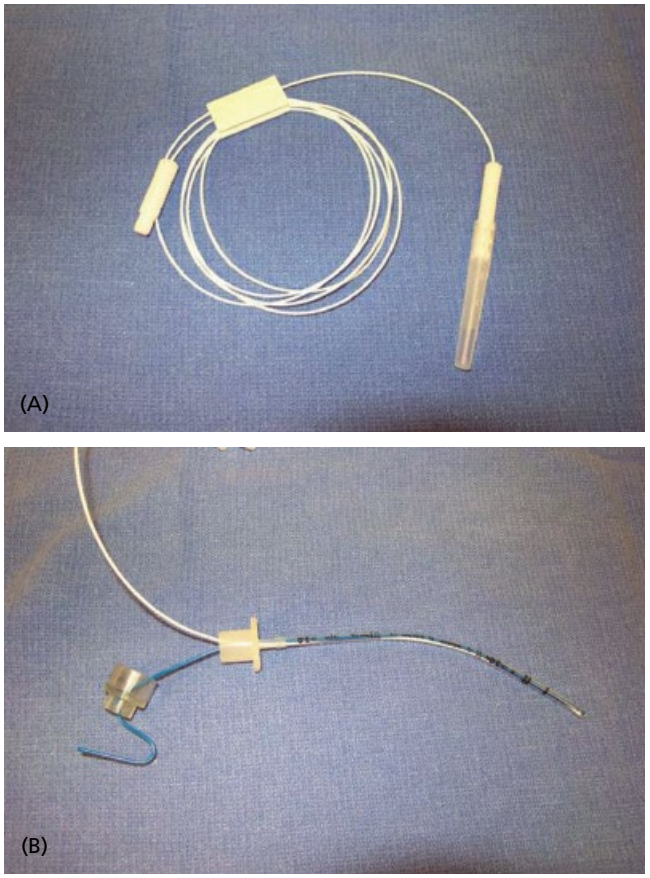


Figure 16.24 Lighted stylets for use with tube diameters less than 3.5 mm can be fashioned by inserting a single fiberoptic light pipe adjacent to an appropriately sized stylet for the selected tracheal tube. (A) Narrow gauge single fiberoptic light pipe. (B) Final assembly of fiberoptic light pipe, stylet, and endotracheal tube. See text for further explanation.

and then the finger is advanced further until the aryepiglottic folds are located. The dominant hand holds a styletted tracheal tube in a C-shaped configuration like a pencil and slides the tube alongside the non-dominant finger. The tip of the tracheal tube is directed through the glottis by the non-dominant finger and tracheal intubation is confirmed by the usual means. In a report of 39 digital intubations in 37 neonates, the mean time to intubation was 7 s. All the patients were successfully intubated; one patient required two attempts [403].

Extubation of the difficult airway

Extubation of the difficult airway can occasionally be more challenging than the intubation and requires careful planning and preparation to avoid complications. The operating room should be prepared in a similar fashion to the set-up for intubation and the device successfully utilized in securing the airway should be available in the operating room. In select cases, the use of an airway exchange catheter (Cook, Bloomington, IN) may be beneficial in the extubation of children with difficult airways. The Cook catheter is placed through the lumen of the tracheal tube into the trachea and is left in place after extubation. The catheter allows the administration of supplemental oxygen through a central hollow core. In a series of 20 pediatric difficult airway patients with an exchange catheter in place, five underwent successful reintubation over the catheter. No sedatives were required with the exchange catheter in place [404].

Surgical and invasive airway management

On extremely rare occasions, the anesthesiologist may encounter a dire "cannot ventilate, cannot intubate" situation associated with prolonged hypoxemia, which if left untreated, will likely result in patient mortality. Therefore, every pediatric anesthesiologist should have a reasonable approach to obtaining a surgical airway should this rare event occur. Cricothyroidotomy was first described in 1969 [405]. There are three methods of achieving oxygenation via the cricothyroid membrane: the small cannula (often an intravenous angiocatheter) approach, the commercially available large cannula approach using the Seldinger technique, and the open surgical technique in which a tracheostomy tube is inserted. The traditional techniques of choice for anesthesiologists and others not trained in open surgical tracheostomy are the needle cricothyroidotomy and Seldinger guided placement techniques. In an animal model of the infant airway, invasive airway access was difficult (60% overall success rate) and complications were common, including a 42% incidence of puncturing the posterior tracheal wall [406]; another animal model study had similar findings (67% success rate) but found that an emergency surgical tracheotomy could be performed within 4 min with a low rate of complications [407]. In small infants, identification of the cricothyroid membrane may be impossible, which is why some advocate for direct tracheal access using a scalpel. This skill can be practiced in a small animal model and requires very few steps.

Angiocatheter technique

The angiocatheter technique is probably the most plausible in pediatric patients requiring emergency surgical airway access. A needle cricothyroidotomy can be achieved using a 14-, 16- or 18-gauge angiocatheter that is placed through the cricothyroid membrane. While extending the cervical spine, the angiocatheter connected to a syringe of saline is introduced in the midline in the lower half of the cricothyroid membrane at a 45° angle in an inferior and posterior direction [408]. The syringe attached to the angiocatheter is gently aspirated during insertion, and return of air confirms tracheal entry. The catheter is then advanced off the needle into the trachea. A high-pressure oxygen source (such as a wall oxygen supply or jet ventilator) is needed to overcome the resistance of the catheter in order to deliver effective oxygenation (ventilation is not readily achieved). The oxygen source can be connected to the catheter by a 3 mL syringe with the plunger removed and attached to a 15 mm tracheal tube adapter. Barotrauma is a risk of ventilation through the angiocatheter, particularly in situations where exhalation is not possible because of upper airway obstruction. Structures at risk during the puncture are the superior thyroid artery along the lateral border of the membrane, the cricothyroid arteries, and the pyramidal lobe of the thyroid. The posterior tracheal wall could also be injured during the puncture attempt, thus confirmation of correct placement is critically important as insufflation of high-pressure gas outside the trachea can cause life-threatening tension pneumomediastinum

and tension pneumothorax. Even after correct placement, reassessment of positioning should occur frequently as children have little margin for error and a correctly placed catheter can become dislodged with minimal movement [409]. Oxygenation after accessing the trachea is particularly risky in neonates and infants: pneumothorax, barotrauma, hypotension due to air trapping, and increased intrathoracic pressures are known complications. One study compared rescue ventilation through an angiocatheter using the Enk oxygen flow modulator (Cook Medical, Bloomington, IN) to a jet ventilator in a rabbit model. The Enk flow modulator is a device for transtracheal ventilation consisting of a non-compliant tube with a distal Luer lock connector and openings for adjusting flow. Although it was a small study (9 rabbits), there were no differences in time to achieve adequate oxygenation between the two devices, and the authors concluded that both devices facilitated rescue ventilation through needle cricothyrotomy [410]. A potentially revolutionary device (Ventrain®; Ventinova, Eindhoven, The Netherlands) may transform ventilation after needle or surgical access in children. The basic concept and function of the device are very simple and address the major drawback of oxygenation through a small cannula, gas egress. Based on the Bernoulli principle, the Ventrain creates active expiration through small-bore cannulas by a jet-flow-generated suction. A small hole is occluded to enable ventilation, and release of the hole generates active expiration, reducing the risk of barotrauma [411].

The Ventrain has been used successfully in two infants with severe traumatic upper airway obstruction. Cook airway catheters were placed in the trachea and successful ventilation achieved using the Ventrain. The Ventrain may become a key ventilation tool in the severely obstructed child given its simplicity and novel function. Pediatric studies are needed to establish its efficacy and safety [412].

Large catheter Seldinger approach kits

Cricothyroidotomy kits based on the use of the Seldinger technique are now available for pediatric use. There are several manufactured kits that share common steps. A limited skin incision is made after identifying anatomical landmarks, a needle is inserted through the incision and cricothyroid membrane into the trachea, a guidewire is placed through the catheter, and the catheter is removed leaving the guidewire in place. A dilator airway catheter assembly is advanced over the wire into the trachea and the guidewire and dilator are removed [413]. Ideally, pediatric anesthesiologists should develop expertise with this approach using an animal model or a specially designed patient simulator. One commercially available kit, Quicktrach baby™ (VBM Medizintechnik GmbH, Sulz am Neckar, Germany) for infant emergency cricothyrotomy, was evaluated in 10 rabbits. The researchers found the Quicktrach baby to be a reliable technique with minor complications, and successful placement was possible in all attempts by the two anesthesiology trainees who used the device. This kit uses the cannula-over-needle technique and may be easier and quicker than other methods. The median time to place the device was 31 s with an interquartile range of 23–43 s. One rabbit had injury to the posterior tracheal wall mucosa and two animals had fractures of the cricoid cartilage. Although the device is designed primarily for cricothyrotomy it can also be directly placed in the trachea as a needle tracheotomy [414].

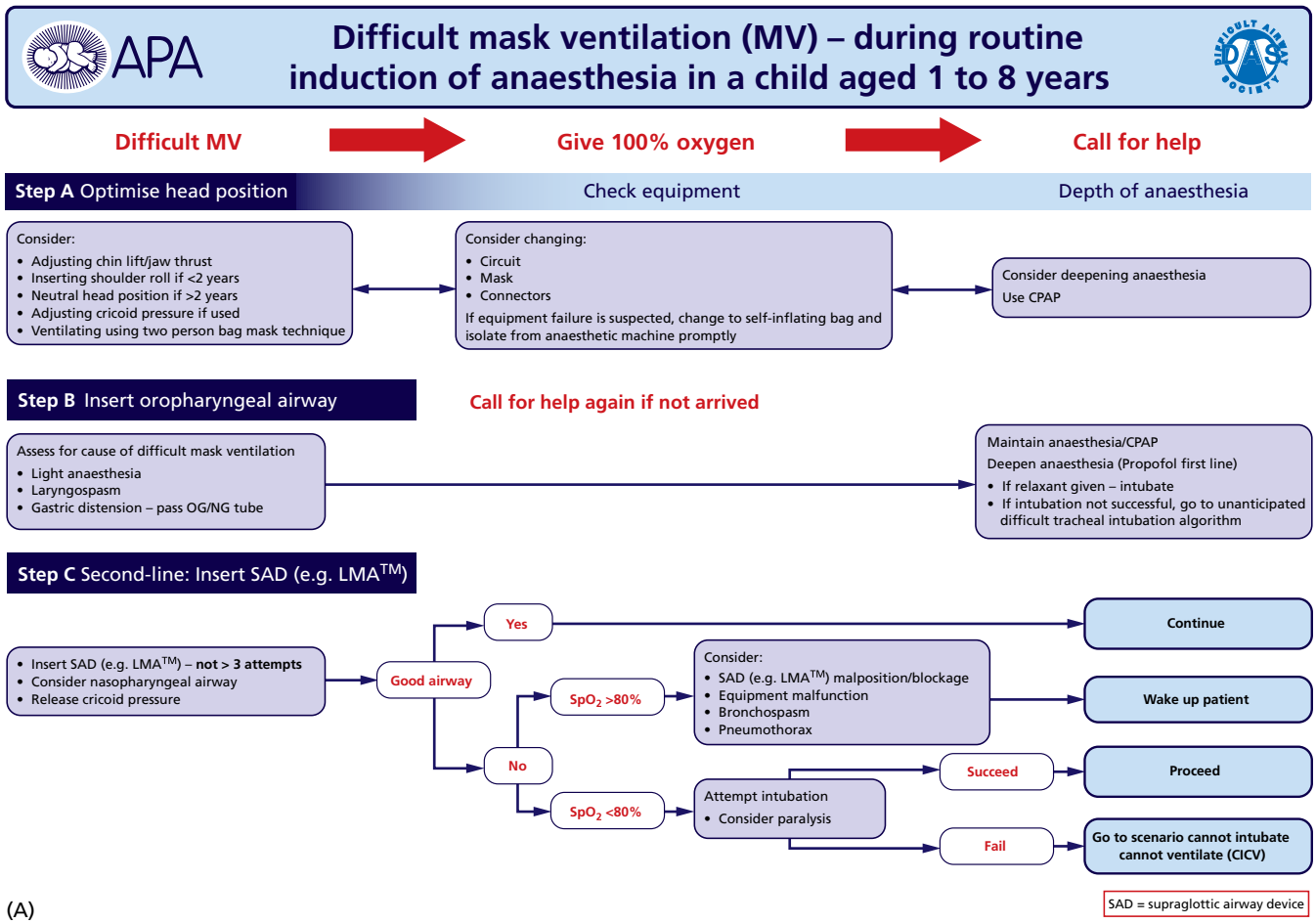
Intentional muscle relaxation for difficult airway management

In recent years, the traditional dogma of maintaining spontaneous ventilation and avoiding neuromuscular blockade for management of the difficult airway has been challenged. Case reports and case series in both adults and children indicate that mask ventilation may improve in the "cannot ventilate, cannot intubate" situation with muscle paralysis [415–417]. Functional airway obstruction, such as laryngospasm, opioid-induced muscle rigidity, and oropharyngeal obstruction with increased muscle tone, can be overcome with this strategy. In addition, if hypoxia with bradycardia has occurred, intravenous epinephrine can be administered to delay the onset of cardiac arrest while oxygenation is improving. Additional time is then available to intubate the trachea with specialized equipment, at times avoiding a surgical airway or significant hypoxia and cardiac arrest. Succinylcholine has been described in this scenario, but some authorities recommend non-depolarizing neuromuscular blocking agents. The recent availability of sugammadex, which in large doses can reverse even dense neuromuscular blockade with rocuronium or vecuronium, would appear to make this approach safer and more feasible [418]. Indeed, some difficult airway management algorithms in both adults and children now recommend considering muscle relaxation in the "cannot intubate, cannot ventilate" scenario before proceeding to a surgical airway [419,420].

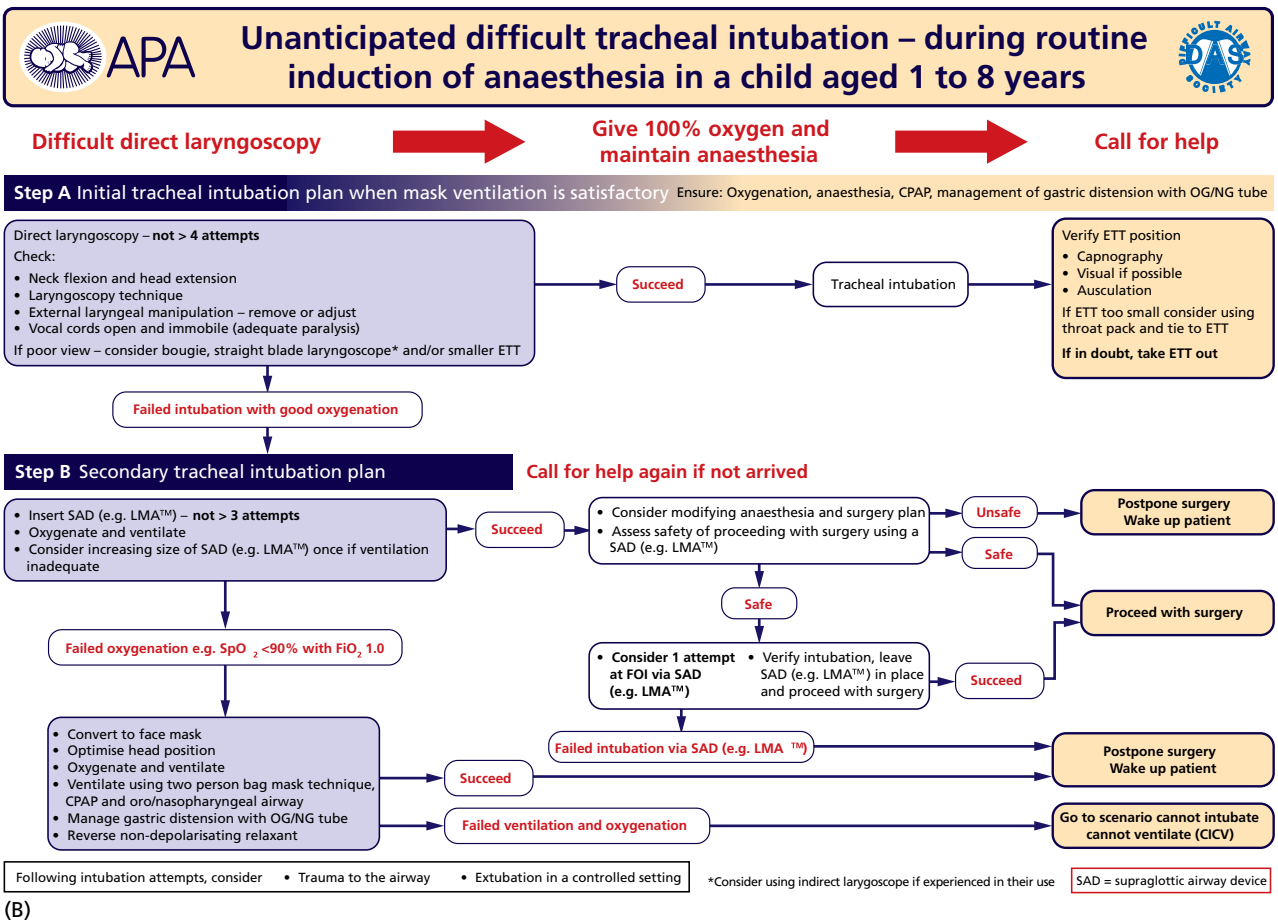
Figure 16.25 presents algorithms for management of difficult mask ventilation, intubation, and "can't ventilate–can't intubate" scenarios for the pediatric patient, from the Difficult Airway Society [419].

KEY POINTS: THE DIFFICULT PEDIATRIC AIRWAY

- General anesthesia is utilized for the majority of pediatric patients with difficult airways; sedation with airway topicalization is less frequently used; awake intubation is reserved for emergency situations in small infants
- Preanesthetic IV access, maintaining spontaneous ventilation, and ensuring upper airway patency with CPAP, positioning, and an oral or nasal airway are important principles for the difficult airway
- Difficult mask ventilation with a difficult airway may be improved with neuromuscular blockade; availability of sugammadex is important for rapid reversal if necessary
- The fiberoptic bronchoscope can frequently be utilized for difficult intubation; oral or nasal routes or utilizing a laryngeal mask airway as a conduit are all effective techniques
- The pediatric videolaryngoscope has added significantly to effective management of the difficult airway and is now the first choice in many scenarios
- The need for surgical airway management is very rare; effective planning and immediate availability of a videolaryngoscope should avoid this scenario

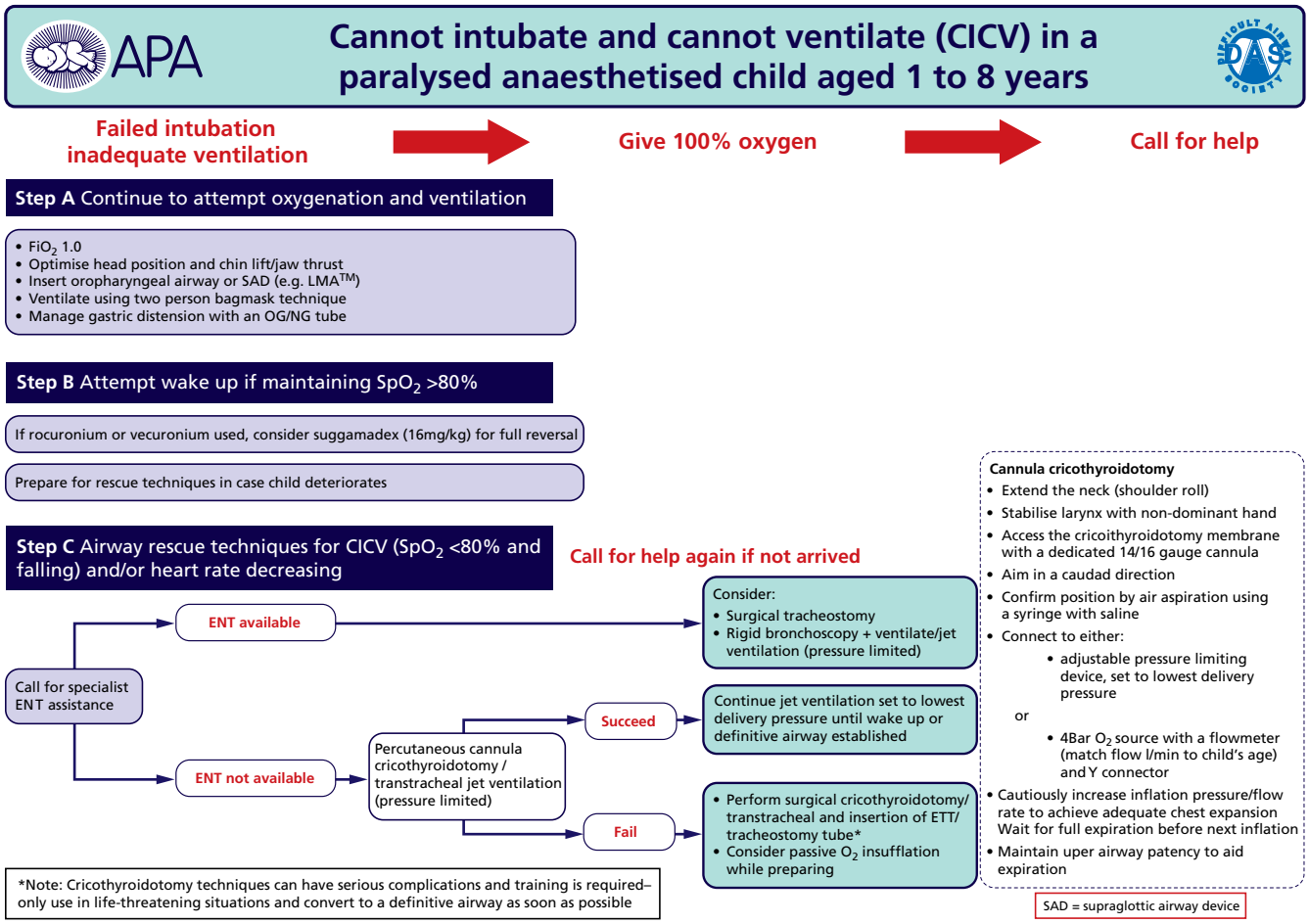


(A)



(B)

Figure 16.25 Difficult Airway Society algorithms. (A) Difficult mask ventilation algorithm. (B) Unanticipated difficult intubation algorithm. (C) Cannot intubate and cannot ventilate algorithm. *Source:* Reproduced from the Association of Anaesthetists of Great Britain and Ireland [419] with permission of APAGBI and DAS.



(C)

Figure 16.25 (*Continued*)

CASE STUDY

A 2-month-old, male, former 31-week premature infant with Pierre Robin sequence presented for repair of bilateral large inguinal hernias, and open gastrostomy tube. Birthweight was 1600 g and it was evident after birth that the patient had significant micrognathia, with cleft palate. The patient had no other congenital anomalies, including no cardiac disease. He had moderate upper airway obstruction in the supine position without airway support. His airway had been maintained with nasal CPAP of 5–7 cmH_2O, with FiO_2 0.21–0.30 and flows of 1–2 L/min. In addition, he was nursed in the lateral or prone positions. He had no major apnea/desaturation events, had grown slowly with nasogastric tube feeds, – and now weighed 1950 g. The multidisciplinary team of neonatologists, otolaryngologists, pulmonologists, and craniofacial anomaly specialists was considering tracheostomy to maintain airway patency. However they were undecided at this point and wanted to address the hernias and a long-term feeding solution before attempting to wean the patient from CPAP and committing him to a tracheostomy. The patient's trachea had never been intubated, and he had not had previous surgery or imaging procedures. Medications were multivitamins and iron, and he had no drug allergies. On physical examination, the patient had obvious significant micrognathia, normal cervical range of motion, and very mild retractions with no obvious upper airway obstruction on nasal CPAP of 5 cmH_2O, FiO_2 0.21. There was a small 6 Fr nasogastric tube in the right naris. The lungs were clear to auscultation bilaterally, there was no cardiac murmur, and a 2 Fr percutaneously inserted central catheter (PICC) was present in the right arm. SpO_2 was 96%, chest radiograph revealed clear lung fields, normal heart size and configuration, and the PICC was present in the mid-superior vena cava. Preoperative laboratory studies included hemoglobin concentration of 10.1 g/dL, and a capillary blood gas of pH 7.36, $PaCO_2$ 44 mmHg, PaO_2 44 mmHg, and calculated base excess of +3 meq/L. After a discussion with the parents about the risks of difficult airway management and possible postoperative mechanical ventilation had occurred the day before, consent for anesthesia was obtained and the patient transported to the operating room (OR).

The following equipment had been assembled in the OR: standard Miller 0 and 1 laryngoscope blades; styletted uncuffed endotracheal tubes (ETT) of 2.5 and 3.0 mm sizes;

oral airways size 000, 00, and 0; disposable straight laryngeal mask airways (LMA) size 1 and 1.5; and the GlideScope Cobalt video laryngoscope with the small video baton and size 1 plastic laryngeal blade, and neonatal Magill forceps. Succinylcholine, 4 mg, and propofol, 6 mg, were drawn up in syringes. After discussion with the pediatric anesthesia fellow, it was decided to use the LMA as a conduit for fiberoptic intubation. A second attending anesthesiologist was present for induction of anesthesia and tracheal intubation, and the patient's otolaryngologist, who was operating with a series of short cases in the adjacent OR, was alerted the case was to start and available for emergency backup.

Standard monitors were placed, glycopyrrolate 0.02 mg was administered intravenously, the patient was preoxygenated with a facemask and FiO_2 1.0 for 3 min, and a #1 LMA, lubricated with 2% lidocaine gel, was inserted gently with the cuff deflated and the patient awake. He tolerated this well, the cuff was inflated with 3 mL air, and the airway was patent with audible crying. After gentle awake assisted ventilation demonstrated good chest excursion, inhalation induction with sevoflurane, 2% inspired, and 5 L/min oxygen flow, was begun. Inspired sevoflurane was increased slowly to 4%, the patient had a patent airway throughout and passed through Stage II of general anesthesia without incident and, with manually assisted ventilation and end-tidal (ET) sevoflurane of 3%, had SpO_2 99%, heart rate (HR) 135, and blood pressure (BP) 60/35. $ETCO_2$ was 24 mmHg. An extended 3.0 mm uncuffed ETT had been fashioned beforehand, made up of a standard 3.0 ETT with the connector removed and the upper half of a second ETT taped with a single layer of clear plastic tape with the connector removed. The extended ETT was loaded onto a 2.2 mm pediatric fiberoptic bronchoscope (FOB), pushed up to the proximal end of the scope. The video image was displayed on three large screens in the OR. The FOB was lubricated, had antifog solution applied to the tip, and was inserted into the end of the LMA with a standard FOB elbow adaptor, and advanced easily down the shaft of the LMA, with the second anesthesiologist gently assisting ventilation and stabilizing the LMA. When the aperture of the bowl of the LMA was reached, the glottis was in clear view, with the epiglottis stented up by the LMA. Slight vocal cord abduction was observed with inspiration. Propofol, 2 mg, was administered to deepen anesthesia and produce apnea, and the FOB was advanced carefully, always with the airway lumen in view, until the vocal cords had been passed, and the cartilaginous tracheal rings and pars membranosa were clearly in view. The scope was advanced further to just above the carina, to avoid carinal stimulation. Then, the ETT was advanced down the scope, through the LMA, and very gently through the glottic opening, rotated so that its beveled tip would be parallel to the vocal cord alignment. After passage of the ETT below the vocal cords, FOB position was checked and was still just above the carina. The FOB was withdrawn slowly, and the ETT tip could be seen in mid trachea. The ETT connector was placed on the end of the extended ETT, and manual ventilation produced excellent chest rise, equal bilateral breath sounds, and persistent $ETCO_2$ of 45–50 mmHg. SpO_2 had decreased to 91% but quickly recovered to 99% after 30 s of manual ventilation. HR was 120, BP slightly lower at 52/30, but with reduction in sevoflurane concentration to 2% and 10 mL lactated Ringer's solution bolus, returned within 2 min to 65/35. There was a leak around the ETT at 20 cmH_2O. While grasping the ETT in the back of the oropharynx with the Magill forceps, the LMA cuff was deflated, and the LMA removed gently over the extended ETT after the connector had been removed. The tape was removed from the extended ETT, producing a standard 3.0 ETT, the connector replaced, correct ETT placement and ventilation again verified, and the ETT secured in standard fashion. After the ETT was secured, a direct laryngoscopy was performed, and a Grade IV Cormack and Lehane view was evident, even with external laryngeal manipulation. All airway procedures were detailed in the electronic anesthesia record, and a patient alert for difficult airway clearly noted. A caudal anesthetic and rectal acetaminophen were used for intra- and postoperative analgesia. The case proceeded uneventfully, and it was decided to transport the patient back to the neonatal intensive care unit (NICU) with the endotracheal tube in place. Analgesia was provided with morphine, and the patient spent 48 h on mechanical ventilation, with good pain control. Extubation occurred in the NICU, with the patient awake, the anesthesiologist present at the bedside with LMA and fiberscope, and nasal CPAP ready to apply immediately after extubation. The patient was successfully extubated to nasal CPAP, spent another month in the NICU, and was weaned from CPAP, with improved upper airway obstruction and good somatic growth, and was discharged home with pulse oximetry and apnea monitoring, without tracheostomy, at age 3 months. The parents were well aware of the difficulty with tracheal intubation.

This case illustrates the principles outlined in this chapter, including thorough discussion and preparation for the difficult airway, assembling all airway equipment and drugs beforehand, choosing one primary method of intubation with at least one backup method available, having expert assistance immediately available, and planning for the difficult extubation. In addition, communication with other providers and parents, and documentation of airway procedures, are very important in the care of the patient with a difficult airway.

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

83 Stafrace S, Engelhardt T, Teoh WH, Kristensen MS. Essential ultrasound techniques of the pediatric airway. Paediatr Anaesth 2016; 26: 122–31. This review details the equipment, probes, ultrasound scanning techniques, and basic views and uses of ultrasound to image the oropharynx, larynx, trachea, pleura, lungs, and diaphragm. Applications such as confirmation of endotracheal tube placement and position, detection of pneumothorax, assessment of lung consolidation and edema, and vocal cord paresis are discussed.

107 Luce V, Harkouk H, Brasher C, et al. Supraglottic airway devices vs tracheal intubation in children: a quantitative meta-analysis of respiratory complications. Paediatr Anaesth 2014; 24: 1088–98. A meta-analysis of 19 studies comparing supraglottic airway devices to tracheal intubation in children found that during recovery from anesthesia the incidence of desaturation (OR = 0.34 (0.19–0.62)), laryngospasm (OR = 0.34 (0.2–0.6)), cough (OR = 0.18 (0.11–0.27)), and breath holding (0.19 (0.05–0.68)]) was lower when a laryngeal mask airway was used. Postoperative incidences of sore throat (OR = 0.87 (0.53–1.44)), bronchospasm (OR = 0.56 (0.25–1.25)), aspiration (1.33 (0.46–3.91)), and blood staining on the device (OR = 0.62 (0.21–1.82)) did not differ between laryngeal mask airway and tracheal intubation.

249 von Ungern-Sternberg BS, Boda K, Chambers NA, et al. Risk assessment for respiratory complications in paediatric anaesthesia: a prospective cohort study. Lancet 2010; 376: 773–83. An important prospective cohort study demonstrating that the incidence of laryngospasm is increased in children with active or recent upper respiratory tract infection, especially within 2 weeks of anesthesia. A history of eczema, exercise-induced wheezing, nocturnal dry cough, and wheezing more than three times in the prior year are strongly associated with bronchospasm, laryngospasm, and other perioperative adverse respiratory events. Having parents that smoke or a strong family history of asthma or atopy is associated with these perioperative adverse airway events.

277 Heinrich S, Birkholz T, Ihmsen H, et al. Incidence and predictors of difficult laryngoscopy in 11,219 pediatric anesthesia procedures. Paediatr Anaesth 2012; 22: 729–36. In this large cohort study, the overall incidence of difficult laryngoscopy (Cormack and Lehane (CML) grade III and IV) was 1.35%. In patients younger than 1 year, the incidence of CML III or IV was significantly higher than in the older patients (4.7% versus 0.7%). ASA physical status III and IV, a higher Mallampati score (III and IV) and a low BMI were all associated ($p < 0.05$) with difficult laryngoscopy. Patients undergoing oromaxillofacial surgery and cardiac surgery showed a significantly higher rate of CML III/IV findings.

279 Fiadjoe JE, Nishisaki A, Jagannathan N, et al. Airway management complications in children with difficult tracheal intubation from the Pediatric Difficult Intubation (PeDI) registry: a prospective cohort analysis. Lancet Respir Med 2016; 4: 37–48. This analysis contained over 1000 intubations in children with difficult airways and demonstrated that complications were associated with multiple intubation attempts, weight less than 10 kg, short thyromental distance, and three direct laryngoscopy attempts before the use of an indirect technique. This analysis also indicated that the addition of supplemental oxygen during the intubation attempts will decrease the incidence of hypoxemia during intubation attempts.

284 Apfelbaum JL, Hagberg CA, Caplan RA, et al. Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology 2013; 118: 251–70. The most recent version of the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Although the general principles of difficult airway management are similar between adults and children, these guidelines did not specifically address management of pediatric patients.

415 Engelhardt T, Weiss M. A child with a difficult airway: what do I do next? Curr Opin Anaesthesiol 2012; 25: 326–32. A comprehensive review of assessment and management of the difficult pediatric airway, advocating the somewhat controversial approach to intentionally paralyze the patient with difficult mask ventilation and intubation.

418 Tobias JD. Current evidence for the use of sugammadex in children. Paediatr Anaesth 2017; 27: 118–25. A comprehensive review of suggamadex use in children, including for emergency reversal of profound neuromuscular blockade in the "cannot ventilate, cannot intubate" scenario.

422 Thomas R, Rao S, Minutillo C. Cuffed endotracheal tubes for neonates and young infants: a comprehensive review. Arch Dis Child Fetal Neonatal Ed 2016; 101: F168–74. A thorough review of the use of cuffed endotracheal tubes in anesthesia and intensive care, emphasizing the demonstrated safety and efficacy for short-term use in anesthesia, but lack of many longer-term intensive care studies, particularly in neonatal intensive care.

Further reading

Park R, Peyton JM, Fiadjoe JE, et al; PeDI Collaborative Investigators. The efficacy of GlideScope® videolaryngoscopy compared with direct laryngoscopy in children who are difficult to intubate: an analysis from the paediatric difficult intubation registry. Br J Anaesth 2017; 119: 984–92. A recent analysis of 1295 difficult intubations from the Pediatric Difficult Intubation (PeDI) Registry found that video laryngoscopy had a higher first-attempt success than direct laryngoscopy (53% versus 4%); however patients who weighed less than 10 kg had lower success rates with video laryngoscopy.

Video clips

This chapter contains the following video clips:

Video clip 16.1 Fundamentals of fiberoptic intubation.
Video clip 16.2 Oral fiberoptic intubation.
Video clip 16.3 Nasal fiberoptic intubation.
Video clip 16.4 Fiberoptic intubation via laryngeal mask airway.
Video clip 16.5 Videolaryngoscope intubation.

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CHAPTER 17

Induction of, Maintenance of, and Emergence from Anesthesia

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Evaluation of preoperative data and conditions

Preoperative evaluation including laboratory tests

The preoperative assessment of a child for general anesthesia requires a focused and systematic review of the history and all organ systems. The assessment should include details of the past medical history, current and recent medications, allergies, family history of anesthesia-related complications, nil per os (NPO) status, physical examination, and ancillary laboratory testing.

Before beginning a detailed medical history, a review of the child's vital signs, fasting status, and weight should be documented. Fasting guidelines before surgery can be found in the section "Nil per os." The child's weight should be assessed to determine whether the child's weight is normal or excessive (overweight or obese). An estimation of the child's ideal bodyweight may be calculated using the formulae in Box 17.1 [1,2].

The identity and legal status of the parent or guardian of all minors and cognitively challenged patients must be established preoperatively to ensure the consents for anesthesia and surgery are legal and the medical information is accurate. If the patient is >18 years of age, he/she may consent for anesthesia and surgery. If the child is female, <18 years, and either pregnant or has given birth in the past, in most jurisdictions she is deemed to be an emancipated minor and can consent to surgery. If the child is cognitively challenged, a health proxy (i.e. legal guardian) is required to consent for surgery, irrespective of the patient's age.

A family history of inheritable disorders or serious reactions that are potentially fatal under anesthesia should be sought. Specific mention should be made of malignant hyperthermia and muscle wasting diseases (e.g. Duchenne muscular dystrophy), both of which are discussed in the section "Medical conditions."

In reviewing the past medical history, the child's gestational age at birth is important, because infants who were born prematurely (i.e. <37 weeks' gestational age) and who are <60 weeks' postconceptional age may require overnight observation for perioperative apnea (see section "Ex-premature infants"). In addition, full-term neonates up to 4 weeks' postnatal age should not undergo general anesthesia as outpatients; they too should be admitted and monitored for at least 12 postoperative apnea-free hours.

A complete review of systems should be performed during the preoperative assessment including the cardiac, respiratory, central nervous system, gastrointestinal, genitourinary, endocrine and musculoskeletal systems.

Children with congenital heart disease should be questioned regarding: the nature and status of the heart defect; whether the defect resolved spontaneously or required surgery; if surgery was performed, the nature and date of the surgery; recent admissions or cardiology follow-up appointments related to the cardiac defect; and current cardiac medications. In most instances, a recent cardiology evaluation should be available in which a recent echocardiogram provides evidence of the heart function as well as the need for antibiotic prophylaxis for infective endocarditis. If the child's feeding, activity, color, or vital signs have changed substantially since the last cardiac evaluation, consideration should be given to delaying the surgery until a further cardiac evaluation is performed.

If a murmur is detected during the preoperative assessment, it is important to establish whether it is new or old and

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

Box 17.1: Ideal bodyweight in children [1,2]

- Infants 1–11 months: weight (kg) = (age (mon) + 9)/2
- Children 1–4 years: weight (kg) = 2 × (age (yr)+ 5)
- Children 5–14 years: weight (kg) = 4 × age (yr)

whether a cardiologist has evaluated it in the past. Assess the quality, duration, and location of the murmur, whether it radiates, and to where, and during which phase of the cardiac cycle it occurs. Evidence of heart failure should be ruled out before proceeding. If the murmur is possibly pathological in nature, if there are concomitant signs or symptoms of growth or activity delays, shortness of breath, cyanotic spells, syncope, or feeding problems, then a cardiology consult should be sought. Chapters 27 and 28 present additional information about congenital heart disease.

Illnesses that affect the respiratory system range from minor to major and life-threatening. Almost 30% of children present for surgery with an upper respiratory tract infection (URTI) that is most commonly self-limited. Apart from congenital anomalies that may present in the perinatal period (such as congenital diaphragmatic hernia or congenital lobar emphysema), it is important to question the parents about acquired infections such as recent croup or respiratory syncytial virus (RSV) and whether the child had been admitted to the hospital for any other respiratory problems. Children who present for tonsillectomy and adenoidectomy are diagnosed with either chronic infectious tonsillitis or obstructive sleep apnea (OSA). In the case of OSA, most children have a clinical diagnosis based on the otolaryngologist's assessment of the severity of the symptoms. There are no clinical metrics to confirm a diagnosis of OSA in children. The clinical presentation consists of non-specific signs and symptoms: their weight is normal or increased; they snore very loudly at night; they may have periodic nocturnal apneas and arouse without awakening during sleep; they are often fatigued in the morning despite having slept the entire night; and they may experience nocturnal enuresis, display signs of hyperactivity or inattention, and exhibit behavioral and learning difficulties at school. The definitive diagnosis can only be established by polysomnography, which evaluates the severity of the condition and guides subsequent treatment [3]. If a polysomnogram has been performed, it is important to be aware of the recorded saturation nadir during the sleep study. Children whose nadir is <85% show greater sensitivity to the respiratory depressant (apnea) effects of small doses of opioids [4]. In the absence of a polysomnogram, opioid sensitivity can be evaluated by observing the child's respiratory responses to small doses of opioids during general anesthesia. If apnea occurs in response to a small dose of opioids, no additional doses should be administered as these children are exquisitely sensitive to opioids. Additional opioid dosing only increases the risk of perioperative adverse airway events.

Gastroesophageal reflux (GER) is a normal physiological occurrence in the majority of infants that resolves in 95% of the population by 12 months [5]. Infant irritability and daily regurgitation are sometimes treated as symptoms of gastroesophageal reflux disease (GERD) with no improvement in symptoms. However, the prevalence of GER and GERD in children and adolescents has been estimated to be 4.1% and 7.6%, respectively [6]. Most children with documented GER undergo inhalation inductions, including anesthesia for procedures such as upper endoscopy, as this medical problem does not increase the risk for regurgitation and aspiration during anesthesia. Accordingly, we proceed with our usual anesthetic technique in children with GER.

Children with renal insufficiency or failure require a complete blood count, serum creatinine and blood urea nitrogen, and electrolyte concentrations preoperatively. If the child has renal failure, the type of dialysis and the timing of the last dialysis as well as the volume of fluid that was removed should be documented.

Children with Down syndrome present a number of significant challenges to the anesthesiologist. These children range in cognitive function from having very difficult behavioral problems to being high-functioning, very pleasant children. It is important to complete a cardiac history in these children, as congenital heart disease (e.g. ventricular septal defect and endocardial cushion defect) is common. These children have large tongues and narrow subglottic regions. Accordingly, tracheal tube sizes 0.5–1 mm internal diameter (ID) smaller than expected for their age should be immediately available. Much has been written about the instability of the cervical spine in Down syndrome, although reports of neurological sequelae associated with general anesthesia and surgery in these children are exceedingly rare [7]. Evidence of a pre-existing neurological complaint (the child favors one hand or foot over the other suddenly or has had a change in gait, complains of pain in the neck, is unable to turn the head to one side or the other, or complains of dizziness or fainting) should be noted and reason for concern regarding the stability of the cervical spine. In such cases, a neurological investigation should be sought before proceeding with anesthesia. Although the American Academy of Pediatrics recommends cervical spine imaging in all children with Down syndrome between 3 and 5 years of age, there is no evidence that these investigations are predictive of adverse neurological outcomes in the perioperative period. A survey of 171 pediatric anesthesiologists reported that only 18% obtain preoperative radiographs and/or consultations (in 9%) in asymptomatic children; the majority base their evaluation on the signs and symptoms present [8]. During anesthesia and tracheal intubation, we maintain the neck of children with Down syndrome in a neutral position at all times. Chapter 43 presents additional information about Down syndrome and other genetic conditions.

Children with diabetes mellitus present a number of challenges in the perioperative period [9]. Those with diet control or oral medications should have their morning blood glucose level checked. These children do not usually require additional care and can resume their diet and medications postoperatively. Insulin-dependent diabetics present a more complex management problem. A thorough history should detail their diabetes control, whether they experience hypo- or hyperglycemia, their typical HbA_{1c} level (with a goal of <7.5% in children and adolescents), the type and frequency of insulin and whether they use an insulin pump [10]. In many instances, the endocrinologist responsible for managing their diabetes provides a protocol to the patient and staff recommending appropriate management in the perioperative period [9]. Children who are prone to hypoglycemia should have a glucose

infusion during surgery with periodic measurement of the blood glucose concentrations during anesthesia. If the preoperative blood sugar is >250 mg/dL, a sliding scale of insulin should be started to reduce the blood glucose concentration. More commonly, a correction factor is applied to determine how much 1 unit of regular insulin will decrease the blood glucose concentration in the child. The factor is calculated as the ratio of 1500 and the total daily dose of insulin. For example, if the child takes 30 U of insulin per day, then 1 unit of regular insulin should decrease the blood glucose concentration by 1500/30 or 50 mg/dL. Children who use insulin pumps should also have a fasting glucose measured and their pump set to basal rate during surgery. If the pump is equipped with a continuous glucose monitoring system and alarms with high or low blood sugar concentrations during surgery, the blood glucose concentration should be determined to validate the alarm with an appropriate action being taken based on the result. Chapter 24 contains additional information about diabetes.

In adolescents, it is important to ascertain their use of tobacco and illicit drugs. This may not be possible until the child is separated from the parents. If there is any suspicion that illicit drugs such as cocaine, methamphetamines, opiates, or other cardio- or neurotoxins have been consumed recently, then a toxicology screen, an electrocardiogram, and a neurological examination should be obtained. Chapter 24 presents further information about the approach to the adolescent patient.

A list of medications, the frequency of their consumption, and when they were last taken should be compiled. Liquid medications may be taken on the morning of surgery. Children who take medication in the form of pills will often only take the medications if they are mixed with food. These medications, often antiepileptic drugs, should not be taken before surgery if they cannot be given without solid food. Medications such as β-blockers and α_2-agonists should be continued in the perioperative period, as suddenly stopping them may cause rebound. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) taken on the morning of surgery have been reported to cause profound hypotension in adults after induction of anesthesia [11,12]; although controversial, many recommend withholding these drugs on the day of surgery. Herbal medicines and supplements, more commonly ingested by adults, are taken by 6–10% of children in one survey, with Echinacea and arnica being the most commonly used herbals, but St John's wort, valerian, garlic, and gingko also widely used [13]. Valerian and kava may prolong the duration of anesthesia, and feverfew, garlic, ginger, and ginkgo increase the risk of perioperative bleeding. St. John's wort induces P-glycoprotein and CYP3A4 interactions, thereby decreasing the concentrations of critically important drugs, such as cyclosporin A. Furthermore, goldenseal inhibits CYP3A and 2D6, possibly prolonging the duration of ondansetron. Valerian and St John's wort should be tapered at least 1 week before scheduled anesthesia to minimize the risk of drug reactions [14–16].

Allergies present a very serious conundrum for anesthesiologists. Any reaction that a parent or child reports as abnormal should be listed as an allergy or sensitivity in the medical record. The reactions may be known side-effects of the drug (i.e. an erythematous skin rash after amoxicillin). Once listed as an allergy on a child's chart, it is often difficult to expunge the drug alert. Examples of allergic reactions that are not allergies that the authors have direct knowledge of include allergy to epinephrine because it causes headaches, a diaper rash from oral sulfonamide antibiotic, and a penicillin rash that occurred in the parent, not the child, but was listed on the child's chart. In fact, most allergies listed in the patients' charts have no immunological basis [17,18]. In a child, a flat skin rash produced by oral liquid antibiotic is often non-immunological in origin and warrants re-challenging the child with the antibiotic if the sentinel event occurred ≥5 years ago. Egg allergy is not a contraindication to propofol [19]; soy and peanut allergy are contraindications only to propofol manufactured with those additives, most commonly by European manufacturers. Latex is commonly cited as an allergy in children. Skin (and hand) latex reactions generally are non-immunological and do not proceed to systemic anaphylactic reactions. With the removal of latex from most medical products, children with spina bifida and congenital urological abnormalities are no longer exposed to latex products repeatedly and are far less likely to develop latex allergy [20]. Latex allergy is an acquired susceptibility after repeated exposures to latex; it is not congenitally acquired. The most important question to ask regarding latex susceptibility is whether the child develops any reaction when he/she touches a toy balloon to his/her lips or the dentist inserts a rubber dam in the mouth. If the lips or tongue swell, then the child is likely to be immunologically allergic to latex. A latex-free environment in the operating room will ensure safe conduct of these children. See Chapter 45 for further discussion of latex and other allergies.

Before every child is anesthetized, physical examination of the head and neck, chest, and heart must be performed. Physical examination of the head and neck includes evaluating the extent of mouth opening, the ability to extend the tongue and neck, the state of the dentition, and any detachable plates or oral appliances. All metal piercings and objects must be removed from the oropharynx to prevent aspiration, bodily injury if undergoing a magnetic resonance imaging (MRI) scan, or a skin burn if electrocautery is used in the vicinity (although bipolar cautery is safer than unipolar) [21]. Concerns over a piercing hole closing can be addressed by inserting sterile sleepers (non-metallic spacers), such as a large-diameter suture or epidural catheter, through the lumen for the duration of the procedure [22,23]. Tongue piercings may close quickly, within a few hours or less.

Auscultation of the heart and lungs should be performed and recorded on the preoperative record. Any abnormal findings should be recorded.

Routine laboratory testing such as complete blood count, chemistry panels, and urinalysis are not indicated for most elective surgical procedures involving children. However, in the event that the surgery may entail a large blood loss, a preoperative complete blood count along with type and screen or cross-match should be performed. In some children, it may be necessary to wait until they are anesthetized and intravenous access is established before sufficient blood can be obtained for the tests required.

The most recent recommendation by the American Society of Anesthesiologists (ASA) Task Force on Preanesthesia Evaluation states "the literature is insufficient to inform patients or physicians on whether anesthesia causes harmful

effects on early pregnancy. Pregnancy testing may be offered to female patients of childbearing age and for whom the result would alter the patient's management" [24]. We require a preoperative pregnancy test for all menarcheal females who require anesthesia at our institution. If the test is positive, we inform the child of the result and work towards a decision whether to proceed with surgery and anesthesia. If we proceed with anesthesia, the optimal anesthetic technique for the mother and fetus must be reached by consensus with the pregnant mother. Chapter 24 contains further discussion about pregnancy testing.

The clinical value of a chest radiograph in a child about to undergo surgery is typically less than an oxygen saturation reading. An oxygen saturation reading <95% is abnormal and may suggest deterioration of the child's pulmonary or cardiac status. In both instances, it warrants further investigation.

Specialized tests such as electrocardiography and echocardiography can be an invaluable clinical tool in a child with known congenital heart disease or myocardial dysfunction. These tests help to evaluate the cardiac anatomy, intracardiac shunting, ventricular function, right-sided heart pressures, valvular function, and the presence of pleural or pericardial effusions.

Radiological investigations such as computed tomography (CT) or MRI may be useful not only to the surgical team but also to anesthesia to evaluate the scope of the disease process such as that involving airway anatomy.

Once all of the relevant preoperative data have been compiled, an assessment of the "ASA physical status" of the child should be performed. This metric is an assessment of the child's pre-existing diseases, but it is not intended as a measure of perioperative risk (Table 17.1).

Medical conditions

Nil per os

All children scheduled for elective surgery should be fasted according to the ASA guidelines (Table 17.2) [25]. Note that there are no age-adjusted fasting intervals. Recently, a shift in philosophy in Sweden allows clear fluids until the time the child is "called" to the operating room, i.e. approximately 30 min since the last oral fluids, changing the fasting intervals to a 6–4–0 rule: 6 h for solids, 4 h for breast milk, and 0 for clear fluids. This has resulted in an incidence of aspiration of 3:10,000, consistent with the previously published data with more restrictive fasting guidelines [26]. Children who present with chewing gum must expectorate it before induction of anesthesia. Chewing gum increases both gastric fluid volume and gastric fluid pH, rendering the risk of pneumonitis should aspiration occur no different from those who do not chew. As a result, induction of anesthesia need not be delayed [27–29].

In emergency surgery, the bowels cease peristaltic action as soon as the injury occurs. The administration of opioids also impairs peristalsis. Hence, all foods present in the stomach at the time of the injury are likely to remain there until peristalsis resumes. The time until peristalsis resumes after an injury and/or opioid administration is unpredictable. The only time interval that correlates inversely with the risk of aspiration pneumonitis (i.e. gastric fluid pH <2.5 and volume >0.4 mL/kg) is the interval between the last oral intake and the injury [30]. Bowel sounds alone do not confirm that intestinal peristalsis and gastric emptying have resumed although, if gas is passed, one may conclude that peristalsis has resumed. We consider all children who undergo emergency surgery to be at risk for regurgitation and aspiration of gastric contents and take appropriate precautions including a rapid-sequence induction (RSI) and tracheal intubation to manage the airway.

Table 17.1 American Society of Anesthesiologists physical status classification system

Classification	Explanation
I	A normal healthy patient
II	A patient with mild systemic disease
III	A patient with severe systemic disease
IV	A patient with severe systemic disease that is a constant threat to life
V	A moribund patient who is not expected to survive the operation
VI	A declared brain-dead patient whose organs are being removed for donor purposes.

The addition of "E" denotes Emergency surgery: an emergency is defined as existing when delay in treatment of the patient would lead to a significant increase in the threat to life or body part.

Table 17.2 Fasting intervals before elective surgery

Clear fluids/jello	2 h
Breast milk	4 h
Infant formula/light solids	6 h
Heavy/fatty solids	8 h

Upper respiratory tract infection

Children who have had a recent URTI are at increased risk of perioperative respiratory adverse events after general anesthesia [31]. Ideally, they should not undergo elective anesthesia for 4–6 weeks after the infection to ensure residual pathological effects in the small airways have resolved. However, because many young children have frequent URTIs (6–7 episodes per year), most clinicians will proceed with anesthesia 2–4 weeks after the original infection. In children who present for elective surgery with a URTI, we recommend canceling the anesthetic if any one of the criteria in Box 17.2 is present [32], as each increases the risk of perioperative airway events. For infants <1 year of age, a URTI may herald RSV infection, posing a risk for serious morbidity and increased mortality particularly in preterm infants [33,34].

Children with clear rhinorrhea, whether due to a mild URTI or allergic rhinitis, should receive 1–2 drops of oxymetazoline (0.025%) or phenylephrine (0.125%) nose drops per nostril to reduce nasopharyngeal secretions during anesthesia. We prefer to manage these children with a facemask to reduce the risk of airway reflex responses, but if an airway must be used,

Box 17.2: Criteria for canceling elective surgery in a child with an upper respiratory tract infection (URTI)

1. Fever >38.5°C
2. Behavioral and eating changes
3. Mucopurulent secretions
4. Lower respiratory tract wheezing or rhonchi that do not clear with deep coughing

a supraglottic airway such as a laryngeal mask airway (LMA) is less likely to trigger airway reflex responses than a tracheal tube [35].

Asthma

Up to 20% of children have asthma or an asthmatic history, but significantly fewer present with severe asthma that may complicate anesthesia [36,37]. Children with a history of asthma should have their pulmonary condition optimized and be free of a recent exacerbation or hospitalization for asthma before proceeding with anesthesia [37,38]. The preoperative assessment should elicit the age of onset of asthma, number of and date of the most recent hospital admissions for asthma, current treatment (use of β_2-agonists or steroids by inhalation) and current state of the asthma. Most children have never stayed overnight in hospital for asthma; if they have, the asthma is severe and should be carefully assessed. If oral steroids have been recently prescribed for an acute exacerbation of asthma, careful preoperative examination of the chest must be performed to ensure that there is no lingering reactive airway component. Current evidence indicates that genetic and/or environmental interactions (β_2-adrenergic receptors) may predispose children to the presence and severity of asthma as well as to the individual's responses to β-agonist agents [39–41]. Pediatric anesthesiologists vary in their preoperative management of children with asthma [42]. On the morning of surgery, the child's lungs should be examined for wheezing. Preoperative bronchodilator therapy may be administered to children with mild to moderate asthma who are not wheezing as it reduces airway resistance during sevoflurane anesthesia and tracheal intubation by approximately 25% [43]. If wheezing is present, the child should be instructed to cough deeply to clear secretions present in the airways and bronchodilator therapy should then be administered. If the wheezing persists, the child should be referred to their pulmonologist for reassessment and further treatment, and the anesthetic should be deferred.

For children who present for emergency or urgent non-airway surgery and are wheezing, preoperative bronchodilator therapy should be administered. If tracheal intubation can be avoided, a facemask or LMA should be used. Equipment should be prepared to administer intraoperative bronchodilator therapy should the need arise (see section "Bronchospasm").

Ex-premature infants

Infants who were born premature (<37 weeks' gestational age) and are <60 weeks' postconceptional age (defined as the sum of the gestational and postnatal ages) require 12–24 h of postanesthesia apnea monitoring, irrespective of the nature of the surgery [44]. Some institutions use a younger age cut-off for apnea monitoring, i.e. 46 or 50 weeks' postconceptional age. Factors that increase the risk of perioperative apnea in ex-premature infants include age (<60 weeks' postconceptual age), anemia (Hb <12 g/dL), and a secondary diagnosis (e.g. intraventricular hemorrhage) [44,45]. Caffeine 10 mg/kg intravenously may be administered intraoperatively to reduce the frequency of perioperative apneas, but it cannot be relied upon to eliminate them completely. Once the infant has been apnea free for 12 h, he/she may be discharged home.

In contrast to general anesthesia, regional anesthesia does not appear to confer a similar risk of perioperative apnea and does not require perioperative monitoring unless the infant was also sedated or has multisystem disease or a history of perioperative apneas [46]. Spinal or caudal anesthesia should provide sufficient anesthesia to perform hernia surgery, the most common surgery in ex-premature infants [47]. If the infant is >44 weeks' postconceptional age, he/she may be discharged home from the postanesthesia care unit (PACU) following regional anesthesia alone. If the parents have an apnea monitor at home and have been trained to manage apnea, the child may be discharged home in the parents' care. See Chapter 23 for further discussion of the former premature infant.

Obesity

Obesity is an epidemic, and almost one-third of children worldwide are obese. Because growth in childhood is non-linear, obesity for a particular age of a child and sex is defined as >95th centile for body mass index (BMI; weight/height^2, kg/m^2) on growth curves. Obesity is a multifactorial disorder affecting cardiovascular, respiratory, renal, and endocrine systems and the liver. The severity of these disorders in children is usually relatively minor because the duration of the obesity in children has not been sufficient to adversely affect most organ systems. However, asthma and OSA are more common in obese children [48]. Moreover, nocturnal desaturation may upregulate the sensitivity to opioids (if the nadir of the nocturnal desaturation is <85% repeatedly) in children with OSA. It is important to have empathy for these children and recognize the child's psychological immaturity. These children are often emotionally unprepared for the stress of surgery and serious consideration should be given to preoperative anxiolysis for them.

Complications in the perioperative period occur more commonly in obese children compared with asthenic children, particularly airway and respiratory adverse events in terms of mask ventilation, laryngospasm, oxygen desaturation, and bronchospasm [49].

Before induction of anesthesia, the child should be positioned 45° head up to optimize preinduction oxygenation [50]. Airway management requires meticulous attention to maintaining a patent upper airway using a jaw thrust together with continuous positive airway pressure. Tracheal intubation is not difficult providing the occiput is elevated (double the usual displacement) such that in the profile view the tragus is above the level of the sternal notch [51]. During surgery, positive end-expiratory pressure should be applied to prevent atelectasis.

The greatest challenge in obese children is to determine the appropriate scalar for drug dosing. Total bodyweight is comprised of fat and fat-free masses. The fat mass is the depot in which lipophilic drugs are sequestered whereas the fat-free mass is the depot in which hydrophilic drugs are deposited. The fat-free mass is analogous to the lean body mass or the sum of the ideal body mass plus the mass that has accrued to support the physical and metabolic demands of the fat mass (i.e. excess weight in muscle, heart, liver, and other organs). Equations for the ideal bodyweight are shown in Box 17.1). The lean or adjusted body mass is the ideal bodyweight plus 0.3 or 0.4 of the difference between the total bodyweight and

Table 17.3 Tissue/blood partition coefficients for inhaled agents and nitrous oxide

Partition coefficients	Sevoflurane	Desflurane	Isoflurane	Enflurane	Halothane	Nitrous oxide
Blood:gas	0.65	0.42	1.46	1.9	2.4	0.46
Brain:blood	1.7	1.3	1.6	1.4	1.9	1.1
Muscle:blood	3.1	2.0	2.9	1.7	3.4	1.2
Fat:blood	47.5	27.2	44.9	36	51.1	2.3

ideal bodyweight. Loading doses depend on the volume of distribution of the drug; these have been reported in obese children [52,53]. The maintenance doses of anesthetics depend on the clearance of the drugs, and many of these have been reported [52,53].

Inhalation agents partition among the fat mass and the fat-free mass depending on their tissue solubilities and the duration of exposure: sevoflurane > isoflurane > desflurane > nitrous oxide (Table 17.3) [54]. Although sevoflurane is the preferred induction agent, desflurane and nitrous oxide are the preferred maintenance agents for surgery >2 h based on their fat solubilities (see Table 17.3). The latter two agents facilitate a rapid decrease in the context-sensitive half-life and therefore recovery from anesthesia [55]. See Chapter 10 for further discussion of pharmacology and Chapter 24 for further discussion of obesity.

Full stomach and rapid-sequence induction

The term "full stomach" refers to the possible presence of residual solid or liquid food in the stomach at induction of anesthesia and is usually associated with hypokinetic or akinetic intestinal peristalsis. In such cases, the child is at risk for regurgitation and possibly aspiration of residual gastric contents into the lungs during general anesthesia and sedation, a potentially fatal perioperative complication. The full stomach occurs most often during emergency surgery, but also in children with gastric dysmotility syndromes and diabetes. In most cases of emergency surgery, the time interval between ingestion of food and induction of general anesthesia is too brief to ensure complete evacuation of the gastric contents. The trauma, pain, and stress of the injury, coupled with the administration of opioids, lead to gastric and intestinal paresis and food remaining in the stomach for a prolonged period.

There are three important principles to remember in such cases. (1) There is no safe time interval after an injury that guarantees the stomach is empty of food. (2) There is no safe time interval after an injury that guarantees no risk of regurgitation of food present in the stomach. (3) All children (even those treated with prokinetic motility medications) are at risk for regurgitation and aspiration during induction of, maintenance of, and emergence from anesthesia.

The only variable that has been associated with an increased gastric fluid volume and decreased pH after a trauma is the time interval between the last ingested food and the occurrence of the trauma. The smaller the interval, the greater the risk that a large gastric volume and reduced pH are present [30].

To protect the airways in children who are at risk for regurgitation and aspiration during induction of anesthesia, rapid-sequence induction (RSI) was created to swiftly establish anesthesia and secure the airway expeditiously and safely. Although there is no evidence that RSI is the optimal strategy to prevent regurgitation, it seems sensible to induce anesthesia quickly and insert the tracheal tube into the larynx as quickly as possible. In order to perform RSI, one must prepare the appropriate equipment (see Box 17.3).

In most institutions, RSI is performed using intravenous anesthesia. The most common induction agent is propofol (2–4 mg/kg), although ketamine (1–2 mg/kg) and etomidate (0.2–0.3 mg/kg) may be used for hemodynamically unstable children. We recommend intravenous (IV) succinylcholine 2 mg/kg (preceded by atropine 0.02 mg/kg) for paralysis, although rocuronium 0.8–1 mg/kg has also been used. However, if the airway appears to be difficult or precarious, alternative strategies to secure the airway should be considered, including an inhalation anesthetic or topical local anesthetic and total intravenous anesthesia (TIVA). If an inhalation induction is performed, the child may need to be turned to the left lateral decubitus position emergently if regurgitation occurs. Topically anesthetizing the airway during TIVA while maintaining spontaneous respiration may be required.

There is much debate regarding the importance and relevance of cricoid pressure, a key element in RSI [56]. Currently, there is no evidence to support or refute the use of cricoid pressure during RSI. However, there are some concerns regarding the application of cricoid pressure in infants and children. In young children, the cricoid ring and trachea are

Box 17.3: Rapid-sequence induction for children

Pre-induction

- Laryngoscope handle/blades sized for age
- Age-appropriate tracheal tubes with a stylet
- Active Yankauer suction
- Induction agents and muscle relaxants in weight-appropriate doses
- Preoxygenation through a tight-fitting mask and breathing circuit (as tolerated)
- Optimal positioning of the head and neck
- Suction and removal of an existing nasogastric tube

Induction

- Rapid intravenous induction of anesthesia using predetermined drug doses
- Cricoid pressure, if utilized, should be age appropriate and not compress or distort the airway
- Maintenance of a tight facemask seal (100% O_2) without assisted ventilation (except for infants)
- Once fasciculations are visible after succinylcholine or suppression of the twitch response after a non-depolarizing relaxant, laryngoscopy and tracheal intubation are performed rapidly
- A predetermined size tracheal tube is then inserted
- If a cuffed tracheal tube is used, the cuff is inflated before the lungs are auscultated. Cuff pressure is adjusted once auscultation is performed

mobile and deformable. In fact, a force of only 10 Newtons can compress the lumen of the airway by 50% in young children, one-third the force recommended for cricoid pressure in adults [57]. Cricoid pressure may also increase the difficulty of tracheal intubation by distorting the anatomy or compressing the cricoid ring. Very few assistants are trained properly in the location of the cricoid ring and in the magnitude of the force required to occlude the esophagus [58,59]. It remains our view that cricoid pressure is not required for RSI to be a rapid and safe technique to secure the airway in children.

Malignant hyperthermia

Preparation of the anesthetic machine for an elective case of malignant hyperthermia (MH) begins with scheduling the child as the first case of the day since the concentration of inhaled anesthetics in the operating room is at its nadir if the room is unused overnight [60]. The vaporizers should be removed from the machine, the anesthetic breathing circuit and carbon dioxide canister replaced with new equipment, and the anesthetic workstation purged of all residual inhalation anesthetic by flushing the machine with a fresh gas flow of ≥10 L/min (air/oxygen mixture) while the ventilator is operating. Although the threshold vapor concentration above which MH reactions occur is unknown, older studies aimed to reduce the inhaled agent concentration in the machine to ≤10 ppm whereas the Malignant Hyperthermia Association of the United States (MHAUS) currently recommends limiting the concentration of triggering anesthetic to <5 ppm; neither concentration is measurable without sophisticated detectors. The times required to purge all anesthetic workstations to these trace concentrations of inhalational anesthetics vary 15-fold, from 10–15 min for the Datex-Ohmeda Excel workstation to 140 min for the Drager Fabius CE (Table 17.4) [60]. To reduce the flush times of the latter to <10 min, one may replace the integrated breathing circuit with autoclaved circuit components or insert a charcoal absorbent filter into the inspiratory (and expiratory in the case of a full-blown MH reaction) limb of the breathing circuit [61].

Table 17.4 Time to wash out inhalational anesthetics to less than 10 ppm

Anesthetic workstation	Time (min)
Datex-Ohmeda-GE	
Modulus 1	5–15
Excel 210	7
AS/3 c	30
Aestiva (sevoflurane)	22
Aisys (sevoflurane)	25
Avance	39
Other	
Narkomed (Dräger)	20
Dräger Primus	39–70
Dräger Fabius GS	104
Dräger Zeus	35–85
Kion (Siemens)	>25
Perseus (Dräger)	15
Felix AInOC (Taema, Air Liquide)	135
Flow-i b (Maquet)	46
Leon (Heinen + Löwenstein GmBH)	106

Once the breathing circuit has been flushed, a trigger-free anesthetic regimen including propofol, opioids, non-depolarizing muscle relaxants, nitrous oxide, benzodiazepines, and regional anesthesia may be used [60]. In addition to the basic monitors, end-tidal CO_2 (the earliest sign of an evolving MH reaction) and temperature should be monitored. IV dantrolene (Revonto, Louisville, KY) should be available in sufficient quantity to treat, should a reaction occur (2.5 mg/kg IV based on total bodyweight stops most reactions, but doses as great as 10 mg/kg or greater may be necessary). This preparation is lyophilized dantrolene, 20 mg/ampoule containing 3 g mannitol and an adjusted pH 9.8. The elimination half-life of intravenous dantrolene is 10 h; recrudescence may occur after 6 h when the blood concentration of dantrolene is below the 3 μg/mL threshold [62]. Redosing the dantrolene at half the original dose at 6 h will prevent recrudescence. Ryanodex (Eagle Pharmaceuticals, Woodcliff Lake, NJ) is a new rapidly soluble formulation of dantrolene that includes 250 mg of dantrolene with only 125 mg mannitol and requires only 5 mL water for dissolution [60]. There is no role for prophylactic preoperative dantrolene in children with MH. Children who are MH susceptible may undergo ambulatory surgery provided they are observed for signs of MH for about 2 h postoperatively and given instructions to call the anesthesiologist on call for a fever that does not respond to acetaminophen or signs of MH for 24–48 h after discharge. Chapter 45 contains additional information about MH.

Myopathies [63,64]

The muscular dystrophies, Duchenne (DMD), Becker (BMD), and Emery–Dreifuss (EDMD), are X-linked degenerative muscle dystrophies that demonstrate progressive weakness first in the skeletal muscles and later the cardiac muscles at varying rates. The pathogenesis of the dystrophies is the absence of dystrophin (<3% of normal) in skeletal muscle. As a result, administration of an inhalation anesthetic (halothane >> sevoflurane) with or without succinylcholine destabilizes the muscle membrane causing rhabdomyolysis, hyperkalemia, and myoglobinuria [65]. DMD, which occurs in 1:3500 of the population, affects skeletal muscles in young males (<8 years of age) [63]. As these children reach adolescence, the skeletal muscle wasting wanes and the predominant effect is a progressive cardiomyopathy. BMD is a milder form of muscular dystrophy, with a later onset (second decade) and a much less frequent occurrence of 1:50,000. Cardiac involvement in BMD consists of dilated cardiomyopathy in one-third of those affected, as well as hypertrophic cardiomyopathy and arrhythmias [66]. In the case of EDMD, this rare defect stems from mutation in genes that encode for emerin and the lamins A and C in skeletal muscle membrane [63]. The inheritance pattern, X-linked or autosomal dominant, leads to the slow progression of contractures, muscle wasting and weakness, and cardiac conduction defects (from sinus bradycardia to complete heart block leading to syncope) or a generalized cardiomyopathy. Hence, preoperative echocardiogram and electrocardiogram are warranted before anesthetizing these adolescents.

The interaction between anesthetics and mitochondrial myopathies is far less clear [67]. Those infants who develop lactic acidosis in association with their mitochondrial myopathy should receive normal saline (with glucose as needed) for their IV solution rather than lactated Ringer's solution.

Although MH is associated with only two muscle disorders, the King–Denborough and central core diseases, rhabdomyolysis as a distinct entity can theoretically occur in children with mitochondrial myopathies who receive an inhalation anesthetic. Hence, it is reasonable to purge the anesthetic workstation of inhalational agents and avoid triggers. Even though many children with mitochondrial myopathies have received inhalation anesthesia without complications, it seems reasonable to consider alternative anesthetics (e.g. TIVA) when possible. See Chapters 33 and 43 for further discussion of myopathies.

Sickle cell disease

Sickle cell disease (SCD) or sickle cell anemia occurs primarily in children of Sub-Saharan descent, with a frequency in North America of 1:5000. Characterized by an autosomal recessive inheritance pattern, this defect is a single nucleotide polymorphism of glutamate for valine on chromosome 11 that results in the replacement of Hb AA with Hb SS in every red blood cell. Homozygous individuals have the full-blown disease, SCD, whereas heterozygous individuals have an asymptomatic version, known as sickle cell trait (SCT). In children with SCD, 100% of the cells are at risk for sickling; these children have chronic low hemoglobin concentrations (6–8 g/dL), may have acute vaso-occlusive crises, and may receive multiple red blood cell transfusions. The vaso-occlusive crises involve a number of organs including bone, chest, and brain, arise almost randomly, occur in some children more than others, are unrelated to the presence of hypoxia, hypovolemia, or hypothermia, and may be fatal [68]. Evidence now suggests that those with SCD who develop vaso-occlusive crises have markers of a systemic inflammatory response to the disease which upregulates endogenous factors, including an adhesive factor, which traps sickle red cells in arterioles and precipitates occlusive crises [69]. Whether the traditional factors of hypoxia, hypovolemia, and hypothermia exacerbate the initial process or compound the inflammatory process has not been clearly established.

Sickle cell may also present in a heterozygote form, Hb AS, known as sickle trait. Children with Hb AS have normal hemoglobin concentrations; they are unlikely to sickle or present complications during most anesthesia and surgery, providing extreme conditions such as hypothermia or cardiopulmonary bypass are not employed. Two additional hemoglobinopathies, Hb SC and Hb SD, occur less frequently in the population than Hb SS; the hemoglobin concentrations in these children are also normal, but they are as likely to sickle as those with Hb SS.

SICKLEDEX® (Streck Inc., La Vista, NE, USA) is a screening test that determines the presence of sickle hemoglobin in blood without, however, differentiating between SCD and SCT. It can be performed rapidly, inexpensively, and reliably in infants >6 months of age. In infants <6 months of age, however, the presence of Hb F interferes with the SICKLEDEX test, rendering the results non-confirmatory. In fact, infants <6 months of age rarely sickle because of the presence of Hb F. The definitive diagnostic test for the type of sickle hemoglobin is hemoglobin electrophoresis or high-performance liquid chromatography. These tests identify the specific normal and abnormal hemoglobins present in blood in infants and children of any age.

To attenuate the risk of a perioperative sickle crisis during elective surgery in children with SCD, some hematologists recommend transfusing packed red cells to increase the total hemoglobin of 10 g/dL [70]. This practice was shown to reduce the frequency of acute vaso-occlusive crises in children with SCD. Others disagree with both the practice of prophylactic blood transfusions as well as the indications for transfusions in children undergoing minor surgery. The disadvantages of frequent transfusions in children who are at risk for sickle crises include sensitizing the recipient to minor antibodies (i.e. Kell and Duffy), iron overload, and transfusion reactions. For surgeries and conditions in which the risk of sickling is great, exchange transfusion is advisable to reduce the percent of cells that are capable of sickling. It is important to consult your local hematologist regarding the institutional management of children with SCD before the day of surgery to avoid surgical delays. See Chapters 12 and 24 for further discussion of sickle cell disease.

Anterior mediastinal mass

Children with an anterior mediastinal mass (AMM) present a life-threatening risk for anesthesia when they present for a tissue (lymph node) biopsy, CT scan for diagnosis, or indwelling central line for chemotherapy [71]. These tumors grow (in some cases, very rapidly) in a small and confined space, the anterior mediastinum. In this space, growing tumors can compress vulnerable mediastinal structures, specifically the tracheobronchial tree and/or right side of the heart (superior vena cava, right atrium, or pulmonary artery). Four tissues can be found in AMMs in children: lymphomas, teratomas, thymomas, and ectopic thyroid masses. The most rapidly growing tumor in the anterior mediastinum is the lymphoblastic lymphoma, a non-Hodgkin lymphoma with a doubling time of only 12–24 h. These children may present with minor findings (e.g. night sweats) that rapidly progress over 1–2 days to life-threatening symptoms (e.g. orthopnea, superior vena cava syndrome). In children, investigating the effects of the tumor on the mediastinal structures as well as acquiring tissue for the cell type usually requires general anesthesia. The decision to proceed with local or general anesthesia depends on the age and level of cooperation of the child, the extent of mediastinal organ compromise, and the accessibility of the node or tumor for biopsy. All radiological and preoperative data should be reviewed by a multidisciplinary team that involves the surgeon, anesthesiologist, and oncologist before embarking on the surgery.

In children who can tolerate local anesthesia and sedation, the decision to proceed with the surgery is clear. However, for children who cannot tolerate local anesthesia with sedation and who have tumors that severely compromise the airway and/or pulmonary artery, steroids or radiation should be considered for 12–24 h to shrink the tumor (usually a lymphoblastic lymphoma). The risks associated with prediagnosis treatment include tissue necrosis that may render diagnosis of the tumor cell type difficult and the development of tumor lysis syndrome. As a result, many oncologists are reluctant to treat these children with steroids or radiation, even for brief periods, before establishing the diagnosis. Determining the tumor cell type is critical to ensuring the most appropriate treatment regimen and minimizing complications.

Box 17.4: Cardiac indications for infective endocarditis prophylaxis

1. Prosthetic cardiac valve
2. Previous infective endocarditis
3. Cardiac transplantation children who develop a valvulopathy
   Congenital heart disease (CHD):
   i. Unrepaired cyanotic heart disease (including palliative procedures)
   ii. Repaired CHD with prosthetic material or device during the first 6 months after procedure
   iii. Repaired CHD with residual leak at or adjacent to prosthetic patch or device

For most children who require radiological investigation, tumor biopsy, or chemotherapy access, general anesthesia with spontaneous respiration is ideal. If the child cannot lie flat, preparations must be made to induce anesthesia and intubate the trachea with the child in the left lateral decubitus position. We recommend that the trachea is intubated at induction of anesthesia to secure the airway should the child have to be turned prone to maintain cardiorespiratory homeostasis. We also caution against using muscle relaxants to facilitate tracheal intubation in order to maintain spontaneous respiration and keep the tumor from pressing on the heart. It is important to recognize that the capnogram may be the key to establishing whether pulmonary circulation (and cardiac output) is present; sudden compression of the pulmonary artery will either reduce the end-tidal CO_2 level of the expiratory plateau or abolish it altogether before systemic manifestations are present. See Chapter 26 for further discussion of AMM.

Infective endocarditis prophylaxis

In 2007, the American Heart Association extensively revised the indications for infective endocarditis (IE) prophylaxis [72]. The new recommendations were crafted for dental procedures and adopted by the dental societies. Prophylaxis is no longer recommended for IE in children undergoing routine gastrointestinal, urological, and genitourinary surgeries although many specialists in these areas continue to request endocarditis prophylaxis. Also, there must be a cardiac, as well as a procedural indication for IE prophylaxis. Accordingly, it is incumbent upon the anesthesiologist to communicate with the specific specialist to determine whether endocarditis prophylaxis should be administered.

For dental procedures, Box 17.4 presents the only cardiac indications for IE prophylaxis. The antibiotic regimen for endocarditis prophylaxis has not significantly changed since it was previously published [72,73].

KEY POINTS: EVALUATION OF PREOPERATIVE DATA

- There is no substitute for a thorough, detailed history, and physical examination during preoperative evaluation
- Children should not be subjected to prolonged preanesthetic fasting; clear liquids can be ingested until 2 h before induction in most patients
- Preoperative testing is guided by the patient's underlying conditions and surgical procedure, and is not automatically done if not needed
- Upper respiratory infections, asthma, prematurity, and obesity are commonly encountered and deserve special attention and anesthetic planning

Preparation of operating room, equipment, and monitors

Anesthetic workstation

A thorough machine check must be completed before commencing the anesthetic. Modern anesthetic machines provide complete start-up checks that, for the most part, are entirely automated. These will be machine specific, must be performed unless there is insufficient time due to a pending emergency, and are not discussed any further. Refer to the operations manual for the specific machine to conduct the machine check.

As part of the anesthetic workstation preoperative evaluation, the emergency tank pressures must be checked. An emergency oxygen cylinder is required on all machines should the line oxygen supply fail. Because oxygen is a gas in pressurized cylinders, the pressure in the tank decreases linearly as the tank empties. The volume (in liters) of oxygen that is present in the emergency E cylinder is the product of the number of liters of oxygen in a full cylinder (680 L) and the ratio of the pressure within the tank to 2200 psi (the pressure of a full cylinder of oxygen). The number of minutes of oxygen remaining in the E cylinder for a given oxygen flow rate (Q) (with the ventilator turned off) is:

$$\text{Time}\,(\text{min}) = \frac{\text{Tank pressure}\,(\text{psi}) \times 0.28}{\text{Q}\left(\frac{\text{L}}{\text{min}}\right)}$$

A source of air should also be available in order to deliver less than 30% oxygen for infants at risk for oxygen toxicity and for those with congenital heart disease in whom excess oxygen may cause excess pulmonary blood flow (i.e. hypoplastic left heart syndrome). This is usually provided by a wall source, although an emergency air cylinder should be available. Supplementary nitrous oxide cylinders are not essential to maintain anesthesia should the wall source fail. Moreover, they can be a source of operating room pollution and costly to replace. Nitrous oxide in E cylinders contains both liquid and gaseous nitrous oxide at 745 psi. The pressure within the cylinder remains constant until all of the liquid nitrous oxide has evaporated. Up to that point, the content of nitrous oxide cylinders can only be determined by their weight. When the pressure gauge on the cylinder begins to decrease, the cylinder is nearing empty and must be replaced quickly.

Anesthetic equipment

To ensure that the anesthetizing location is properly and completely prepared, it is useful to refer to a checklist as shown in Box 17.5, the SALTED mnemonic.

Box 17.5: SALTED mnemonic

S	Suction, stylet and solution (IV fluids Ringer's lactate or normal saline)
A	Airways oral and nasal – different sizes
L	Laryngoscope – Miller blades from sizes 0–3; MAC 2 or 3
T	Tubes – tracheal tubes of appropriate sizes, tape
E	Equipment – anesthesia machine with breathing circuit, McGill forceps, facemasks, back-up self-inflating AMBU bag, fluid warmer, venous cannulation kit, and standard monitors
D	Drugs (anesthesia and resuscitation drugs)

Airway

Appropriately sized equipment should be available for each child. A range of sizes of facemasks, oral airways, laryngoscope blades, tracheal tubes, and LMAs should be present. We prefer cushioned clear facemasks that fit the contour of the faces of all children and permit the rapid identification of either fluid or solid material within the mask. The importance of oral airways in establishing a patent upper airway in children has been supplanted in our practice with the jaw thrust maneuver (see section "Laryngospasm"). We advocate the use of a Miller or Wisconsin straight blade for tracheal intubation in infants and children although when used properly, these blades are as effective for laryngoscopy as the Macintosh blade in this age group [74]. A range of sizes of laryngoscope blades should be available in every anesthetizing location. We advise against placing a roll under the shoulder of neonates and infants during laryngoscopy unless the laryngoscopist is seated; the shoulder roll raises the larynx, which is already anterior and cephalad in the neonate compared with older children, making it more difficult to align the axes while the laryngoscopist is standing. In neonates with limited oxygen reserve or when an awake intubation is being performed, a straight blade fitted with a source of oxygen at the tip may prevent desaturation during laryngoscopy [75].

The classic laryngeal mask airway (cLMAs–LMA® Classic™ Airway, Teleflex® Medical Europe, Westmeath, Ireland) was introduced to replace the facemask in adults and has subsequently proven to be a versatile and useful airway device in children as well [76]. To fit pediatric airways, the dimensions of the adult cLMA were scaled down in size, although the mask was otherwise unmodified. The cLMA has proven to be effective in circumstances other than elective anesthesia, such as neonatal resuscitation and fiberoptic intubation. A range of sizes of the cLMA should be available (Table 17.5).

Although effective, the cLMA does not "protect" the airway from regurgitation and laryngospasm. Since the tone of the gastroesophageal sphincter is reduced in children compared with adults, children may be at greater risk for regurgitation in the presence of a full stomach or positive pressure ventilation. Hence, it is best to avoid LMAs in these clinical situations. Modifications of the cLMA to include a vent for regurgitant gas or liquid from the esophagus as in the LMA®-ProSeal™ (Teleflex® Medical Europe, Westmeath, Ireland) supraglottic airway may better protect the airway against aspiration. A recent meta-analysis of a range of supraglottic devices concluded that in children the LMA-Proseal airway may be the preferred airway as it has the greatest leak pressure and smallest risk of difficulty seating [77].

Table 17.5 Airway equipment

Laryngoscope blade size		
Age (years)	**Miller blade size**	
0–0.5 years	Miller 0	
0.5–2 or 3 years	Miller 1	
2–4 years	Miller 1.5	
3–8 years	Miller 2	
Classic LMA size		
Weight (kg)	**LMA size**	**Max. ETT size**
0–5 kg	#1	3.5 mm ID
5–10 kg	1½	4.0
10–20 kg	2	4.5
20–30 kg	2½	5.0
30–50 kg	3	6.0

ETT, endotracheal tube; ID, internal diameter; LMA, laryngeal mask airway.

Complications of the cLMA in children include gastric inflation, aspiration, airway obstruction, and laryngospasm. The frequency of complications with the cLMA in infants may be greater than that in older children; caution should be exercised when using LMAs in children <2 years [78]. Fiberoptic studies have demonstrated that the epiglottis folds down into the bowl of the cLMA in an otherwise properly functioning device, although the relevance of this finding remains unclear.

A range of diameters of tracheal tubes should always be available for the child's age as well as tubes 0.5 mm ID smaller and larger. The appropriate size of uncuffed tracheal tube is based on the ID of the tube. Guidelines for tracheal tube sizes in infants and children are: infant's weight <1500 g, 2.5 mm ID; 1500 g to full-term gestation, 3.0 mm ID; neonate to 6 months of postnatal age, 3.5 mm ID; and 0.5–1.5 years, 4.0 mm ID. The uncuffed tube size for children ≥2 years may be estimated using the formula: age (in years)/4 + 4 (or 4.5) mm ID. For cuffed tubes popularized by the high-compliance, low-volume Microcuff® (Halyard Health, Alpharetta, GA, USA) tubes, the tube size (mm ID) for children <2 years is estimated as age (in years)/4 + 3 and for children >2 years, age/4 +3.5.

The length of a tube from the lips to mid-trachea in infants <1000 g in weight is 6 cm, 1000–2500 g is 7–9 cm, in neonates 10 cm, and in infants and children, 10 + age (years) cm.

In the past, uncuffed tracheal tubes were the mainstay for securing the airway in children <8 years of age. The circular shape of the tracheal tube was similar to the shape of the lumen formed by the cricoid ring, allowing a good seal to form without the need for a cuff. Cuffs were avoided in children out of the concern that the loosely adherent pseudostratified columnar epithelium within the cricoid ring would swell and further encroach on this narrowest portion of the upper airway, resulting in stridor, upper airway resistance, and respiratory failure. Because airflow within the upper airway is turbulent, a 50% reduction in the radius of the airway would increase the resistance to airflow by the fifth power of the radius or 32-fold. This increase in resistance would rapidly lead to respiratory distress, fatigue, and ultimately respiratory failure in young infants and children, particularly if they

were also septic. To preclude this potentially serious airway problem in the perioperative period, in addition to avoiding cuffed tubes, we carefully selected the tracheal tube in children which either passed through the cricoid ring without resistance or did so with an audible leak at a peak inspiratory pressure of ~20 cmH_2O. If an audible leak were present at a peak airway pressure ≤10 cmH_2O, the tracheal tube would be changed to one with an ID 0.5 mm greater, otherwise ventilation may prove to be inadequate during the surgery. Before proceeding, the peak inspiratory pressure at which a leak was audible would be retested. This process would be repeated until a satisfactory sized tube was present.

Recently, the shift from uncuffed to cuffed tracheal tubes in children has been in no small part facilitated by the introduction of the soft, high-compliance cuffed Microcuff tube [79]. These tubes have no Murphy eye. Their polyurethane cuff is positioned very close to the tip of the tube, with a cylindrically shaped rather than spherically shaped cuff as in low-compliance cuffed tubes, mimicking the shape of the larynx. The Microcuff tubes confer several additional advantages over the traditional uncuffed tubes, including decreased contamination of the operating room with anesthetic gases, reduced number of laryngoscopies and reintubations, and more consistent tidal volumes (as chest wall and abdominal compliance change during surgery) [80]. Overall, these factors substantially reduce the number of manipulations of the airway in children, the operating room costs, and operating room pollution. However, several relatively small sized studies reported a similar incidence of complications in children with high-compliance cuffed and uncuffed tubes [81,82]. A recent Cochrane review concluded that the results of published studies were of low quality and failed to prove either tube type was superior to the other [83].

A functioning wall suction with suction tubing (that is long enough to reach the operating room table) and a plastic Yankauer suction tip is mandatory. Yankauer suction must be used carefully to avoid trauma to oropharyngeal tissues. To achieve this in young children who have not received their molar teeth, the Yankauer should be inserted between the cheek and the teeth and passed behind the premolars to reach the hypopharynx. With this approach, the child cannot damage their central incisors if they bite down on the suction while it is in the mouth. In addition, the suction should sweep the hypopharynx to avoid applying prolonged negative pressure to tissues (such as the uvula) that may lead to edema and bleeding. We prefer to use a Yankauer suction rather than a suction catheter in the operating room because the former is capable of suctioning large volumes of blood, thick secretions, and/or vomitus expeditiously should the need arise, and the latter is often difficult to pass into the hypopharynx.

The optimal ventilation strategy for infants and children during surgery has been the subject of much interest [84]. For many years, volume-controlled pressure-limited ventilators were the standard for ventilating the lungs of infants and children during surgery. However, these ventilators could not compensate for either the circuit compliance or the variable leak around the tracheal tube. There was additional concern regarding the shape of the pressure tracing during inspiration and the risk of delivering high pressures. Pressure-controlled ventilation has been used successfully in the neonatal intensive care unit (NICU) for many years, in part because it limited the peak pressure and avoided barotrauma with its constant inspiratory pressure pattern. It also provided a more even distribution of inspiratory gas in the lungs, thus reducing ventilation/perfusion (V/Q) mismatch. Despite the clear advantages of the pressure-controlled ventilation strategy, many anesthesia ventilators were simply unable to ensure reliable tidal volumes as they failed to compensate for decreases in the compliance of the abdomen and chest as a result of external pressure by the surgeons, their instruments, or peritoneal insufflation of the abdomen or chest during laparoscopy. A new generation of anesthetic machines offers markedly improved ventilators and ventilation strategies that are hybrids of the best aspects of both volume- and pressure-regulated ventilation. These new ventilators may prove to be ideal for infants as small as preterm and term neonates. The hybrid pressure-regulated volume-controlled mode in which a fixed tidal volume, which accounts for the compressible volume of the breathing circuit, is used during controlled ventilation and a pressure support mode, is used once spontaneous respiration commences. With all ventilators that are used in small neonates, it is essential to avoid barotrauma by presetting weight-appropriate respiratory parameters before commencing ventilation.

Emergency drugs

Emergency drugs should always be available before inducing anesthesia. Syringes of weight-appropriate doses of atropine and succinylcholine should be immediately available with a small gauge (23 or 25 G) needle to facilitate intramuscular or sublingual injection in an emergency. A syringe of propofol (1–2 mg/kg) should also be available to facilitate tracheal intubation or LMA insertion, as well as to break laryngospasm and increase the depth of anesthesia quickly [85]. Vasopressors and inotropic drugs are not routinely prepared for healthy children undergoing elective surgery, but may be prepared for children with congenital heart disease or those who are unstable hemodynamically.

Monitors

The ASA and similar authorities all over the world mandate basic monitoring for all anesthetics (Box 17.6). Monitoring children during anesthesia must include the standard five parameters: electrocardiogram, blood pressure, oxygen saturation, capnogram, and temperature, as well as any additional monitors specific for the child's medical or anesthetic condition, such as a depth of anesthesia monitor. Many infants and preschool age children do not accept the application of monitors while they are awake. Although induction of anesthesia is usually well tolerated and safe in expert hands, we recommend that every effort should be made to apply at least a pulse oximeter before anesthesia is induced. The remainder of the monitors should be applied as soon as the child loses consciousness.

Electrocardiogram

A standard three- or five-lead continuous electrocardiogram should be used in every anesthetic to detect arrhythmias (bradycardia) and peaked T waves or ST segment changes (hyperkalemia or local anesthetic). The most common rhythm disturbance in healthy children is bradycardia; ventricular

Box 17.6: Basic mandatory monitoring for anesthesia and other monitors

- Electrocardiogram
- Arterial blood pressure
- Pulse oximetry
- End-tidal CO_2
- Temperature
- Secondary optional monitors
  - anesthetic depth monitoring
  - cerebral oxygenation monitoring
  - invasive monitors

Box 17.7: Causes of bradycardia

1. Hypoxia
2. Vagal reflex response (e.g. prolonged laryngoscopy, traction on the extraocular muscles)
3. Medication (e.g. succinylcholine)
4. Congenital heart defect, cardiac conduction defect, heart failure, and cardiomyopathy
5. Raised intracranial pressure
6. Electrolyte imbalance (hyperkalemia, hypocalcemia)
7. Massive air embolism
8. Tension pneumothorax

arrhythmias are exceedingly uncommon. The most common causes of bradycardia in children are hypoxia and vagal reflex responses but bradycardia may transiently occur during induction of anesthesia with sevoflurane (Box 17.7). The most common causes of ventricular arrhythmias in children are hyperkalemia and intravascular injection of an amide local anesthetic.

Blood pressure

Blood pressure is usually measured non-invasively using an automated oscillometric technique every 3–5 min during elective surgery. The cuff width should cover approximately two-thirds the length of the humerus. In children, systolic pressure is used as a measure of the volume status and, second, cardiac function. Diastolic pressure is not as closely regarded as peripheral vascular resistance is low in infants and children. Invasive pressures are usually reserved for surgeries that may be prolonged, those associated with large blood loss or congenital heart disease, or for sick children who require inotropic support or repeated blood gas measurements.

Pulse oximetry

Pulse oximetry displays the hemoglobin oxygen saturation by measuring the transmittance of two wavelengths of red light, 660 and 940 nm, through the blood in arterioles, and in most critical care settings changes pitch as the saturation decreases. The probe is commonly affixed to a digit, but may also be applied to the earlobe, the hypothenar eminence, or lateral aspect of the foot in infants. Finally, most oximeters include motion-artifact compensation software to display the oxygen saturation continuously, even if the child is moving, as is often the case during induction or emergence from anesthesia. Pulse oximetry measures accurate saturations between values of 70% and 100%. Most nail polishes do not interfere with the accuracy of oximeter readings, although we prefer that the oximeter be applied to an unpainted surface. Pulse oximeters may fail to detect a pulse in the presence of a low cardiac output, low blood pressure, hypothermia, or vasculopathy. It should be noted that carbon monoxide is neither sensed nor measured by current standard pulse oximeters (Masimo Rainbow SET™, Masimo Corp., Irvine, CA, USA, is one example of a device that can measure carboxyhemoglobin). The importance of oximetry cannot be overstated, with the incidence of desaturation reported to increase with decreasing age [86]. However, this review expressed the view that caution should be exercised when extracting desaturation rates from automated record-keeping systems as up to 35% of recorded hypoxemic events were due to factors other than hypoxemia.

Capnography

Infrared analysis of the end-tidal carbon dioxide tension in the breathing circuit has been used to estimate the partial pressure of carbon dioxide in blood. Two distinct techniques have been used to display the end-tidal carbon dioxide tension: sidestream capnography, which continuously aspirates gas from the breathing circuit and analyzes the carbon dioxide tension in a remote sensor; and mainstream capnography, which analyzes the carbon dioxide tension directly within the breathing circuit. The accuracy of sidestream capnometry improved dramatically when circle system breathing circuits replaced T-piece circuits, by reducing the dilution of expiratory gas. Sidestream capnometry measured at the elbow of the circle breathing circuit is accurate even in infants as young as neonates (with small tidal volumes) without cyanotic heart disease. Alternatively, mainstream capnography may be used, although this technique is unpopular, particularly in infants and neonates, because they increase the deadspace in the circuit and the bulky and heavy sensors may kink small pediatric tracheal tubes. A range of light, small-deadspace, mainstream capnography sensors, marketed as cap-ONE (Nihon Kohden, Surrey, UK), can be utilized with facemasks and tracheal tubes, with applications both in pediatric and adult settings [87]. Recent studies have pointed towards a high degree of accuracy. Capnography may also be accurately monitored at the elbow of a circle circuit while the child breathes through a facemask, and through baffled nasal prongs during sedation.

Temperature

With induction of anesthesia, children redistribute heat from the core to the periphery via peripheral vasodilatation. Heat loss from the body occurs by four routes in the following proportions in children: 39% by radiation, 34% by convection, 24% by evaporation, and 3% by conduction [88]. To preclude substantial heat loss, the following strategies should be utilized.

As soon as the case is scheduled or the operating room is vacated by the previous patient, the operating room temperature is increased to ~28°C, which may take up to 1 h to achieve. Increasing the temperature within the operating room increases both the temperature of the walls and ceiling as well as the air within the room, thereby attenuating both radiation and convective heat losses [88]. Forced air warmers are the

single most effective strategy to minimize heat loss for any surgery of 1 h duration or greater [89]. Although it is comforting to prewarm the air mattress before the child enters the operating room, commencing the forced air warmer before the child is anesthetized does not alter their temperature at the end of surgery, however it may predispose to airborne contamination of the operating room, resulting in the possibility of a surgical site infection [90]. Until further evidence is forthcoming, we recommend that forced air warmers be switched on after the skin is prepped and draped for surgery.

Supplemental warming devices such as warming blankets, overhead heat lamps, and fluid warmers should also be available for infants to maintain normothermia should the need arise.

The temperature of all children who receive anesthesia or sedation should be monitored continuously during surgery and in the PACU. Core temperature is ideally measured in the mid-esophagus, immediately retrocardiac. The optimal location of the probe can be confirmed when using a combination esophageal stethoscope and thermistor, by inserting the stethoscope until the heart sounds are maximal. Alternative sites to measure core temperature include the rectal, nasopharyngeal, and axillary sites, although each measurement site has its limitations. Rectal temperature probes may yield inaccurate temperatures if the probe exits the rectum or is immersed in stool. The nasopharyngeal site may underestimate the core temperature if it is cooled by gas passing through the ventilation circuit. Axillary temperature may underestimate core temperature because of IV fluid infusing through the ipsilateral arm, because the probe is not positioned against the axillary blood vessels, or because the probe is adjacent to the forced air warmer.

Anesthetic depth monitoring

Reports of awareness in up to 1% of children undergoing elective surgery surprised many experienced pediatric anesthesiologists [91,92]. Although most consider the frequency of awareness in children to be much less than this, children rarely self-declare their awareness, so it is conceivable that our experience underestimates the true incidence.

Analysis of these reports of awareness in children suggests that many of the episodes could be attributed to institutional anesthetic practices that expose children to low concentrations of anesthesia during periods of intense stimulation. In some cases, these occurred during the transport of children from the induction room to the operating room [91] or when the anesthesiologists deliberately decreased the anesthetic concentrations immediately after loss of eyelash reflex to reduce the theoretical risk of seizures [92]. These practices contrast to most of our practices where the anesthetic concentrations of sevoflurane are neither interrupted nor dramatically decreased until an adequate depth of anesthesia is achieved. We believe that the frequency of awareness during pediatric anesthesia is far less than that recently reported, that most instances are explicable by local institutional practices, and that these reports do not justify routine depth of anesthesia monitoring in children.

The Bispectral Index (BIS™, Medtronic Corp., Minneapolis, MN, USA) is the most widely studied anesthetic depth monitor in children in North America, although other monitors such as the Cerebral State Index (Cerebral State Monitor, Danmeter A/S, Odense, Denmark) and Spectral Entropy monitor (E-Entropy™ Monitor, GE Healthcare Finland, Helsinki, Finland) are approved for clinical use. The BIS measures anesthetic depth continuously over a scale from 0 to 100, with readings between 40 and 60 considered adequate for general anesthesia. The BIS monitor requires 30–60 s to display an index value. The probability that recall will occur is significantly increased if the BIS is >60 for more than 30 s. A number of factors may influence the BIS readings. First, the BIS measurements vary with the anesthetic administered [93]. For example, at equipotent concentrations, the BIS measurements during halothane anesthesia are 50% greater than those during sevoflurane anesthesia. In part, the difference may be explained by the very different electroencephalography (EEG) patterns of the two anesthetics: the EEG pattern associated with sevoflurane anesthesia displays more slow waves and fewer fast rhythms activity than halothane. Although the BIS measurements correlate generally with the sevoflurane concentration, the accuracy of the measurement is poor. BIS readings during nitrous oxide and ketamine anesthesia do not reliably estimate the depth of anesthesia and may overestimate the BIS reading for a given depth of anesthesia. Second, young age affects the BIS readings [94–96]: readings in children <5 years of age are less reliable than those in children >5 years of age. The most likely explanation for this effect relates to the maturation of the EEG from birth to school-age children. Third, the depth of anesthesia measurement is substantially affected by the extent of muscle relaxation. Recovery of the twitch response increases the BIS readings while paralysis decreases the BIS. This effect complicates interpretation of the BIS reading. In patients who are not paralyzed, the electromyography (EMG) component contributed by spontaneous respiration may erroneously increase the BIS reading. Fourth, position may affect the BIS reading. Placing the patient in the Trendelenburg position (30° head down) increases the BIS by 20% [97].

There are few indications for the routine use of the BIS monitor in children except for those who cannot tolerate general anesthesia because of hemodynamic instability, those in whom nitrous oxide is not used, and those anesthetized with TIVA. Chapter 19 presents further discussion of monitoring.

KEY POINTS: PREPARATION OF OPERATING ROOM, EQUIPMENT, AND MONITORS

- Although modern anesthesia machines have sophisticated electronic machine checks, the anesthesiologist is responsible for checking the breathing circuit for leaks, that suction is available, and that emergency oxygen and ventilation sources are present
- Atropine, succinylcholine, and propofol should be readily available and drawn up for every case for airway emergencies; resuscitation drugs should be available in close proximity but only prepared for high-risk patients
- Electrocardiography (ECG), non-invasive blood pressure, pulse oximetry, and temperature are mandatory for every pediatric anesthesia case; invasive monitors are used for high-risk cases; anesthetic depth monitoring is of very limited use in children

Methods for inducing anesthesia

Anxiolysis

Anxiolysis is defined as the use of sedative drugs or behavioral techniques to reduce anxiety in a child. Several strategies may be used to achieve preoperative anxiolysis, but in some children multiple techniques may need to be used concurrently. These may be used to facilitate a smooth separation from parents before entering the operating room and/or a smooth induction of anesthesia.

There are many reasons why a child may be anxious preoperatively: fear of separation (1–6 years of age) or a phobia (e.g. fear of a facemask), which occurs in 2.8–8% of children; a rational fear about their pending surgery (e.g. fear of waking up during the surgery or mutilation – usually occurring in adolescents); an underlying anxiety disorder, which occurs in 15–20% of children; and unsatisfactory experiences during previous anesthetics [98,99].

Children may have varying levels of difficulty expressing their anxiety based on age, language skills, cognitive capabilities, and emotional understanding. In such instances, a compassionate anesthesiologist who addresses the child and his/her fears and questions is certainly reassuring but somewhat less effective than anxiolytic medications.

Preoperative anxiolytics confer a number of disadvantages including possible respiratory or cardiovascular depression, and the need for personnel to monitor the child. The anesthesiologist must be familiar with the possible routes of administration of the premedication, which itself may inject some anxiety (e.g. intranasal midazolam), and the time to peak effect. A panoply of strategies may be used to achieve anxiolysis in children before induction of anesthesia. These are summarized as follows.

Parental presence at induction of anesthesia

Both children and parents may find the process of inducing general anesthesia to be stressful. Parents may truly believe that parental presence at induction of anesthesia (PPIA) will calm their child. However, there is now a substantial body of evidence that refutes this belief: PPIA had no significant overall effect on parental anxiety or parental satisfaction, failed to enhance cooperation during induction or shorten the time taken for induction, and did not reduce the frequency of emergence delirium (ED) or negative behavior up to 6 months after discharge [100–102].

Despite these findings, PPIA is routinely practiced and encouraged at many institutions. Some parents believe that it is their civil right to be present for a procedure that involves their child (by this logic the parent should also be allowed to remain for the entire surgery) [103]. Nonetheless, we believe that there are instances when PPIA may be very helpful, as in cognitively impaired children whose parent can calm and direct them, children with cancer, and with multiple surgeries. Cognitively impaired children may require oral or intramuscular sedation in order to garner a level of cooperation to facilitate induction of anesthesia (see section "Pharmacological sedation"). Such patients frequently require repeated anesthetics and are frightened of the entire hospital environment. We have found it helpful to discuss previous anesthetic experiences with the parent or caregivers, and take their perspective into account when formulating a plan for anesthetic induction. A poorly executed plan may create recurring maladaptive behavior upon return visits.

If PPIA is planned for selected children, a plan for managing the children and their parents should be in place before commencing the program. First, since separation anxiety does not occur before age 8 months, the children for whom PPIA should be considered should be 1–6 years old and slightly older. Second, we recommend that parents attend a training session about how their child may react and appear during induction of anesthesia so they are comfortable before the actual event occurs. The parent should be educated in advance that their child might cry, resist the anesthesia mask, and experience noisy breathing or involuntary movements during induction of anesthesia and that these are all normal responses. Some parents may become very emotional when they see their child become anesthetized, and the training session should defuse the responses around these events. Third, if a parent expresses an unwillingness to accompany their child to the operating room, they should not be forced to do so. Finally, everyone on the operating room team must understand his/her role in this event and someone must be designated to escort the parent from the operating room at the appropriate time or when the anesthesiologist deems it appropriate. The parent must be informed that at any time the anesthesiologist may ask them to leave the operating room and they must comply. We believe that PPIA is not a right but a privilege; only after the anesthesiologist has determined that it is in the best interest of the child for the parent to be present should a parent be permitted to accompany their child to the operating room.

Distraction techniques

A variety of education and distraction techniques have been investigated to reduce preoperative anxiety in children coming for surgery. Preoperative coloring books, stories, videos, and websites have been developed for children of all ages to educate them about the appearance of the operating room, the equipment that will be used, and how children are anesthetized. Whether these videos reduce either parental or child anxiety is unclear [101]. Operating room tours (usually on weekends, where a staff member dresses the family and children in operating room attire and they visit an operating room and play with anesthesia facemasks) are most informative, although they may not be effective anxiolytics [104]. On the morning of surgery, child-life providers may orient those children who may be at risk for emotional instability and separation anxiety, marking the inside of a facemask with flavored lip balm or scented oils and applying the mask to their faces. The anesthesiologist should conduct his/her preoperative visit by focusing directly on the child to discuss the facemask and the lip balm or oil scent that they chose and then later engage the parents.

Distraction techniques including video games, video glasses, earphones, portable internet devices, smart phones, play dough, table-based games, magic, clowns and clown doctors, and music all reduce preoperative anxiety to varying extents [101,105–109]. The children of parents who received acupuncture before their child's surgery were less anxious and more cooperative at induction of anesthesia, an indication of the important role of the parent's anxiety in the child's behavior.

To complement the above strategies, the circulating nurses and/or anesthesiologist should be skilled and trained to facilitate smooth and rapid separation of the child from the parents and then distract the child by pointing out wall designs, pictures, and other features as they travel to the operating room. Once the child enters the operating room, the anesthesiologist should establish rapport by telling a story, engaging them in conversation about a recent birthday, holiday, or vacation, or singing as they prepare for induction of anesthesia.

Pharmacological sedation

Some children require premedication to facilitate a smooth separation from their parents. Several medications and routes of administration have been investigated with oral midazolam, the most widely used premedication in North America and elsewhere.

Oral premedication

The benzodiazepine midazolam has received widespread acceptance as a premedication for children that is very reliable with few complications. Midazolam has been administered via the oral, intravenous, nasal, rectal, and intramuscular routes, with the most common route being the oral route. Midazolam may depress respiration when it is administered by any route, although apnea is infrequent in the absence of other medications, even in the presence of obstructive sleep apnea [110]. Apnea has been observed during inhalation induction with sevoflurane.

The oral formulation of midazolam in North America is a cherry-flavored syrup in a concentration of 2 mg/mL. It can be injected into the (lateral gutters of the) mouths of toddlers using a needleless syringe or ingested from a cup in older children. This formulation usually leaves a bitter aftertaste (after the oral or nasal route), which may prompt some children to expectorate it. To prevent this, we encourage the child to drink the midazolam in one gulp and reward them with up to 15 mL of water. A new European formulation of oral midazolam (ADV6209) that contains midazolam along with γ-cyclodextrins, sucralose, and orange aroma, is currently under investigation as an improved formulation (lack of bitter aftertaste) of oral midazolam in a dose of 0.25 mg/kg [111]. This formulation was well accepted and provided good sedation; confirmation of these data is pending.

The oral form has a limited (15%) bioavailability, hence large doses of midazolam are required for sedation. A fixed dosing regimen for all ages increases the failure rates in younger children [112]. We recommend the following dosing regimen with age: 1.0 mg/kg for children 1– 3 years of age, 0.75 mg/kg for children 4–6 years of age, 0.5 mg/kg for those 7–9 years of age, and 0.3 mg/kg for children age 10 and over (up to 15 mg) [113]. With these larger doses of midazolam, children are adequately premedicated in a timely manner, within 10–15 min in younger children, although in older children the peak effect may not be achieved until 30 min. Emergence from anesthesia is not usually delayed by oral midazolam, except possibly after very brief surgery [114].

There are few contraindications to oral midazolam; fewer than 3% of children with obstructive sleep apnea experienced transient hemoglobin desaturation [110].

Oral ketamine (5–6 mg/kg) has been successfully used in children, although it offers few advantages over midazolam and may cause more postoperative vomiting [115]. Postoperative hallucinations and nightmares have not been reported after oral ketamine. Some have combined oral midazolam (0.5 mg/kg) and ketamine (3 mg/kg), yielding better sedation than with the individual agents [115].

Oral clonidine, an α_2 agonist, confers several benefits as a premedication including decreased emergence agitation, decreased postoperative pain, and decreased postoperative nausea and vomiting (PONV). Clonidine provides better sedation at the time of induction, equivalent times to extubation and PACU discharge, a lack of respiratory depression, and mild sedation in the PACU compared with oral midazolam. However, the onset of sedation after oral clonidine (2–4 μg/kg) is at least 40 min, much slower than that of oral midazolam. Dexmedetomidine, another α_2 agonist, has also been widely used for preoperative sedation of children. As with clonidine, the oral route has a slow onset, and bradycardia and hypotension may occur [116]. Although these α_2 agonists are effective for premedication, their slow onset of sedation, the frequency of bradycardia, and the fact that sedation persists beyond the duration of most anesthetics limit their use in this regard. When compared with dexmedetomidine (4 μg/kg) and clonidine (4 μg/kg), oral midazolam (0.5 mg/kg) was a more effective premedication and without the side-effects of the α_2 agonists listed above [117].

Intranasal premedication

Most premedications have also been administered by the intranasal (IN) route. IN midazolam (preservative-free 0.2–0.3 mg/kg as a 0.5 mL volume) has good bioavailability, however it leaves a bitter aftertaste that most children report as unpleasant and that persists for quite a while after the anesthetic [118]. In a comparison of two premedications administered by the parents and evaluated by both the parents and an observer, oral midazolam (0.5 mg/kg) was more easily administered and accepted with better parental separation at 30 min after premedication than IN midazolam (0.2 mg/kg) [119]. IN sufentanil 2-4 μg/kg has also been an effective premedication, although it is rarely used in children. In the original studies, it caused chest wall rigidity necessitating succinylcholine administration [120]. IN dexmedetomidine (1 μg/kg) is also well tolerated in children, but its onset of action is slower than with IN midazolam (0.2 mg/kg) [121,122]. IN dexmedetomidine yielded smoother separation from the parents but only modestly better acceptance of the facemask at induction of anesthesia [123]. Additionally, IN dexmedetomidine decreased postoperative agitation and shivering as well as providing more effective postoperative analgesia. Currently, IN dexmedetomidine is not approved by the Food and Drug Administration (FDA) in the USA for use in children.

Intramuscular premedication

Many cognitively impaired patients refuse IN or oral premedications. Intramuscular (IM) ketamine may be very useful in the uncooperative patient before establishing IV access or applying an anesthesia mask. The typical child that presents in this manner is a large, autistic teenager who refuses to ingest or accept any premedication. If the child will not transfer to the operating room under any conditions (including parental guidance), the remaining choices are to either cancel the surgery or premedicate the child with an IM injection.

Unless contraindicated, it is the authors' practice to administer 3–5 mg/kg ketamine IM mixed with 0.02 mg/kg atropine (maximum 0.5 mg atropine). The onset of action is typically within 5 min and the duration of action is 20–30 min. Atropine appears to be superior to glycopyrrolate in preventing hypersalivation after administration of ketamine [124]. In anticipation of the injection, the parent or caregiver along with the child should be seated on a stretcher and IM ketamine is administered into either a bare deltoid region of an arm or through the clothing in the same region [125,126]. The optimal location for IM injection of ketamine is unknown, however one can be guided by consensus recommendations for IM administration of vaccines from the Centers for Disease Control and Prevention (CDC) [127]. In patients over 3 years of age, the deltoid muscle is preferred, although the vastus lateralis muscle (anterolateral thigh) may also be used. A needle length must be selected that is sufficient to penetrate the overlying skin and adipose tissue. The needle length will vary with both the age and size of the patient. Familiarity with anatomical landmarks is essential to prevent injury to neurovascular structures when performing an IM injection. Once ketamine is administered, it may take up to 5 min for the child to become sedated. In most instances, this premedication will be metabolized before the end of anesthesia.

Induction techniques

Induction of anesthesia is defined as the transition from the awake to the anesthetized state. In North America, general anesthesia in children is most commonly induced by inhalation of potent anesthetic gases, although alternate routes including the IV, IM and rectal routes may also be used in certain circumstances. The choice of the technique depends on several factors including the child's age, level of cooperation, clinical condition, and preoperative status. For some techniques such as an IV induction or a single-breath induction, a qualified assistant should be present.

Inhalation induction

All infants and children, including those who are crying and upset, can undergo a smooth inhalation induction given the proper atmosphere and attitude by the staff. On many occasions we have engaged upset children in the operating room in a warm and reassuring manner and successfully induced anesthesia by mask without tears. It is our belief that holding children down and forcing a mask on their face (derisively known as "brutane") has no place in pediatric anesthesia and may psychologically scar the child for life. When presented with a fearful or emotional child preoperatively, we first address the child's (and their parents') fears, providing an age-appropriate explanation of the process, and use preoperative anxiolytic strategies and/or sedation as appropriate. If fearfulness and resistance persist at induction of anesthesia, another set of strategies is used. In short, the optimal preoperative process is one that is tailored to the needs of the child and parents, with the overriding goal of patient safety taking precedence.

Preschool-age children often present the greatest challenges at induction of anesthesia. Distraction techniques and premedication are key strategies that should be used to minimize anxiety and distress during separation from parents and induction of anesthesia in this age group. We have designed our induction strategy to empower children during the induction and maximize their participation. Upon arrival in the operating room, we apply as many monitors as the child permits. The child chooses his/her favorite of two or three choices of scented lip balm and then colors the inside of the mask with it or, if the child is too young (<3 years of age), we apply it to the facemask. With the child seated on the operating table and his/her back to our chest (or on our lap if the patient has a diaper), we bring the facemask slowly and gently to the nose and mouth, while 70% nitrous oxide in oxygen is flowing in the breathing circuit at 5–7 L/min total fresh gas flow. We often challenge the child to try to "blow up the balloon" (reservoir bag) by breathing as deeply as possible. We employ a 1 L reservoir bag in the pediatric breathing circuit to reduce the time to wash-in anesthetic into the circuit. It is critically important to ensure the adjustable pressure limiting (APL) valve is wide open so the child does not feel he/she cannot exhale as a tight mask fit is applied. During this time, we distract the child by singing a song, or telling a joke or a story until the end-tidal and inspired nitrous oxide concentrations equilibrate or the child ceases to respond to verbal stimulation. At this time, children are sufficiently sedated that they will not recall any unpleasant anesthetic odor. Accordingly, we then dial in 8% sevoflurane in a single move and, once the end-tidal sevoflurane equilibrates, we reduce the total fresh gas flow to 2–3 L/min. As soon as the child loses consciousness (and their neck becomes too supple to hold their head), we place them supine while they continue to breathe 8% sevoflurane in 70% nitrous oxide. The remaining monitors are then applied. During this early period of the induction, we maintain near complete silence in the operating room and the surgeons are prohibited from stimulating or manipulating the child. If the child becomes apneic during this period (particularly after a premedication), we gently assist ventilation. To reduce the risk of awareness, the concentrations of sevoflurane and nitrous oxide are maintained until IV access is established. Once IV access is established, we administer an IV dose of propofol (1–2 mg/kg) and discontinue the nitrous oxide to facilitate laryngeal mask insertion or tracheal intubation [128]. Anesthesia is continued with 8% sevoflurane in 100% oxygen until we have verified that the airway device has been placed successfully. If apnea occurs after the airway is secured, the inspired concentration of sevoflurane may be decreased by 25–35% or more, until spontaneous ventilation resumes. If nitrous oxide is not contraindicated, it may be reintroduced at this time, together with an appropriate concentration of anesthetic vapor. Only after the airway is secured may the surgeon begin to examine the child.

Another strategy to achieve a deep level of anesthesia with sevoflurane is to slowly increase the inspired concentration of sevoflurane in a stepwise manner (2% per min). Although this approach achieves the same outcome, it has several disadvantages including a prolonged induction time and an exaggerated excitement phase.

Another distraction strategy is known as troposmia. Troposmia is a distorted perception of an odor that, in this case, can be attributed to the presence of inhalation anesthetics. The anesthesiologist asks the child his/her favorite flavor after applying a standard (i.e. strawberry) lip balm to the facemask. The child is then told that as he/she is anesthetized, the

anesthetic will magically change the strawberry flavor to the child's favorite flavor. In one study, 80% of the children confirmed that they smelled their favorite flavor when they breathed the anesthetic gas [129].

The child with mask phobia poses a very real challenge for those attempting to induce anesthesia by inhalation [130]. Besides refusing a mask, these frightened children often steadfastly refuse needles (and therefore an IV induction), leaving clinicians few options for inducing anesthesia. Several different solutions have been devised to address this problem ranging from removing the mask from the breathing circuit to forcing the facemask on a child's face, which we do not condone. We believe that induction of anesthesia with the former strategy is the preferred approach, whereas induction with the latter approach is potentially traumatic and psychologically harmful and cannot be recommended.

There are many reasons why children may be fearful of facemasks including the unappealing odor of 8% sevoflurane administered at the outset, lack of premedication for a child who became traumatized at a previous induction, a partly closed APL valve, which may prevent the child from completely exhaling during the induction, and claustrophobia. Irrespective of the reason, we believe that if the mask is the focal point of the fear, it should be eliminated from the induction. To induce anesthesia without a facemask, we interlace our fingers, with the elbow of the breathing circuit positioned between our fingers, delivering 70% nitrous oxide in oxygen (Fig. 17.1). We cup our hands under the child's chin (since nitrous oxide is heavier than air) and gradually bring them closer and closer until they cover the child's mouth. Although this approach may increase operating room pollution, we believe it is the optimal approach to manage the child with mask phobia. Once the hands are tight over the mouth, we dial 8% sevoflurane into the fresh gas flow. When the child is adequately anesthetized, we attach the facemask to the breathing circuit and continue the anesthetic. When interviewing these children during the recovery period, the children are thrilled that they avoided the "feared" mask.

Another approach to deliver anesthesia by mask if the anesthesiologist wishes to include sevoflurane from the outset (i.e. without premedication or nitrous oxide first) is to rotate the facemask 90° and use the balloon of the cuff to occlude the nares as anesthesia is induced. In this way, the child cannot smell the sevoflurane and anesthesia is smoothly induced.

Children who are older (usually >6 years of age) and understand how to hold their breath can perform a single-breath induction of anesthesia [131,132]. In order to perform a single-breath induction, the anesthesia circuit must be first primed with 8% sevoflurane (with or without 70% nitrous oxide) by compressing the reservoir bag three to four times with a large gas flow. A 2 L reservoir bag is preferred to provide a sufficient reservoir in the event the child takes a particularly large or additional breath. Before taking a single breath through the breathing circuit, the child practices vital capacity breathing, inhaling through the mouth and exhaling to residual volume (instructing the child to exhale until there is no air left in their lungs) through the mouth. Once the child has mastered the breathing maneuvers, the child exhales to residual volume at which point the facemask is applied tightly to the face. The child is instructed to take a single vital capacity breath through their mouth and to hold it for as long as possible. While the child is holding his/her breath, the anesthesiologist counts aloud slowly. Published data suggest that children lose their eyelash reflex within 1 min, whereas in our experience, the child loses consciousness before our count reaches 20 (s). At that point, the head and neck are supported and the child is slowly reclined to the supine position.

Intravenous induction

Most children do not want an IV induction because they fear the pain associated with establishing IV access. Three factors increase children's responses to IV insertion even in the presence of topical local anesthesia: age (≤1 year), activity level, and the endothelin receptor A TT genotype polymorphism [133]. If a child requires an IV induction, such as one with a full stomach, there are several options available to anesthetize the skin: topical anesthetic creams, vapo-coolants, or skin infiltration with local anesthetic. Several creams are available including: EMLA® (eutectic mixture of 2.5% lidocaine and 2.5% prilocaine; AstraZeneca LP, Wilmington, DE, USA), which requires 45–60 min to establish topical anesthesia; Ametop® (4% tetracaine gel; Smith & Nephew, Mississauga,

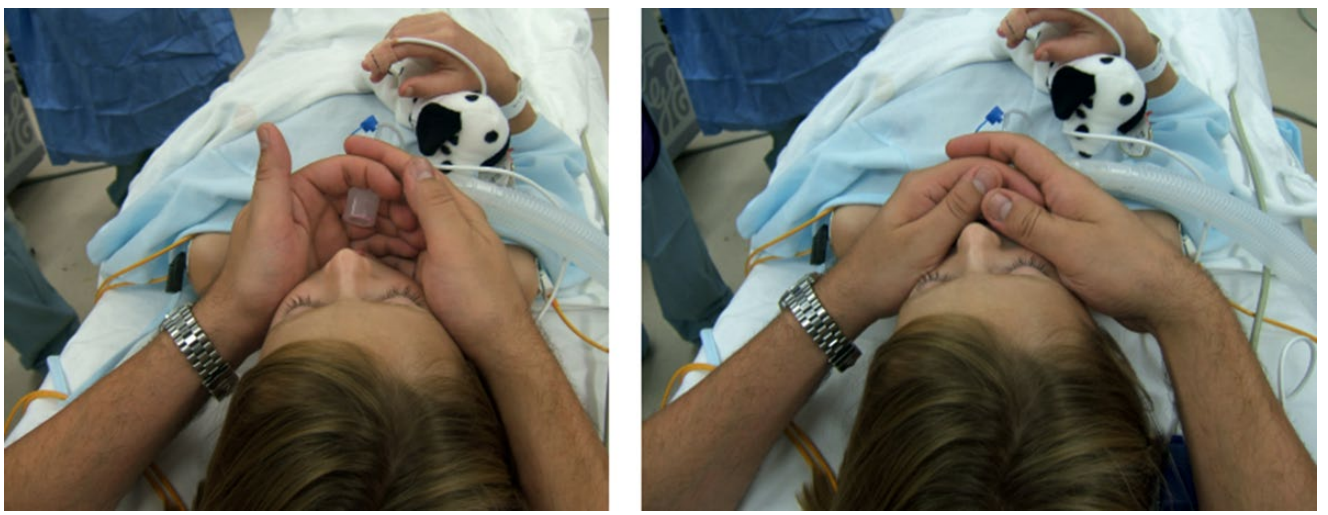

Figure 17.1 Inhalational induction without using a facemask.

ON, Canada), which requires 30 min to establish anesthesia and does not blanch the skin or cause venoconstriction; LMX4® (liposomal 4% lidocaine; Eloquest Healthcare, Ferndale, MI, USA); and Synera® patch (eutectic mixture of 70 mg lidocaine and 70 mg tetracaine; Galen Ltd., Craigavon, UK), which also requires 30 min for topical anesthesia [134]. We commonly offer older children the option of breathing 50% nitrous oxide before establishing IV access in the operating room while anesthetizing the skin. To successfully anesthetize the skin, a small intradermal wheal of 1% or 2% plain lidocaine is made directly over the target vein with a 27 g or 30 g needle and then a small amount of local anesthetic is deposited in the underlying subcutaneous tissue. Larger-gauge needles and large-volume injections are associated with much more pain. Vapo-coolants (e.g. ethyl chloride) have also been widely used to reduce the pain of injection, and do not cause venoconstriction. A recent Cochrane Review concluded that vapo-coolants reduce pain moderately during IV cannulation in both adults and children [135]. Some studies have found that ethyl chloride does not reduce the pain from IV cannulation. In these instances, it may be that ethyl chloride has not been applied correctly: it should be sprayed for 4–10 s after the tourniquet is applied and IV cannulation should follow immediately, since the analgesic effect lasts only 60 s [136]. A new device (J Tip™; National Medical Products, Irvine, CA, USA) for anesthetizing the skin before IV cannulation employs a needleless subcutaneous jet injection of lidocaine. It has not been widely adopted or extensively studied. Transillumination and near-infrared light devices (e.g. Accuvein®, Accuvein Inc., Huntington, NY, USA; VeinViewer®, Christie Medical Holdings Inc., Memphis, TN, USA) have been advocated as aids for finding peripheral veins in children, however they have not proven to reliably increase the first-pass success rate of IV cannulation [137].

Currently, the only induction agents available for use in the US are propofol, ketamine, and etomidate. Since 2011, sodium thiopental has been unavailable in the US, although it remains available in other countries.

Propofol (2,6diisopropylphenol) (1–3 mg/kg IV bolus) is the most widely available induction agent. It is available as Diprivan® (Fresenius Kabi USA, Lake Zurich, IL, USA) in a 1% solution that includes intralipid (long-chain triglycerides from soy oil), EDTA (ethylenediaminetetraacetic acid), egg lecithin, and pH adjustment. Since propofol is a phenol derivative, it is painful when injected into the small peripheral veins in children. Numerous strategies have been investigated to attenuate or prevent the pain of injection, with two techniques appearing superior to the rest at ameliorating the pain at injection: pretreatment with 70% nitrous oxide in oxygen by inhalation or a modified Bier block using 0.5–1 mg/kg 1% lidocaine injected into the vein that is occluded for 45–60 s [138].

Propofol is a very safe induction agent for children. When propofol was originally released, it was contraindicated in children with egg allergy. Egg lecithin is derived from egg yolk, a product to which children are not known to be allergic [19]. A second concern relates to children with soy allergy who may develop anaphylaxis to propofol. This theoretical concern has not been reported in the literature, in part because all soy proteins are removed in the manufacturing process of propofol, according to Fresenius Kabi, USA, the manufacturer. However, non-North American manufacturers caution against the use of propofol in children with soy and peanut allergy as children with soy allergy share epitopes with peanuts and develop peanut allergy [139]. Fortunately, >80% of children who claim to have peanut allergy are actually hypersensitive to peanuts, not immunologically allergic [140]. If children with peanut allergy have not been tested immunologically, the clinician may either avoid propofol or administer a small aliquot of propofol to assess their allergic sensitivity to propofol.

Ketamine (1–2 mg/kg) may be used for induction of anesthesia, although the associated concern of rare postoperative nightmares has relegated it to a second-tier anesthetic, given for specific indications such as sepsis or cyanotic heart disease. In children with tetralogy of Fallot, ketamine has divergent effects: it increases pulmonary blood flow in the presence of mild cyanosis but decreases the flow in those with moderate to severe cyanosis [141].

Although etomidate is not approved for use in children in North America, it has been used off-label. Its primary indication is for patients in septic shock. In adults, etomidate (0.3 mg/kg) suppresses adrenal function when administered as a bolus for rapid-sequence induction or a continuous infusion [142]. A single dose of IV etomidate in children during elective surgery suppresses cortisol levels for 24 h without affecting outcomes [143]. Pharmacokinetic data suggest that infants >6 months and young children may require larger doses of etomidate than older children [144]. Etomidate may cause myoclonic jerking and pain upon IV injection. The latter may be addressed by IV lidocaine pretreatment.

Sodium thiopental (5–6 mg/kg in healthy non-premedicated children, 3–4 mg/kg in neonates) has been used for almost half a century as an IV induction agent but in the past two decades has been supplanted by propofol. The induction dose should be reduced in premedicated children and debilitated patients. Thiopental induces anesthesia very rapidly, and its effect is terminated equally rapidly, primarily by redistribution. Only 10% of thiopental is metabolized per hour, which delays emergence, particularly if repeat doses are administered. Hence, this anesthetic is not suitable to be given by continuous IV infusion

Intramuscular induction

Intramuscular inductions are infrequently used in children because they are painful and induce anesthesia slowly. The only anesthetic currently used for IM injections is ketamine, in a dose of 3–5 mg/kg. This induction technique is usually reserved for cognitively impaired and combative adolescent children. The onset of sedation is approximately 3–5 min, with a duration of approximately 30–45 min.

Rarely, children who require their airways secured emergently present without IV access. In such cases, any one of several approaches may be undertaken. IV access may be established before induction of anesthesia, after induction of anesthesia with an inhalation agent, or after IM injection of ketamine (3–5 mg/kg), atropine (0.02 mg/kg), and succinylcholine (4 mg/kg).

Rectal induction

Rectal induction was a popular strategy for induction of anesthesia in young children (<5 years of age) in the past, particularly for those unwilling to take oral premedication or who

were very frightened. Several regimens have been used for rectal induction: methohexital 15–25 mg/kg, midazolam 1.0 mg/kg, ketamine 5 mg/kg, or thiopental 30–40 mg/kg [145–147]. Rectal inductions suffer from several issues including poor bioavailability of the induction agent (due to unpredictable rectal venous absorption or evacuation of the drug from the rectum), risk of laryngospasm (with methohexital), and possible delayed recovery from anesthesia. Currently, rectal inductions are rarely employed. Most prefer to involve the parents to manage the child's behavior at induction of anesthesia rather than administer a rectal premedication.

KEY POINTS: METHODS FOR INDUCING ANESTHESIA

- Parental presence has limited ability to reduce anxiety; oral midazolam and distraction techniques are more successful
- Inhalation induction with nitrous oxide and sevoflurane is by far the most common technique; a "maskless" induction or single-breath induction can be accomplished in appropriate settings
- IV induction, normally with propofol, can be accomplished after IV placement with a variety of topical anesthetics, with minimal upset to the child
- IM induction with ketamine is reserved for uncooperative developmentally delayed children, or patients with congenital heart disease with poor IV access who might not tolerate an inhaled induction

Problems during induction of anesthesia

Desaturation

The SpO_2 of healthy, awake children breathing room air should be >95%. A similar saturation should be maintained after induction of anesthesia and airway instrumentation, particularly with a FiO_2 ≥33%. However, in some children, the SpO_2 decreases to <94% in the early anesthesia period and does not increase substantively despite an increase in the FiO_2. In the presence of a normal capnogram, the most common diagnosis is an endobronchial intubation, followed by asthma, mucous plug, and atelectasis. Once air entry in the left chest is confirmed, the lungs are clear to auscultation, and the tracheal tube is devoid of purulent secretions, the next most probable diagnosis is segmental atelectasis. Atelectasis develops with induction of anesthesia. This, combined with reduced tidal volumes and respiratory effort, decreases lung volumes and chest compliance. The result is that most of the pulmonary circulation perfuses the basal segments of the lungs whereas most of the ventilation preferentially inflates the upper lung segments. This V/Q mismatch is relatively unaffected by an increase in FiO_2 from 30% to 100% because of the sigmoidal shape of the oxyhemoglobin dissociation curve. Thus increasing the FiO_2 is ineffective; to restore the saturation to >94%, the atelectatic alveoli must be recruited [148]. This is achieved by manually inflating the lungs to 20–30 cmH_2O pressure for 20–30 s (known as an alveolar recruitment maneuver). This maneuver should be applied cautiously to the child with an unstable circulation. Alveolar recruitment shifts the ventilation up the pressure–volume curve where right-to-left shunting is minimal. The effectiveness of alveolar recruitment is independent of the FiO_2. Once the recruitment is completed, spontaneous respiration may resume with a physiological positive end-expiratory pressure (~5–10 cmH_2O). An underappreciated cause of atelectasis is gastric distension caused by assisted ventilation using excessively large peak pressures in small children. To decompress the stomach, a soft 8–14 F catheter should be passed into the stomach and attached to low suction.

Bronchospasm

Bronchospasm occurs infrequently during induction of anesthesia with sevoflurane and halothane [149] but is more common during inductions with isoflurane and desflurane [150] and after tracheal intubation in children, particularly in those with irritable airways such as severe asthma. Bronchospasm is defined as a sudden constriction of the walls of the airways. Wheezing on the other hand, which literally means "hissing," is whistling (high- or low-pitched) noises in the airways. To keep these two terms distinct, remember the expression: "all that wheezes is not bronchospasm." Bronchospasm occurs more commonly in children with asthma, pulmonary infections, and anaphylaxis. Wheezing can occur at multiple levels in the airway including the larynx (e.g. stridor) and intrinsic to the airway (e.g. asthma) or extrinsic to the airway (e.g. pneumothorax).

The factors that predispose to bronchospasm during anesthesia include a recent upper respiratory tract infection, asthma, foreign body in the airway (e.g. peanut or tracheal tube), first- and second-hand smoking and GER [151]. Preoperatively, the chest should be auscultated for breath sounds. If new-onset wheezing is detected, elective surgery should be canceled and the child referred to the pediatrician or pulmonologist for investigation. The reason for canceling elective surgery is that wheezing is a sign of unstable pulmonary disease that increases the perioperative risks after general anesthesia. If the surgery is urgent/emergent, bronchodilator therapy should be instituted preoperatively, airway management should be aimed at avoiding a tracheal tube, and equipment prepared to provide intraoperative bronchodilator therapy. If the child wheezes chronically despite maximum pulmonary therapy and no acute exacerbation is present, a dose of bronchodilator should be administered preoperatively and, if possible, a tracheal tube avoided.

If bronchospasm occurs after tracheal intubation, the cause should be diagnosed and treated. First, rule out an endobronchial intubation by auscultating the lungs bilaterally and verifying the depth of the tracheal tube from the lips. Second, suction the tracheal tube to remove any mucous plugs that may be present in the airways. Although passing a suction catheter down the tracheal tube does not rule out the presence of mucus or a defective cuff on the tube, it reduces the probability that one is present. If the bronchospasm is not resolved with either of these maneuvers, a dose of albuterol should be administered via the tracheal tube. To deliver an albuterol aerosol, a metered dose inhaler (MDI) adaptor (RTC 24-VP; Instrumentation Industries, Bethel Park, PA, USA) is attached

between the tracheal tube and the anesthesia breathing circuit. Alternatively, a non-MDI albuterol canister may be inserted into the barrel of a 30 mL syringe in the inverted position (after removing the syringe plunger) and the plunger reinserted on top of the canister to activate the puffer into the elbow of the breathing circuit. When activated at the elbow of the breathing circuit, 3–12% of the aerosolized albuterol reaches the tip of the tracheal tube, depending on the ID of the tracheal tube (from 3 to 6 mm ID) [152]. Hence five to ten activations may be required in order to deliver sufficient albuterol to affect the bronchial tone. If these maneuvers fail and bronchospasm continues, 1–2 μg/kg epinephrine may be administered IV. If bronchospasm persists despite these treatments, then an extrinsic cause for the bronchospasm should be sought, diagnosed, and treated.

Laryngospasm

Laryngospasm is an infrequent but potentially life-threatening emergency that occurs during induction or emergence from anesthesia. The frequency of laryngospasm in children varies dramatically among studies, the study populations, and predisposing factors from 0.4% to 10% [153–156]. Factors that increase the risk of laryngospasm in children are shown in Box 17.8 [156,157].

Laryngospasm is defined as reflex closure of the false and true vocal cords, although the precise pathogenesis of this reflex remains unclear. Complete laryngospasm is defined as closure of the false vocal cords and apposition of the laryngeal surface of the epiglottis and inter-arytenoids resulting in the complete cessation of air movement and noisy breathing, lack of movement of the reservoir bag, and an absent capnogram. In contrast, incomplete (or partial) laryngospasm is defined as apposition of the vocal cords leaving a small gap that permits a persistent inspiratory stridor and limited movement of the reservoir bag with progressively increasing respiratory effort. Some assert that incomplete laryngospasm is not laryngospasm at all, but for treatment purposes this is a moot point.

Laryngospasm begins as faint inspiratory stridor during induction of or emergence from anesthesia associated with cues that suggest upper airway obstruction. These visual cues of airway obstruction include suprasternal and supraclavicular indrawing as inspiratory effort increases, increased diaphragmatic excursions, and flailing of the lower ribs.

Box 17.8: Factors that increase the frequency of laryngospasm

- Young age (infants and young children)
- History of reactive airways disease
- Recent URTI (<2 wk)
- Exposure to second-hand smoke
- Airway anomalies
- Airway surgery
- Airway devices (tracheal tubes, possibly LMA)
- Stimulating the glottis during a light plane of anesthesia
- Secretions in the oropharynx (e.g. blood, excess saliva, gastric juice)
- Inhaled anesthesia (versus intravenous anesthesia)
- Inexperienced anesthesiologist

LMA, laryngeal mask airway; URTI, upper respiratory tract infection.

As greater inspiratory effort is expended, the stridor increases in intensity and volume, and the chest wall movement resembles that of a "rocking horse." As the laryngospasm progresses, air movement through the almost closed glottis ceases and the inspiratory effort becomes completely silent. This is an ominous sign. If progression of the laryngospasm is not stopped, the limited reserve of oxygen in the lungs will be exhausted and desaturation will ensue. This will be followed immediately by a decrease in heart rate, and can result in cardiac arrest. This downward spiral must be interrupted as follows.

The management of laryngospasm requires a multifaceted and immediate response as depicted in Figure 17.2 [154]. As soon as the diagnosis is suspected, a tight-fitting facemask should be applied to the child's face, 100% oxygen delivered with positive end-expiratory pressure (to a maximum of ~15–20 cmH_2O to limit gastric inflation). If the triggering event is blood, secretions. or foreign material in the airway, these should be removed to eliminate the source of glottic stimulation. As soon as the offending agent (if one is present) has been removed, a jaw thrust maneuver should be applied. The jaw thrust maneuver requires familiarity with the anatomy of the retromandibular notch, an area subtended by the condylar process of the ascending ramus of the mandible anteriorly, the mastoid process posteriorly, and the external auditory canal superiorly [158]. Digital pressure applied (initially bilaterally) to the most cephalad point on the posterior edge of the condylar process of the ascending ramus of the mandible should be directed toward the frontal hairline. Pressure on the edge of the condylar process should be applied for 3–5 s at a time and then released, all the while sealing the facemask tight against the child's face. By applying and releasing pressure on the condylar processes, the repeated painful stimuli may result in sufficient pain to cause the child to cry. If the child cries, the vocal cords must open and this would terminate the laryngospasm. In addition to delivering 100% oxygen and positive end-expiratory pressure to the upper airway, this maneuver confers the additional benefit of pain and the "flight and fright" response, which stimulates the child and results in an increase in respiratory effort and vocalization, possibly breaking the laryngospasm. Remember that laryngospasm is unlikely to develop or persist if the vocal cords are moving and the child is vocalizing or crying. If positive pressure ventilation, 100% oxygen, and the jaw thrust maneuver fail to break the laryngospasm, further intervention should be administered immediately before desaturation and bradycardia develop. Appropriate treatment at this stage includes IV atropine (0.02 mg/kg) and IV propofol (<1 mg/kg) [159,160]. If the laryngospasm breaks, ventilation should be assisted with 100% oxygen and an inhalation anesthetic. However, if the laryngospasm does not abate and the heart rate and oxygen saturation continue their downward course, succinylcholine (1–2 mg/kg IV or 4–5 mg/kg IM) should be administered and the trachea intubated.

An interesting report suggests that gentle chest compressions effectively break laryngospasm in children [161]. To add chest compressions to the management of laryngospasm, one requires a pair of free hands to perform the compressions rather than abandoning any or all of the maneuvers described previously. It is uncommon that a

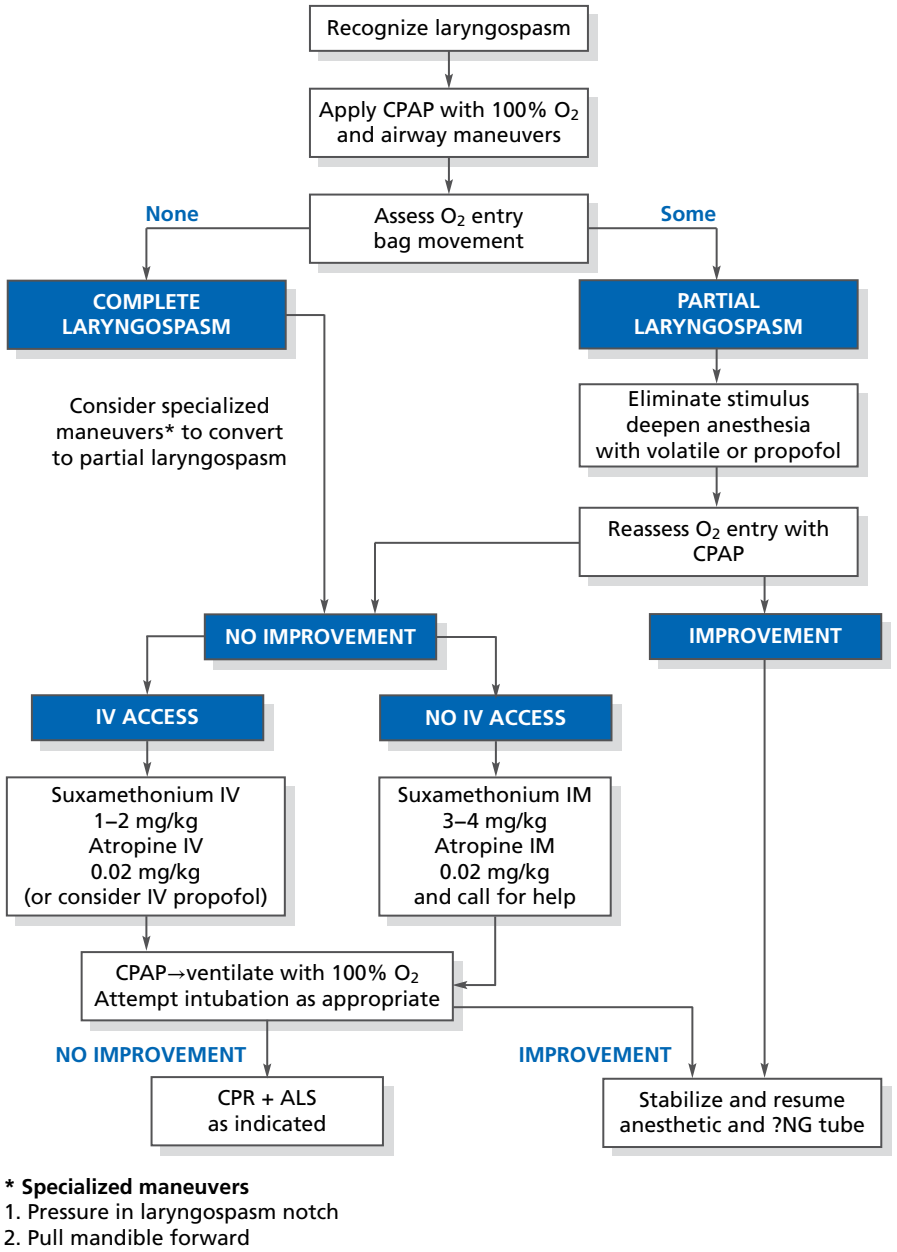

Figure 17.2 Algorithm to diagnose and manage laryngospasm in children. *Source*: Reproduced from Hampson-Evans et al [154] with permission of John Wiley and Sons. ALS, advanced life support; CPAP, continuous positive airway pressure; CPR, cardiopulmonary resuscitation; IM, intramuscular; IV, intravenous; NG, nasogastric.

free pair of hands would be readily available to provide chest compressions, but it may be worthy of consideration. The risks associated with performing chest compressions include sternal or rib fractures, which must be explained to the parents if they occur. It is our opinion that the current evidence is insufficient to recommend the routine use of chest compressions to relieve laryngospasm in children. Chest compressions are indicated for severe bradycardia (<60 beats/min (bpm) with poor perfusion, and poor or non-existent pulse).

A number of authors have used either topical or intravenous lidocaine to prevent laryngospasm on emergence from anesthesia in children. A recent systematic review of the subject concluded that 1–2 mg/kg IV lidocaine or topical lidocaine administered within 5 min of extubation was effective in preventing laryngospasm in children [162,163].

Bradycardia

Bradycardia is a slowing of the heart rate below age-defined limits. The threshold for infants (<1 year of age) is 100 bpm, for young children 1–5 years of age, 80 bpm, and for older children >5 years, 60 bpm. Since cardiac output in infants and children depends to a large extent on the heart rate, a slow heart rate means a reduced cardiac output. If the heart rate falls below these limits, corrective action should be taken to restore the heart rate while cardiopulmonary resuscitation begins.

Although hypoxia is the foremost cause of bradycardia in children, drugs are also well-known causes. Since sevoflurane replaced halothane, the frequency of bradycardia during inhalation anesthesia has diminished dramatically [149]. Succinylcholine remains a cause of bradycardia in children even after a single dose, although it is no longer recommended for elective tracheal intubation in children. Recently, the

frequency of bradycardia during the first 6 min of sevoflurane anesthesia in children with Down syndrome was found using an electronic database to be five-fold greater than in matched control children [164]. This may occur even with a structurally normal heart. Intervention (atropine or isoproterenol) may be required in children because cardiac output is dependent upon heart rate.

The causes of bradycardia in healthy children are listed in Box 17.7. In order to stop the progressive slowing of the heart rate, the underlying cause of the bradycardia should be treated (e.g. oxygenate the hypoxic child) and atropine 0.02 mg/kg IV administered. Atropine is only effective when electrical activity is present within the heart and the etiology of the bradycardia is vagal in origin. If asystole occurs, the definitive treatment is epinephrine (10 μg/kg); atropine is not indicated. Secondary treatment may include isoproterenol. Further details of cardiopulmonary resuscitation are presented in Chapter 13.

Hypotension

The incidence of hypotension during induction of anesthesia in children is small. In minimum alveolar concentration (MAC) studies, we defined hypotension as a >30% decrease in systolic blood pressure from baseline. At 1 MAC, systolic blood pressure in both neonates and infants 1–6 months of age anesthetized with halothane [165], and all children as old as adolescents anesthetized with sevoflurane or desflurane, was maintained, that is, within the defined limits (<30% decrease from baseline) [166,167]. The decreases in systolic and mean blood pressures in healthy children at >1 MAC sevoflurane and halothane were neither remarkable nor in need of intervention [131,168]. The combination of induction of anesthesia with 8% sevoflurane and an intravenous bolus of propofol (1–2 mg/kg) is a popular technique for securing the airway in an unparalyzed child without causing either bradycardia or hypotension [128].

In addition to the effects of induction agents, direct and indirect factors may lead to hypotension during induction of anesthesia in children. Direct causes include prolonged preoperative fasting, bleeding, chronic vomiting, and anaphylaxis. Indirect causes of hypovolemia include impending brainstem herniation, septic shock, cardiac tamponade, tension pneumothorax, major vascular compression (pulmonary arterial compression from an anterior mediastinal mass) and, rarely, hypothyroidism.

The treatment of hypotension must first address the underlying cause, by restoring euvolemia rather than administering pressors. Balanced salt solutions such as lactated Ringer's solution should be administered in bolus doses of 10–20 mL/kg, repeating as necessary, while the inspired concentration of inhaled anesthetic is decreased.

KEY POINTS: PROBLEMS DURING INDUCTION OF ANESTHESIA

- Desaturation during induction can be caused by airway obstruction, laryngospasm, bronchospasm, endobronchial intubation, or atelectasis as the main causes; prompt diagnosis and treatment are essential
- Bradycardia is less common now that halothane has been replaced by sevoflurane, but can still be caused by hypoxemia, high-dose sevoflurane, succinylcholine, vagal reflex, and others. It is more common in Down syndrome patients
- If hypotension is defined as >30% decrease from baseline, the incidence of hypotension is low, and even 8% sevoflurane plus propofol bolus 1–2 mg/kg for intubation is usually very well tolerated in healthy children

Maintenance of anesthesia

Methods

The most widely used prescription to maintain anesthesia in infants and children is inhalation anesthetics. Over the past 150 years, the molecular structure of inhalation anesthetics has been refined to the point that today these anesthetics are effective, reliable, easy to deliver, offer favorable qualities, and are safe. One key advantage that distinguishes inhalation anesthetics from IV agents is that we can continuously measure the end-tidal concentration of the former. This measurement provides invaluable knowledge regarding the accuracy of our delivery system and the patient's responses to the anesthetic. Currently, the three inhalation anesthetics, isoflurane, sevoflurane, and desflurane, are used to maintain anesthesia. Although a discussion of the pharmacology of inhaled anesthetics is beyond the scope of this chapter (see Chapter 10 for a more extensive discussion), several key principles can be summarized. All three anesthetics preserve cardiorespiratory homeostasis in healthy children. The only caveat relates to the use of desflurane in severe asthmatics and children exposed to second-hand smoke, who may experience more adverse respiratory events related to changes in pulmonary resistance during and after administration of desflurane [169]. In addition, if desflurane is used to maintain anesthesia with an LMA, perioperative adverse respiratory events are more common [170,171].

The speed of emergence after isoflurane and sevoflurane anesthesia is similar when the anesthetic concentration is tapered during maintenance, although the speed of emergence after desflurane will be more rapid than after both isoflurane and sevoflurane, particularly if (1) it was the sole anesthetic during the maintenance period, and (2) it was supplemented with short-acting opioids or non-opioid analgesics and if the surgery was prolonged [172]. Alternately, if large doses of opioids were used for analgesia, it is possible that the sedative effects of the opioids may delay emergence and result in similar emergence times with all anesthetics.

Nitrous oxide is the oldest anesthetic still in use and is commonly used during maintenance of anesthesia in children. Although it has several disadvantages, we believe none warrant its withdrawal from practice. Nitrous oxide is contraindicated in several clinical scenarios (including bowel obstruction, middle ear surgery, spinal surgery with motor evoked potential, and cardiopulmonary bypass), but has provided a background of anesthesia, sedation, and analgesia during painful procedures for decades. Omission of nitrous oxide increases the risk of awareness [173]. However, its effect on PONV remains debated: in a very large study in adults, the contribution to PONV was minimal [174], and in children its contribution to PONV increased with time, with a substantial effect

evident after 3 h of administration [175]. Side-effects from nitrous oxide include those mentioned previously as well as depression of methionine synthetase and atmospheric pollution. The environmental concern regarding nitrous oxide relates to its effects on global warming and depletion of the ozone layer. With an estimated life in the troposphere of 110 years [176], nitrous oxide is not environmentally green, although it is estimated that <5% of the nitrous oxide released in the atmosphere originates from medicinal use. Methods to reduce the medical footprint on the troposphere include combining desflurane with nitrous oxide, reducing the use of desflurane, using sevoflurane or isoflurane with an oxygen/air fresh gas flow, and improved carbon dioxide absorbents [177].

TIVA has generated much interest as the primary anesthetic for children with malignant hyperthermia, for those undergoing spinal surgery with motor evoked potential monitoring, and for those with a history of severe PONV. The primary general anesthetics for use in TIVA are propofol and ketamine. Propofol has antinausea properties that have been exploited in children with histories of PONV. Side-effects from propofol include pain on injection and propofol infusion syndrome (PRIS). Pain on injection of propofol may be obviated by pretreatment with 70% nitrous oxide or by applying a modified Bier block for 30–45 s with IV lidocaine (0.5–0.75 mg/kg) [138]. However, its major liability remains PRIS, which in some jurisdictions has resulted in it being proscribed for use as a sedative in children [169]. To date, propofol has caused PRIS in children sedated with propofol infusion rates >5 mg/kg/h for ≥48 h [178]. Between 1989 and 2004, more than 33 cases of PRIS were reported in children, as evidenced by an evolving lactic acidosis (for no apparent clinical reason) during propofol sedation/anesthesia that either reverted to a normal pH once the propofol infusion was discontinued or resulted in sudden death [179–181]. Currently, continuous propofol infusions are used in North America for sedation for medical and surgical procedures in children, but not in intensive care units where sedation for several days may be required. Sequential blood gas determinations would be prudent in all children who are sedated with propofol for prolonged periods. If an inexplicable lactic acidosis develops during propofol infusion, the infusion should be discontinued and appropriate resuscitation measures instituted.

Propofol infusion rates for anesthesia in infants and children to prevent movement during MRI or surgery range from 200 to 300 μg/kg/min (12–15 mg/kg/h) [182,183]. In the case of surgery, supplemental medications including opioids, muscle relaxants, and sedatives may be required. We have also noted that younger infants as well as those who are cognitively challenged require much greater infusion rates to prevent movement during MRI than older children without cognitive impairment. A word of caution when preparing propofol infusions for infants <1 year of age: the clearance of propofol is lowest in neonates and increases from neonates to infants 1 year of age, after which clearance remains unchanged into adulthood [184]. Thus, after the initial loading dose of propofol, the reduced clearance in young infants may require a reduced infusion rate to facilitate a rapid recovery.

To account for the differing pharmacokinetics of propofol (and other medications) over time and in children with differing physiology, target controlled infusions have been developed [185]. These infusion pumps incorporate software that automatically adjusts the infusion rate to the child's characteristics and to the desired blood concentration of propofol in that age group. To date, these infusion pumps have been modestly successful but are not widely available and are not expected for use in humans in North America in the near future.

Supplemental analgesics have also been used during either inhalation or IV anesthesia to prevent physiological responses and movement to pain. Remifentanil (with a zero context-sensitive half-life) 0.05–0.1 μg/kg/min may be administered as an infusion, whereas other opioids (fentanyl and morphine) are administered in IV boluses. Fentanyl (1–2 μg/kg) or morphine (0.05–0.1 mg/kg) may be administered IV with the dose adjusted up or down depending on the child's exposure to opioids, the severity of the pain, and concomitant analgesics.

Age versus minimum alveolar concentration

The MAC is defined as the minimum alveolar or end-tidal concentration of inhalation anesthetic at which 50% of the subjects move in response to a noxious stimulus, usually a skin incision in humans. In children, the MAC values for most inhalation anesthetics increase with decreasing age, reaching a peak during infancy. For example, the MAC of halothane and isoflurane increases with increasing gestational age and through early infancy, reaching its zenith in infants 1–6 months of age. It then decreases with increasing age (Fig. 17.3) [186]. The MAC for desflurane also increases during infancy but reaches its zenith in infants 6–12 months of age and then decreases with increasing age [167]. In the case of sevoflurane, the pattern of MAC and age differs substantially from that of the other inhalation anesthetics; the MAC of sevoflurane is constant, 3.2%, in neonates and infants 1–6 months of age and then decreases abruptly to 2.5% in infants from 6 months up to adolescence [166]. The neurobiological reason why MAC changes with age in childhood and why the relationships differ among the inhalation anesthetics has eluded researchers, although several theories have been proposed including

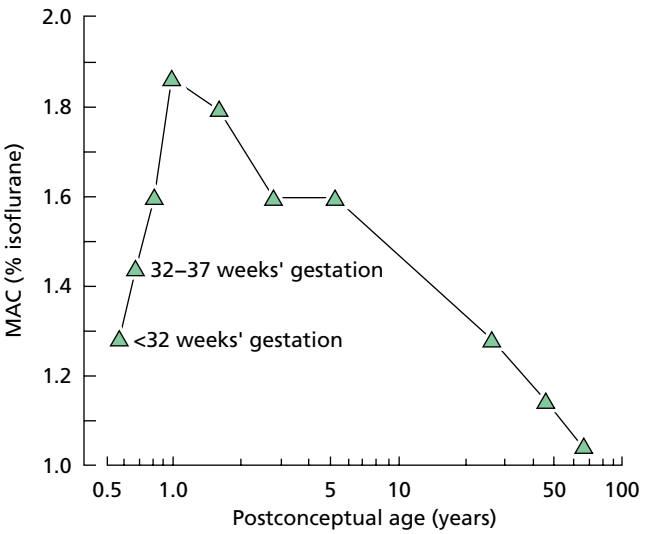

Figure 17.3 Age and the minimum alveolar concentration (MAC) of isoflurane from premature infants to adults. Reproduced from LeDez and Lerman [186] with permission of Wolters Kluwer.

differences in central nervous system (CNS) development and neurohumoral factors.

The concept of MAC includes the notion that the contributions of all concurrently administered inhaled anesthetics are additive towards the total MAC. Thus, 60% nitrous oxide with 1% isoflurane is equivalent to 0.6 + 1.0 or 1.6 MAC of inhalation anesthesia. This notion applies to isoflurane and halothane in children as well as to all the inhalation anesthetics in adults. However, when the MAC values of sevoflurane and desflurane in children were determined in combination with nitrous oxide, the MAC contribution of 60% nitrous oxide was only 20%, two-thirds less than the effect of nitrous oxide in the presence of isoflurane and halothane [166,187]. The reason for this substantially diminished effect of nitrous oxide with these two relatively insoluble anesthetics has not been explained.

A number of factors influence the MAC of inhalation anesthetics. Approximately 90% of adults who are homozygous or heterozygous for the melanocortin-1 receptor gene (i.e. redheads) require 20% more anesthesia than those without this mutation [188].

Children with cerebral palsy and severe mental retardation require 25% less halothane than healthy children [189]. Other variables that must be taken into consideration when determining MAC levels in children include chronic anticonvulsant therapy.

In addition to the traditional nociceptive stimulus of skin incision, the MAC responses to other stimuli including tracheal intubation and extubation, LMA insertion and extubation, tracheal intubation/skin incision ratio, and wakefulness have been reported in children [190]. The tracheal intubation to skin incision ratio in children is ~1.33 for halothane and sevoflurane. MAC awake for sevoflurane in children 2–5 years of age, ~0.66%, is almost 50% greater than in children 5–12 years, 0.44% [191].

Fluid management

General principles

Intravenous fluid sets should be prepared before the child arrives in the operating room. For infants and children, a 500 mL bag of lactated Ringer's solution with a buretrol is appropriate, although for neonates and preterm infants, a 250 mL bag and/or an infusion pump is preferable. For children >8 years of age, the IV infusion set may be prepared with a macro- or micro-drip without a buretrol and either a 500 or 1000 mL bag of balanced salt solution. All pediatric IV sets should include a manual controller, a one-way valve (to prevent medications from passing retrograde up the IV tubing), and needleless ports and/or three-way stopcocks for medication administration.

For neonates and preterm infants from the NICU, we continue the clear maintenance infusion from the NICU, i.e. 10% glucose and supplemental calcium. The infusion rate should remain unchanged during surgery since unexpected intraoperative hypoglycemia may occur if the hyperglycemic infusion rate is suddenly reduced. If sequential blood glucose concentrations are measured during surgery, it is possible to titrate the NICU infusion to maintain normoglycemia. Intralipid infusions are best discontinued before transfer to the operating room to reduce the risk of contaminating the Intralipid and central venous access line with repeated line accessing.

Most IV fluids administered to healthy children during elective surgery now consist of a non-glucose isotonic salt solution, commonly lactated Ringer's solution in North America. These solutions replaced glucose-containing hypotonic solution after reports of seizures, aspiration, and brain damage. Worldwide, the shift to isotonic solutions for intraoperative fluid maintenance in children has occurred more slowly [192]. Lactated Ringer's solution is slightly hypotonic (280 mOsm/L) and contains small concentrations of potassium as well as lactate. Normal saline (0.9% NaCl) is isotonic (308 mOsm/L) and contains no ionic moieties, but has a pH of 5.0. It is not routinely used as the primary maintenance solution since large volumes may lead to a hyperchloremic metabolic acidosis (non-anion gap type). We advocate glucose-containing solutions, such as 1% or 2.5% glucose in lactated Ringer's solution as a maintenance solution for full-term neonates and infants <6 months of age, and for young children who are cachectic, chronically malnourished, tolerate fasting poorly (maple syrup urine disease), and suffer from debilitating disease who may be at risk for hypoglycemia [193,194]. These solutions should avoid both hyperglycemia and hyponatremia intraoperatively. Although the incidence of hyponatremia has been dramatically reduced with the shift in practice to isotonic salt solutions, there may be reason to monitor serum electrolytes in specific surgeries [195].

Children with specific medical conditions should have tailored IV solutions. For children in renal failure or renal insufficiency, normal saline has been the preferred balanced salt solution because it contains no potassium, however there is some evidence that the non-anion gap acidosis that may occur may cause inadvertent hyperkalemia [196]. Thus lactated Ringer's solution may be the preferred solution. Children with a mitochondrial myopathy who developed lactic acidosis during infancy should be fasted for brief periods preoperatively and receive only normal saline with glucose supplementation as needed.

Infants and young children (<2 years of age) who may be hypovolemic should be assessed preoperatively for the magnitude of their fluid deficit: mild, moderate, or severe [197]. The signs of mild dehydration (5% bodyweight loss or approximately 50 mL/kg deficit) include poor skin turgor and dry mouth. The signs of moderate fluid dehydration (10% of bodyweight loss or 100 mL/kg deficit) include sunken fontanel, tachycardia, and oliguria, in addition to the signs of mild dehydration. The signs of severe fluid dehydration (15% of bodyweight loss or 150 mL/kg deficit) include sunken eyeballs, hypotension, and anuria, in addition to the signs of moderate dehydration.

Correction of the hypovolemia requires a staged infusion of fluids. Approximately 50% of the deficit should be replaced in the first hour, 25% in the second, and 25% in the third. A balanced salt solution should be used to restore euvolemia. Chapter 11 presents an extensive discussion of fluid therapy.

Elective surgery

For minor, elective surgery, the traditional calculation for the hourly fluid infusion rate has been based on replacing the triad of fluid deficit during fasting, on-going maintenance, and blood and third space losses. In children, the calculation was predicated on the 4–2–1 mL/kg/h where 4 mL/kg is for the first 10 kg, 2 mL/kg is for the second 10 kg, and 1 mL/kg is

for the third 10 kg and any additional bodyweight thereafter, as popularized by Holliday and Segar [198]. The initial blood loss may be replaced with balanced salt solution at a rate of 3 mL of solution for every 1 mL of blood loss. For third space losses, the replacement volume is based on the severity of the losses: 1–2 mL/kg/h for minor surgery, 2–5 mL/kg/h for moderate surgery, and 6–10 mL/kg/h for major surgery and large third space losses.

In a reappraisal of their 1957 fluid recommendations for children in the perioperative period, Holliday et al reviewed a series of reports of hyponatremia in children (>6 months of age) who had received hypotonic glucose-containing solution and evaluated the risks of using a balanced salt solution for maintenance fluids [199]. They determined that their original formula could lead not only to hyponatremia if excessive volumes were rapidly infused in young children, but that it could lead to water and sodium overload in some children if the formula was used with a balanced salt solution. This was of particular concern in the postoperative period because pain and certain medications may lead to inappropriate antidiuretic hormone secretion and an excess infusion of balanced salt solution might place some children at risk of congestive heart failure. They concluded that their previous 4–2–1 fluid formula that was used with hypotonic glucose-containing solutions should be replaced with a 2–1–0.5 formula with isotonic fluid in the postoperative period. They recommended a two-pronged approach: intraoperative rehydration with 10 mL/kg/h with balanced salt solutions in all children (for 2–4 h), and a postoperative maintenance rate of balanced salt solutions using half their original formula or 2–1–0.5 mL/kg [199].

Although most pediatric surgeons are careful to minimize bleeding during surgery, it is important to remain vigilant throughout the procedure to monitor blood loss. For those procedures that result in significant tissue trauma or blood loss, the provider must ensure appropriate size IV access to transfuse blood and blood products as needed and a measure of volume status/replacement. Packed cells cannot be rapidly infused through either 24-gauge IV catheters or peripherally inserted central catheters (PICC). The smallest intravenous cannula through which blood can be rapidly infused is a 22-gauge catheter. Every effort should be expended to insert the largest IV catheter that the child's size can accommodate. Initial blood loss is replaced with a balanced salt solution in a ratio of 3 mL of salt solution for every mL of blood loss. This replacement, together with the maintenance requirement, should be logged on the anesthetic record. As the combined volume of balanced salt solution approaches 75–100 mL/kg, it is important to consider the possibility of dilutional thrombocytopenia and dilution of coagulation factors; coagulation indices should be measured at this time.

The threshold for triggering packed cell transfusions in children has also undergone a renaissance in the past decade, with evidence that the outcome and complications after a conservative transfusion trigger (i.e. 7 g/dL) were similar to those with a liberal transfusion trigger (9 g/dL [200,201]. The estimated blood volume in a child decreases with increasing age from 95–100 mL/kg in premature infants to 70 mL/kg in adults 202]. Note that obese children have an estimated 10% reduced blood volume compared with similar aged children [193]. To estimate the allowable blood loss during surgery, one may use the following equation [202]:

$$\text{Maximum allowable blood loss (MABL)} = (\text{starting Hct} - \text{target Hct}) / (\text{starting Hct}) \times \text{estimated blood volume}$$

For example, if target Hct for a patient with starting Hct of 35% is 20%,15/35 = 0.43; if an 18-month-old patient weighs 10 kg and has a blood volume of 750 mL, 0.43 × 750 = 323 mL is the MABL.

Some use a modified version of the MABL calculation, replacing the "starting Hct" in the denominator with the "average Hct" to increase the allowable blood loss before transfusion. Irrespective of which equation is used to estimate the allowable blood loss, the actual Hct should be determined before blood transfusion is initiated to ensure that the actual Hct warrants initiating blood. When initiating a blood transfusion to a child, two formulae provide rough estimates of the amount of blood required to increase the hemoglobin concentration 1 g/dL: 4 mL/kg packed cells and 6 mL/kg whole blood. Chapter 12 presents additional information about blood transfusion.

Postoperative nausea and vomiting

The incidence of PONV in children depends on a number of factors that relate to the patient (motion sickness history, age), the anesthetic (inhaled anesthetics, nitrous oxide, opioids, preoperative fluid administration, postoperative fluid ingestion), and the surgery (inguinal/orchidopexy, tonsillectomy and adenoidectomy, strabismus, and middle ear surgery). The importance of each of these factors has been the subject of intense investigation.

Children should be fasted preoperatively for brief periods and not forced to drink oral fluids postoperatively until they request them [203]. Intraoperatively, the child should be adequately hydrated with IV fluids [204] and provided with regional anesthesia and non-steroidal anti-inflammatory agents instead of opioids where possible. If the child is scheduled for emetogenic surgery and has a history of PONV, the optimal anesthetic regimen may include propofol oxygen/air and two antiemetics, although evidence is conflicting regarding the beneficial roles of substituting propofol for inhalation agents and air for nitrous oxide [174,205]. In a recent systematic review, TIVA was as effective as a single antiemetic in preventing PONV after strabismus surgery in children, although the frequency of bradycardia was greater after IV anesthesia [206]. The role of nitrous oxide is not "all or none", but rather depends on the duration of exposure [207].

The optimal prophylactic antiemetic strategy to administer to children during anesthesia is dexamethasone and a 5-HT3 receptor antagonist such as ondansetron [208]. A dose of dexamethasone between 0.0625 and 1 mg/kg (maximum 24 mg) has been shown to be equally effective, although we limit our maximum dose to 10 mg [209]. One report suggested that dexamethasone is associated with an increased incidence of postoperative tonsil bleeding [210], although the preponderance of evidence refutes this association [211–213]. The dose of ondansetron that we recommend for prophylaxis in children is 0.05–0.15 mg/kg.

KEY POINTS: MAINTENANCE OF ANESTHESIA

- Sevoflurane is by far the most common approach to maintenance of anesthesia; TIVA techniques using propofol and opioid infusions are also frequently used
- Isotonic non-glucose solutions, i.e. lactated Ringer's, are now the mainstay of fluid therapy, decreasing the risk of hyponatremia and hyperglycemia
- Transfusion triggers are now more restrictive; for infants and children without significant cardiopulmonary issues, 7 g/dL is usually accepted
- To prevent postoperative nausea and vomiting, two antiemetics, commonly a 5-HT3 receptor antagonist and dexamethasone, are usually quite effective

Emergence and recovery from anesthesia

As surgery concludes, the inspired concentration of inhalation anesthetics or infusion rates of IV drugs are tapered and discontinued. Recovery after inhalation anesthetics follows the order desflurane < sevoflurane < isoflurane < halothane. The degree of paralysis should be assessed and neuromuscular blockade antagonized as required. Before extubation, the child's respiratory effort and motor strength are assessed. Equipment should be available to manage the airway (facemask, 100% oxygen) as well as complications from the extubation (suction).

The primary focus of the entire anesthesia team during emergence is to assess the child's airway, their ability to breathe, and their ability to protect the airway should bleeding or vomiting occur once the airway is extubated. It is our practice to extubate the airway, whether from a tracheal tube or LMA, when the child has fully recovered airway reflexes and is awake. There are very few surgical or medical indications to remove the airway during deep levels of anesthesia, and little evidence that this practice results in better outcomes. Contraindications to deep extubation may include a difficult airway, morbid obesity, severe OSA, and diseases with severely limited pulmonary reserve (e.g. cystic fibrosis). The greatest concern regarding deep extubations is that a child who is deeply anesthetized and transported with an unsecured airway relies totally on extremely high-quality nursing in PACU to monitor the airway until the child is awake. The evidence regarding the frequency of adverse airway events after deep tracheal extubation or awake is mixed [214,215]. In most instances, the anesthesiologist returns to the operating room after transferring the child's airway and care to the PACU nurses. In some institutions, the nurses are trained and qualified to manage the airway in an anesthetized child, although an anesthesiologist should be available to manage airway issues should they occur.

In our experience, children who have an LMA are at increased risk for developing progressive airway obstruction several minutes after they emerge from anesthesia and the device is removed. Accordingly, we remove all LMAs in the operating room before transferring the child to PACU. Recent evidence concluded that safe conditions are optimized when the LMA is removed during a deep plane of anesthesia with the child in the lateral decubitus position [216]. In the case of desflurane, we reported a substantially greater frequency of adverse airway reflex responses when the LMA was removed during a deep level of anesthesia than when it was removed awake or compared with isoflurane [170]. We recommend that all LMAs be removed when the child is awake, especially if desflurane has been administered.

The timing of tracheal extubation is critical for minimizing the risk of adverse airway events during emergence. The optimal time for extubation requires that the child has emerged from anesthesia to the extent that he/she can support their own airway. Recognizing the optimal time for extubation requires an appreciation of the three phases of emergence from inhalation anesthesia in children: early, middle, and late. Each of these phases may last for up to several minutes depending on the anesthetics administered and the age of the child. During the early phase of emergence, the child first coughs intermittently, gags, struggles, and moves non-purposefully. This phase passes relatively quickly as the child enters the middle or quiescent phase. During this phase, the child may appear to be deeply anesthetized, apneic, or "agitated," during which time he/she breathholds, strains, and/or desaturates, the last necessitating assisted ventilation of the lungs to maintain an SpO_2 to >95%. As the child resumes quiet, spontaneous respiration, he/she enters the late or third phase of emergence, which is characterized by purposeful movement, flexing the hips, coughing, and gagging on the tracheal tube, all of which increase in intensity until the child grimaces and opens their eyes spontaneously. Removing the tracheal tube during either the early or middle phase increases the risk of triggering an adverse airway event (e.g. laryngospasm). It is only during the third phase of emergence that adverse airway reflex responses are least likely to be triggered if the tracheal tube is removed. We teach our residents that if you think the time is right to remove the tracheal tube, don't! Leave the tube *in situ* for another minute (or two) until the child is definitely in the late or third phase of emergence. It is at this time that the tracheal tube may be removed with the lowest risk of adverse airway events.

While children emerge from anesthesia, the practitioner can follow one of two strategies: either no-touch or stimulation. With the former technique, the child breathes 100% oxygen undisturbed and unstimulated while the third phase of emergence is awaited. When the end-tidal anesthetic concentration decreases to a level consistent with wakefulness (e.g. sevoflurane concentration <0.6%, depending on adjuvant agents) [191], the eyes will open spontaneously, he/she will reach for the airway, gag, and grimace indicating it is time to remove the airway. Some advocate the "no touch" technique with the child in the lateral decubitus position to reduce the risk of laryngospasm [217]. With the latter technique, the initial recovery is the same as with the no-touch technique, however the transition through the second and third phases is speeded by applying digital pressure (in the direction of the front hairline) to the posterior ramus of the coronoid process, the most cephalad portion of the ascending ramus of the mandible, for 3–5 s [158] when the end-tidal anesthetic concentration of isoflurane is <0.25% or sevoflurane is <0.6%. The child reacts to this stimulus by arousing, gagging on the tracheal tube, moving purposefully, and opening the eyes. Both strategies generate similar outcomes with safe and protected airways.

Box 17.9: Causes of delayed emergence from anesthesia

- Residual drug effects: inhalational anesthetics, opioids, propofol
- Non-anesthesia medications: recreational drug use (cocaine, crack), herbal medicines (valerian, St John's wort)
- Depressed neuromuscular junction: residual neuromuscular blockade or pseudocholinesterase deficiency
- Hypothermia
- Hypo- or hyperglycemia
- Electrolyte imbalance: hyper- or hyponatremia
- Acid–base disturbance
- Hypercapnia
- Cerebrovascular accident/hypoxia: check pupil size and responsiveness to light bilaterally, presence of a gag reflex, symmetrical limb reflexes

In the vast majority of children, emergence progresses smoothly as described previously, with increasing arousal culminating in the child gagging and rejecting the presence of the tracheal tube. However, in rare instances, this sequence of events fails to progress at all, or if it progresses it is not smooth. Children who fail to emerge from anesthesia must be assessed for a variety of potential problems (Box 17.9). The most common cause of delayed emergence is a relative drug overdose as in failure to taper or reduce the dose of inhalation or IV anesthetic. However, rare but potentially catastrophic events such as unexpected hypoglycemia or an intracranial bleed (dilated pupil) may complicate the anesthesia and surgery and lead to prolonged coma. Laboratory tests may be required to diagnose the cause of the coma. Definitive treatment should be administered once the diagnosis is confirmed.

Complications during recovery

The incidence of complications in PACU is 5–10% [218,219]. Of these, 77% are attributable to vomiting and 22% to respiratory issues. The remaining 1% or less are attributable to cardiac issues. The age distribution of the complications is important: vomiting is more than twice as frequent in children >8 years of age than in younger children, whereas respiratory complications occurred twice as frequently in infants <1 year of age than in older children.

Postoperative nausea and vomiting

The frequency of PONV in PACU has decreased dramatically since the introduction of prophylactic antiemetics for most children who are anesthetized. Routine use of two antiemetics, dexamethasone and ondansetron, reduces the perioperative incidence of vomiting by up to 80% or greater [196]. Most children who vomit, vomit after ingesting their first fluids (in the stepdown PACU), in the car, or at home. Hence, we allow children to drink oral fluids after surgery only when they request to drink [203]. If the child continues to vomit, there are few effective interventions to stop the vomiting. Oral fluids should be withheld for a period and ondansetron may be given again, either IV or sublingually. It is important to appreciate that the child may be a rapid metabolizer (CYP 2D6 polymorphism) or have a rapid transporter P-glycoprotein polymorphism, resulting in a poor antiemetic effect [220,221]. Since we do not test for polymorphisms, it is reasonable to administer a second dose of ondansetron if the previous dose was given 2 or more hours before. Alternately, a dose of metoclopramide may be administered IV (at 150 μg/kg). It should be noted that droperidol (prolonged QT syndrome) and promethazine (respiratory depression in patients <2 years of age) both have US FDA boxed warnings (contraindications) for PONV treatment in children.

Emergence delirium

The introduction of sevoflurane into pediatric anesthesia caused a recrudescence in the frequency of emergence delirium (ED) after anesthesia. ED and pain are two conditions that fall under the umbrella term, emergence agitation. ED has been recognized as a sequela of anesthesia for several decades, increasing in frequency every time a new, less soluble inhalation anesthetic was introduced. ED has been characterized as follows: the incidence peaks in children (of both sexes) 2–6 years of age; it is more common after some anesthetics (sevoflurane ~ desflurane ~ isoflurane >> TIVA); it lasts 10–15 min and is terminated either spontaneously or after a single IV dose of propofol, midazolam, clonidine, dexmedetomidine, ketamine, or opioids [222–225].

The challenge in diagnosing ED in children in the PACU after surgery is differentiating it from pain [226]. To that end, ED was assessed in children undergoing MRI with either sevoflurane or halothane [227]. In the absence of any source of pain after the MRI, the frequency of ED after sevoflurane was five-fold greater than that after halothane.

A host of studies continued to report ED after a variety of surgeries, with and without adequate analgesia, and using non-validated delirium scales. This led to much confusion regarding the nature, cause, and treatment of ED. In order to clarify much of the confusion, the pediatric anesthesia emergence delirium (PAED) score was developed and validated as an objective measure of ED where a score >10 was indicative of the presence of ED, although some have suggested that a score >12 may be more specific [228,229].

Laryngospasm, postoperative stridor, and negative pressure pulmonary edema

Laryngospasm, postoperative stridor, and negative pressure pulmonary edema occur not only at induction of anesthesia but also at or after emergence from anesthesia. Factors that increase the risk of laryngospasm include removing the tracheal tube from the larynx prematurely, the presence of blood, secretions, or foreign material within the pharynx, secondhand smoke, and a recent history of upper respiratory tract infection (see Box 17.8). For a full discussion of laryngospasm please refer to the section "Problems during induction of anesthesia."

Postextubation stridor may also occur upon tracheal extubation. Stridor occurs because the epithelium within the cricoid ring swells after the tube is removed, thus reducing the cross-sectional diameter of the airway. Because airflow in the upper airway is turbulent, the resistance to airflow increases as the fifth power of the radius decreases. That is, if the radius of the airway within the cricoid ring decreases by 50%, the resistance to airflow increases 32-fold. In the infant with increased oxygen requirements and metabolic rate, residual opioids, muscle weakness, and anesthesia may further compromise the

ability to maintain an increased work of breathing in the presence of stridor, and that could hasten fatigue and respiratory failure. Children with Down syndrome have a greater risk of postextubation stridor [230]. The treatment for stridor includes humidified oxygen, IV dexamethasone (1 mg/kg IV), and nebulized racemic epinephrine (0.5 mL epinephrine in 2 mL saline). Rarely is it necessary to reintubate the airway for persistent and severe stridor in PACU. If hypoxemia or respiratory failure occurs, the trachea should be reintubated with a smaller size tube than the original one. An audible leak should be present after intubation to avoid further irritating the epithelium. If racemic epinephrine treatment is repeated more than twice, the child should be observed for rebound edema in either the PACU or a monitored unit.

Negative pressure pulmonary edema, or postextubation pulmonary edema, is an infrequent complication, usually occurring immediately or within several minutes after tracheal extubation in healthy, muscular adolescents and young adults, although it has been reported in infants [231–234]. Once the trachea is extubated, the child appears somnolent and unresponsive as the airway appears increasingly obstructed. A cascade of events then occurs with lightning speed beginning with upper airway obstruction and laryngospasm that ranges from very mild to severe. Contemporaneously, the oxygen saturation decreases, almost out of proportion to the severity of the airway obstruction. Despite ventilation by mask with 100% oxygen, tracheal reintubation is usually required to restore the saturation to normal values. Reintubation may be achieved using a muscle relaxant, propofol, or both. Upon reintubation, pink frothy pulmonary edema fluid is suctioned from the tracheal tube. Positive pressure ventilation with sufficient oxygen to restore the oxygen saturation to >94% and positive end-expiratory pressure should be maintained until oxygen, positive end-expiratory pressure, and ventilation are no longer needed to maintain the oxygen saturation. There is usually no need for additional measures to treat the pulmonary edema other than tracheal intubation. Sedation may be required for 12–24 h or more until the pulmonary edema resolves and/or the trachea can be extubated.

The mechanism of the pulmonary edema post extubation is believed to begin with extremely negative intrathoracic pressures generated against a closed glottis (i.e. laryngospasm) (known as the Muller maneuver) that augments transvascular filtration of hypoproteinemic fluid into the interstitium with a secondary surge in venous return [235]. These mechanisms combine to produce pulmonary edema.

Oxygen desaturation

Failure to maintain an adequate oxygenation saturation in the recovery room is a common problem. Unrecognized hypoxia may lead to a deterioration in the child's clinical status with bradycardia and cardiac arrest occurring suddenly. Continuous monitoring of the child's oxygen saturation is essential in the PACU to ensure an early warning indication of this complication. The minimum acceptable oxygen saturation in PACU is ≥94%. Administration of oxygen by facemask may be required to maintain the oxygen saturation, particularly if residual anesthesia or opioids are present, a craniofacial or muscular abnormality is present, or if the child is obese or fluid overloaded. In healthy children, desaturation is generally indicative of hypoventilation and/or airway obstruction. However, oxygen administration may mask the signs of hypoventilation, delaying airway intervention [236]. Because ventilation is not monitored in children without artificial airways en route to and in the PACU, we rely on clinical signs to diagnose and treat airway obstruction and hypoventilation.

Children should be weaned from oxygen dependency (assuming they did not require supplemental oxygen preoperatively) before they are discharged to the floor or the step-down unit. Some children remove the facemasks themselves when they awaken from anesthesia; if their oxygen saturation is maintained while breathing room air, then no additional oxygen treatment is required. If the child requires supplemental oxygen by facemask, it should be weaned to nasal prongs and then removed to room air while the saturation is monitored. If the child cannot maintain their oxygen saturation after attempts to wean them from the oxygen, further investigation (such as a chest radiograph) may be required to rule out organic causes such as aspiration, pneumonia, or pneumothorax. Chapter 18 presents additional information about PACU management.

KEY POINTS: EMERGENCE AND RECOVERY FROM ANESTHESIA

- Delayed emergence has a number of causes including residual anesthetics, opioids, neuromuscular blockers, hypoxia, hypothermia, or CNS injury; investigation must occur immediately and effective treatment be instituted
- Awake extubation of the trachea is recommended, unless very experienced PACU nursing and anesthesiologist response are available to respond to airway emergencies
- Emergence agitation is common in children 2–6 years of age and after inhalation anesthesia; treatment with opioids, propofol, midazolam, or dexmedetomidine can be effective; the Pediatric Anesthesia Emergence Delirium scale can be used to diagnose emergence delirium, but may be confused with pain
- Laryngospasm can result in postobstructive pulmonary edema if severe, and must be addressed immediately with positive pressure ventilation, mandible thrust, and, if necessary, propofol or succinylcholine

Transport to the postanesthesia care unit and intensive care unit

Transferring children from the operating room to either the postanesthesia care unit (PACU) or the intensive care unit (ICU) carries inherent risks that must be anticipated and assessed continuously.

Before being transported to PACU, the child must have a stable airway, be able to maintain adequate oxygenation and ventilation, have stable heart rate and blood pressure measurements, and have adequate pain control. An expert who remains vigilant throughout the transport and who is trained to manage potential postoperative problems should accompany the child.

During transport to PACU, most children breathe spontaneously, without requiring an oral airway in place. The optimal position to transfer a child, particularly after airway surgery, is the lateral decubitus position, known as the "recovery position." In this position, the upper leg is flexed at the hip, and the upper knee is resting on the bed in front of the lower leg. The child's upper hand should be placed under the lower cheek. This position facilitates drainage of secretions, blood, or vomitus out of the mouth rather than onto the larynx, and the tongue falls to the lower cheek or out of the mouth rather than posteriorly onto the larynx. The lateral position combined with airway maneuvers improves airway patency [237]. In addition, this position permits direct intervention in the airway should the need arise.

Supplemental oxygen may be administered by nasal prongs or facemask during transport, although if the child is monitored with pulse oximetry during this time, desaturation may not occur even in the presence of profound hypoventilation. Some advocate pulling up the chin to feel air movement on their palms during transport. We do not encourage maneuvers that close the child's mouth because this often obstructs the airway. Instead, we recommend extending the child's neck with the base of the hand (thenar and hypothenar eminences) applied to the forehead, and holding the fingertips over the mouth/nose to sense expiration.

Others transport the child to PACU in the supine position. This position undermines all of the advantages outlined for the decubitus position and facilitates posterior displacement of the tongue that may obstruct the airway [237]. Opioids have been shown to depress the hypoglossus motor nuclei centrally, which will relax the genioglossus muscle [238]. If the child is positioned supine, relaxation of the genioglossus muscle may cause the tongue to obstruct the laryngeal inlet. When opioids are administered along with inhalation anesthetics, the motor tone of the genioglossus muscle decreases, allowing it to fall back and obstruct the airway. Thus, children who receive opioids along with inhalation anesthetics should be transported in the lateral decubitus position to reduce the risk of airway obstruction during recovery.

Children who have recovered from anesthesia and who have normal heart and lungs generally do not desaturate when breathing room air, unless their airways become obstructed. Administering oxygen en route to PACU came into vogue about 25 years ago, at about the same time as portable pulse oximetry was introduced for transport. Studies at that time demonstrated that children desaturate en route to the PACU. However, in most instances, the desaturation resulted from airway obstruction, not from desaturation during tidal respiration. Rather than administering oxygen during transport, the child should be positioned in the recovery position with the neck extended by the anesthesiologist's thenar and hypothenar eminences and observed carefully for evidence of upper airway obstruction. In this position, the anesthesiologist's fingertips are positioned over the child's mouth and nose to sense the warm air of expiration. If a facemask is used to deliver oxygen, the observation of moisture on the mask is the only means to detect respiration unless portable capnometry is also employed.

If the patient is scheduled for transport to the ICU, additional planning is required before transfer. The medical and nursing staff in the ICU must be given a verbal summary of the child's condition as it relates to anesthetic/drug infusions, cardiorespiratory status, and ventilation requirements in order to prepare the appropriate equipment. The decision to transport the child with or without a tracheal tube should be made in conjunction with the intensive care team with a view to the child's longer-term management. Depending on the reason for admission to ICU, the child should be transferred with appropriate monitoring, emergency drugs, and equipment to maintain cardiorespiratory stability including equipment to re-establish the airway should it be lost during transport. Specifically, propofol, succinylcholine, and atropine should be immediately available (and inotropes depending on the child's needs) as well as a bag, facemask, second tracheal tube, and a functioning laryngoscope.

In the case of neonates, particularly preterm infants, the distance between the operating room and the NICU is usually substantial and over several floors. Given the precarious nature of the neonate's airway and the need for adequate analgesia, it seems prudent to transfer these small infants with their airways secured with a tracheal tube; once in the NICU, a dialogue should take place between the anesthesiologist and the neonatologist regarding the timing of tracheal extubation.

CASE STUDY

A 3-year-old child with loud snoring, brief periods of apnea during sleep, fatigue upon arousal in the morning, and attention deficit disorder presented to the otolaryngology service for possible ambulatory tonsillectomy. The child was small for his age, 13 kg in weight, and otherwise healthy. The review of systems was unremarkable. He had an uneventful bilateral tympanostomy as an infant under general anesthesia. The child had no history of allergies to medications and was receiving no medications. There was no family history of anesthesia-related complications or muscle diseases, although both parents had type II diabetes.

The child was fasted for surgery. To smooth the separation from his parents, 10 mg oral midazolam was administered in a medicine cup and followed with a swallow of water. The nurse accompanied the child to the operating room where he was monitored.

The child chose a flavor from three possible choices and used the lip balm to color the inside of the clear facemask. The mask was then gently applied to his face while 70% nitrous oxide in oxygen flowed. When the child stopped responding to conversation, 8% sevoflurane was added to the fresh gas. After intravenous access was established, a dose of propofol (1.5 mg/kg) was administered and the trachea intubated with an uncuffed RAE tube. After the gag was inserted into the mouth, the child began to breathe spontaneously with a gas mixture of 70% nitrous oxide in

1% isoflurane. Dexamethasone (2 mg) and ondansetron (1 mg) were administered intravenously. Without a polysomnogram, it was unclear whether this child desaturated at night and was hypersensitive to opioids. Accordingly, his opioid sensitivity was evaluated by administering 20 μg/kg morphine. After a single dose intravenously, the child stopped breathing, the oxygen saturation was 94%, and his heart rate decreased from 125 to 96 bpm. A second dose of morphine was administered for a total of 40 μg/kg. At the conclusion of the anesthetic, the child continued to breathe spontaneously but made no effort to reject the tracheal tube.

When the end-tidal isoflurane concentration had decreased to 0.2% and the child had not aroused, concern was expressed. The doses of the propofol and opioids were rechecked to verify that an accidental overdose had not occurred. The ampoules for the dexamethasone and ondansetron were similarly rechecked. A venous blood gas was sent for blood gases, electrolytes, and glucose concentration. All of the laboratory results were within normal limits.

At this time, the child's vital signs were within normal limits. Help was summoned and a differential diagnosis of possible causes was explored. The parents were asked again about recent prescription or non-prescription (including herbal) medications that the child may have taken, but there were none.

No obvious cause for the failure to emerge from anesthesia was forthcoming until one of the anesthesiologists removed the tape from the child's eyes. Lifting the eyelid revealed a shocking finding. The child's left pupil was fixed and dilated, unresponsive to light.

The child remained intubated and was taken for an emergency CT scan which showed an intraventricular bleed, hydrocephalus, and a midline shift. Neurosurgery were consulted and they scheduled the child for a ventriculoperitoneal shunt. Cerebral angiogram later demonstrated an arteriovenous malformation that was successfully coiled by an interventional radiologist. The child made a slow but steady recovery after this completely unexpected and unpredictable neurological catastrophe.

Acknowledgment

The authors thank Dr S. Watt for her prior contributions.

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A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 18
Postanesthesia Care Unit Management

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Introduction

The importance of the postoperative care unit in the safe, successful management of a child who has undergone anesthesia cannot be overstated. Centralization of care by a group of specially trained nurses who are expert in interpreting and responding to the events following anesthesia is key. This phase is beset with potential pitfalls and complications that require rapid assessment and treatment. Not only are there the basic needs that exist of a patient awakening from anesthesia, but in children there are additional unique aspects of postanesthesia care. Particularly in infants, perioperative anesthetic morbidity is higher than in other age groups, which further underscores the importance of the dedicated pediatric postanesthesia care unit (PACU) [1]. The Pediatric Perioperative Cardiac Arrest (POCA) registry supports the importance of proper management in the postoperative period [2]. The increased incidence of adverse events mandates care and consideration in the design and staffing of a pediatric PACU in addition to the essential appropriate postoperative management of potential issues and complications.

Essentials of the postanesthesia care unit

Design

When determining the design of a recovery area, the ideal location of any PACU is directly contiguous to the operating rooms to minimize transfer time and distance. There should be no elevator transport between the operating room and PACU if possible, although clearly many offsite procedure locations (such as magnetic resonance imaging (MRI) or interventional radiology) render this impractical [3].

The floor plan or design of a pediatric PACU need not differ from any other PACU environment. The entry from the OR and exit following recovery need to be different to avoid congestion [3]. Typically a PACU will have an open plan to permit optimum visibility, although this may not be ideal for all recovering children (Fig. 18.1). Not only can the audible distress of another patient be disruptive, but chatter and discourse of the medical staff have been noted as an unwanted feature of postoperative recovery [4]. The importance of lowering environmental stresses such as excessive noise is now being recognized in modern designs [4]. The presence of curtains between each bed space allows some visible privacy, but does nothing to change the noise pollution. Separate rooms would allow for a better sound barrier, but they may be undesirable as they do not allow for vigilant monitoring by a nurse who is covering several patients. Lines of sight are critical. Separate rooms may also be more difficult to navigate in an emergent scenario (Fig. 18.2). A possible compromise is to have rooms with sliding glass dividers and curtains between them that allow flexibility between rooms but the ability to separate the rooms as needed. With any plan, separate isolation rooms are needed, either for barrier purposes or reverse isolation. The number of beds required in the PACU should reflect the surgical volume, with a ratio of 1.5–2 beds to each operating room according to current perioperative environment design models [3].

Finally, there are many general features that are required by the Joint Commission on Accreditation of Healthcare Organizations, for example at least two fire exits, ample handwashing facilities, and separate clean and dirty storage areas, to name but a few. The average temperature in a pediatric PACU should be around 24°C (75° F), relative humidity between 40% and 60%, and in general there should be a slight positive pressure in the unit. Air changes should occur at a minimum rate of six per hour.

Equipment

The equipment in the pediatric PACU needs to have the ability to recover patients of all sizes. The American Academy of Pediatrics and the American Society of Anesthesiologists have

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

Figure 18.1 A modern pediatric PACU with open design, immediate adjacency to operating rooms, parents present, ample staffing with experienced pediatric PACU nurses, and prompt availability of anesthesia providers to respond to emergencies.

Figure 18.2 An alternative pediatric PACU providing more privacy and less noise pollution.

proposed guidelines for the pediatric perioperative anesthesia environment [5]. The essential components were identified to promote the safety and well-being of infants and children by reducing the risk for adverse events. In particular, all pediatric anesthesia equipment and drugs that are required in the operating room should be available for patients in the PACU. It is the authors' recommendation that a replica, fully stocked, mobile anesthesia cart be conveniently located in the PACU. Equally all bed slots should be identical, to facilitate safe delivery of care.

Every child admitted to the PACU must have his or her vital signs monitored, which mandates monitoring equipment that is appropriate for all ages and sizes. Suction apparatus and oxygen delivery, via a flow meter to allow titration of inspired oxygen as required, must be available at each bedside. Equipment for intravenous fluid administration must allow for microadjustments of volume delivery. Particularly

Figure 18.3 A standard emergency cart centrally located within the PACU with age-specific airway supplies and defibrillator on top.

in the smallest children, placing the intravenous fluids on a pump to deliver set volumes on arrival to the PACU is advisable. Due to the increased risk of heat loss in children in the operating room, devices for the maintenance of normothermia must be available and utilized.

The pediatric PACU should also have a focal, easily accessed location for the placement of portable emergency equipment. To prepare for the unexpected, a resuscitation or "code" cart with equipment appropriate for pediatric patients of all ages, including pediatric defibrillator paddles, must be immediately available. Specialized equipment for management of the difficult pediatric airway by a variety of techniques for airway control, intubation, and ventilation, including emergency cricothyrotomy, is desirable. A dedicated airway bag that contains packets of age/weight-specific airway supplies should be a part of the resuscitation cart apparatus (Fig. 18.3). To simplify procedure in the event of an emergency, written pediatric doses for resuscitation drugs, and potentially pediatric advanced life support (PALS) algorithms, should be visible or immediately available. All emergency equipment must be frequently checked and regularly maintained with a checklist system.

Staffing

Staffing of the pediatric PACU is an important component for the success of the environment. For most patients, recovery from anesthesia is uneventful, but it is also a time

when catastrophic events can occur. Pediatric-trained medical and nursing staff are required to be vigilant, caring, and knowledgeable. In 2016 the American Society of Anesthesiologists published updated recommendations specifically for a pediatric PACU [6]. This task force recommended that in order to apply specific expertise in the provision of pediatric anesthesia services, an anesthesiologist or other physician trained and experienced in pediatric perioperative care, including the management of postoperative complications and pediatric cardiopulmonary resuscitation, must be immediately available to evaluate and treat any child in distress.

The intensity of nursing care is typically greater in a pediatric PACU than on the pediatric ward with assignments based on acuity. The requirements of PACU nursing will be institution dependent. Prior pediatric experience and PALS training would clearly be advantageous and is recommended. Mock emergencies and codes, possibly to include scenarios using simulation, should be routinely performed with anesthesia and nursing staff so that the care is seamless in a true emergency. Although not stated by the task force, nursing staff should be pediatric trained and, ideally, have a background in pediatric intensive care. This would suggest confidence in the care of the unconscious child, ability to recognize a child in distress, ability to recognize a lost airway, and having expertise in the safe administration of potent analgesics. To recognize the subspecialty expertise, the pediatric PACU nurses are to be engaged as part of the perioperative team and be members of pediatric perioperative team meetings that include surgeons, anesthesiologists, and nursing staff. This builds a cohesive group for the good of the pediatric perioperative environment.

At our hospital, we have a twice daily debriefing between the PACU nursing staff and the on-call pediatric anesthesiologist. Issues such as staffing levels and resources (e.g. available intensive care beds), patient numbers, level of acuity, and post-PACU plans are discussed to prepare collectively for the work ahead.

Transport

Any hospital patient transport presents a period of significant risk of morbidity and mortality [7,8]. The transport of a child from the operating room to the PACU should not be considered routine. Apnea, loss of a patent airway, vomiting, and emergence agitation are just a few of the potential problems encountered during transfer. To be prepared for these events, it is advisable for the anesthesia provider to have resuscitation drugs and airway equipment that are individualized for the patient or surgery that was performed. Children should be transferred in on a bed or crib with guardrails. The lateral recovery position is often used because it facilitates a patent airway with gravity opening the airway and draining oral secretions and blood (Fig. 18.4). Oxygen must always be available along with a suitable delivery device such as nasal cannulae, facemask, or anesthesia circuit with mask. The use of a monitoring device such as pulse oximetry depends on the status of the patient and distance to the recovery area.

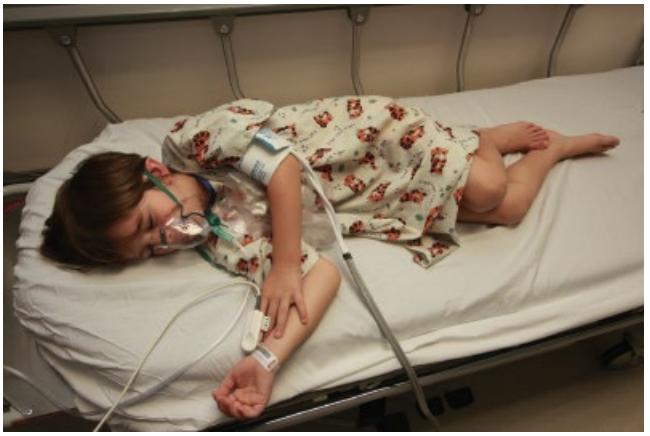

Figure 18.4 Lateral recovery position with airway open to encourage forward drainage of secretions. (Bed rail left down only for purpose of photo.)

KEY POINTS: DESIGN, EQUIPMENT, STAFFING, AND TRANSPORT

- Design of a pediatric PACU is similar to that for adults, but considerations for privacy and noise reduction have become evident in recent designs
- A pediatric PACU needs to have a full range of pediatric anesthesia equipment and drugs for children of all sizes, and an easily accessed location for emergency equipment
- Expertise in pediatric PACU nursing, and availability of an anesthesiologist, as well as formal training in pediatric resuscitation, is important for recovery of pediatric patients
- Transport to the PACU is a high-risk period, and continuous monitoring, either of clinical signs or pulse oximetry, and rapid availability of oxygen and positive pressure ventilation are important

Handover and assessment

The universal criteria by which patients are deemed suitable for the pediatric PACU are variable and depend on many factors including staffing and acuity. Some patients are easily considered candidates for PACU, including healthy outpatients for minor procedures, and others are clearly not suitable, such as the potentially hemodynamically unstable patient with cardiac disease. Other cases fall into a gray area that requires thoughtful consideration of the ultimate location for recovery. Skills and comfort level of the individual PACU and relationship with the floor or intensive care units may affect the decision of disposition post surgery. For example, following a repair of cleft palate, some centers will recover a patient in the PACU while other centers will prefer direct admission to the step-down or intensive care unit. Similarly, some PACUs may be comfortable with an intubated patient and the subsequent extubation procedure, while others may not [9,10]. Programs to increase efficiency in high-turnover otolaryngology operating rooms have been described in which tonsillectomy patients are transferred to the PACU intubated, and the trachea is extubated by a PACU nurse when the

patient is fully awake [11]. An anesthesiologist is immediately available for emergencies, and this approach has been reported to decrease operating room turnover time by 17 min, while not increasing PACU time or the incidence of airway complications. Important to the success and safety of such programs are appropriate patient selection, a well-defined protocol with thorough training, and adequate PACU nursing staffing. It is important, therefore, when determining admission parameters, that there be a clear understanding by the surgical and anesthesia personnel what location is suitable for the recovery of the individual child.

After the decision is made to admit to the PACU, it is important that there be good communication to the PACU from the operating room. Advance communication from the operating room at the very least should include a phone call as the case nears completion. The call alerts the PACU to the new admission and should include details regarding the age, weight, and stability of the patient, any intraoperative complications that would affect postoperative care, and any special needs. This initial call allows the nurses to target care, prepare medication, and reorganize staff assignments as necessary. Once the patient arrives, the admitting staff should perform an initial assessment prior to the handover from the anesthesia staff. This assessment must quickly determine airway patency, oxygen saturation, heart rate and rhythm, temperature, and blood pressure. If all is well, it is then possible to proceed to the medical handover.

With regard to the communication between the anesthesia provider and PACU nurse, and in every aspect of medicine, the handover of patient care is critical. Patient safety is vulnerable, especially when crossing professional boundaries. Not only is there a great gap between documented patient information and information transferred during handover but there is often misunderstanding that can occur simply due to differences in culture, training, norms, attitudes, perspectives, goals, expectations, status, gender, and socio-economic status [12]. Indeed, communication breakdowns are a leading cause of medical errors. In 2006, a Joint Commission of Hospital Accreditation (JCAHO) analysis found that 70% of sentinel events were caused by communication breakdowns, half of those occurring during handovers [13]. To address the problem, the Joint Commission instituted a National Patient Safety Goal in 2006, calling on hospitals to implement a standardized approach to patient handovers.

In order to improve the handover, it is important to recognize the process, a novel example of which was described at Great Ormond Street Children's Hospital in London [14]. The handover of patient and information from the operating room to the cardiac intensive care unit was reviewed by motor racing teams that likened the handover to a racing pitstop. Their recommendations and involvement resulted in standardized handovers, thereby eliminating variation, and resulting in clear and concise instructions to ensure that even if team personnel changes, all members are absolutely clear about their responsibilities. Communication was noted to be a critical factor in success. The same principles must be applied to the handover of a patient from the operating room to the PACU.

It has been advocated that training be instituted using interactive simulation-based sessions of standardized patients, clinicians, and manikin simulators with facilitated video debriefing to stimulate thought and reinforce positive behavior. Also the introduction of mnemonics is useful to ensure timely, accurate, and complete information about a patient's care plan, treatment, current condition, and any recent or anticipated changes. Examples of these techniques include the "Five P's" (patient name, problem list, plan of care, purpose of plan, precautions), as well as "I-SBARQ" and "I PASS the BATON," which are shown in Tables 18.1 and 18.2 [15]. The hope is that the use of any of these measures will facilitate a consistent process, thereby improving patient safety.

Table 18.1 I-SBARQ communication tool.

I	Introduction	• Identify yourself and the patient
S	Situation	• Patient age • Gender • Preop diagnosis • Procedure • Mental status preprocedure • Patient stable/unstable
B	Background	• Pertinent medical history • Allergies • Sensory impairment • Family location • Religion/culture • Interpreter required • Valuables deposition • Meds given • Blood given – units available • Skin integrity • Musculoskeletal restrictions • Tubes/drains/catheters • Dressings/cast/splints • Counts correct • Other – lab/path pending
A	Assessment	• Vitals • Isolation required • Skin • Risk factors • Issues I am concerned about
R	Recommendation/ request	• Specific care required immediately or soon • Priority areas • pain control • IV pump • family communication
Q	Questions	

Table 18.2 I PASS the BATON communication tool

I	Introduction	Introduce yourself
P	Patient	Name: identifiers, age, sex, location
A	Assessment	"The problem": procedure, etc.
S	Situation	Current status/circumstances, uncertainty, recent changes
S	Safety concerns	Critical lab values/reports; threats, pitfalls, and alerts
B	Background	Comorbidities, previous episodes, current meds, family
A	Actions	What are the actions to be taken and brief rationale
T	Timing	Level of urgency, explicit timing, prioritization of actions
O	Ownership	Who is responsible (person/team) including patient/family?
N	Next	What happens next? Anticipated changes? Contingencies?

Monitoring and patient safety

The American Society of Anesthesiologists has published Standards for Postanesthesia Care, most recently updated in 2014 [16]. These standards are minimum requirements, and specify only that, "The patient shall be observed and monitored by methods appropriate to the patient's medical condition. Particular attention should be given to monitoring oxygenation, ventilation, circulation, level of consciousness, and temperature. During recovery from all anesthetics, a quantitative method of assessing oxygenation, such as pulse oximetry, shall be employed in the initial phase of recovery." Pulse oximetry is certainly used universally in pediatric anesthesia during the early phases of recovery, but electrocardiographic (ECG) monitoring is not always used, with heart rate taken from the pulse oximeter or manual counting. An advantage of ECG monitoring is the ability to have a monitor of circulation when the pulse oximeter does not function due to patient movement or poor perfusion. Additional benefits are the ability to diagnose non-sinus rhythms and to measure respiratory rate using impedance plethysmography. In addition, although the utility of capnography via a nasal cannula in non-intubated patients undergoing procedural sedation is well established, newer data suggest it may also be useful in some patient populations in the PACU. Hypoventilation can be masked initially with supplemental oxygen, whereas capnography increases the detection of apnea both earlier and more consistently. This type of monitoring in pediatric patients, prone to apnea, could be more prevalent in the future [17,18].

Detailed nursing standards for postanesthesia care have also been published and are regularly updated [19]. Although the exact details of monitoring and assessment will be governed by regulatory agencies and local institutional policies and procedures, in general, a pediatric patient recovering from general anesthesia should have 1:1 nursing care for the initial recovery period, along with frequent vital signs, i.e. every 5–15 min during the early recovery phases.

Regardless of the policies and guidelines in place, there is no substitute for well-trained PACU nurses with expertise and experience in pediatric anesthesia who can recognize problems, institute treatment, and call for help from their anesthesia and nursing colleagues. The anesthesiologist also must be mindful of the setting, i.e. a busy children's hospital PACU with multiple anesthesiologists and nurses available to address patient problems, versus a freestanding surgical center with one or two operating rooms, PACU nurses with limited pediatric experience, and no readily available anesthesia providers for PACU problems because all are caring for patients in the operating rooms. The setting often determines the preferred treatment strategy, i.e. deep versus awake tracheal extubation, or the type or age of patient treated.

Parental presence

As previously stated, the primary goal of the pediatric PACU is to provide a safe environment for patients to return to their preanesthetic state. However, there is evidence that children may suffer negative behavioral changes following hospitalization for surgical procedures [20]. Although it is difficult to predict which child will do poorly, cohort studies have revealed that particular individual, familial, and procedural variables were able to identify the children at greatest risk of significant negative behavior change [21]. In particular, a factor that predicted negative behavior was increased parental anxiety. Other factors included younger age, overnight admission, lower birth order, and, surprisingly, having a discussion with the anesthetist preoperatively [21].

It would seem intuitive that separation from a parent may compound the child's stress due to hospitalization and procedures. For this reason, many parents request to be present as their child recovers from anesthesia [22,23]. The policy of allowing parents into the PACU, however, is uniquely institutional and varies both culturally and nationally. It is not universally adopted, in part because there is little evidence that having a parent present during recovery from anesthesia results in a positive outcome and, as previously mentioned, parental anxiety may be counterproductive. However, in a randomized prospective study from Canada, a benefit in healthy children undergoing outpatient surgery to parental presence in the PACU was a decrease in negative behavior change at 2 weeks postoperatively [24]. There was no difference in the acute distress (measured by "crying episodes") in the PACU between the group with a parent present versus the group where no parent was present. Despite these findings, parents may be successful with non-pharmacological measures to relieve pain and distress. These non-pharmacological methods, involving imagery, relaxation, breathing techniques, and massage, may make pain more tolerable and give children a sense of control without the administration of drugs [25]. A qualitative interview study of children and parents following tonsillectomy noted that children have their own coping strategies in mind. These included: (1) distraction such as watching TV, thinking of something else, talking, and reading; (2) relaxing, eating ice cream; and (3) simply having someone present [26].

The debate as to the value and appropriateness of parents in the PACU will continue. Most anesthesiologists have an anecdotal experience that colors their perspective on the matter. However the emergence from anesthesia is obviously a potentially stressful time for the child. The sensation of pain, nausea and vomiting, and waking in a strange and foreign environment are all contributors to this stress. The idealized benefit of a familiar and recognized caregiver is compelling although the actual evidence for such an advantage is poor. There are a significant number of studies on the effects of parental presence in the preoperative period and during induction of anesthesia, but the inclusion of the presence of parents in the postoperative period and the PACU environment remains in need of additional study.

KEY POINTS: HANDOVER/ASSESSMENT, MONITORING/PATIENT SAFETY, AND PARENTAL PRESENCE

- After initial assessment, a standardized handover process detailing important information is crucially important for PACU care
- More intensive PACU nursing staffing, i.e. often 1:1, is necessary during the early recovery phases. Pulse oximetry at a minimum is employed, with or without ECG, and blood pressure/temperature are also measured
- Parental presence in the PACU is practiced in many institutions and may reduce stress for many patients and families

Discharge criteria

Discharge criteria have been created to permit an objective evaluation of children leaving the recovery unit. The criteria will depend upon the patient age, surgery performed, and the subsequent destination (home versus floor versus intensive care). The two commonly used and cited scores in the literature are the modified Aldrete score for inpatient care [27] and the postanesthetic discharge scoring systems (PADSS) for patients being discharged home [28]. Both scores use a selection of physiological variables to form an objective measure for discharge eligibility (Tables 18.3 and 18.4). Whether the anesthesiologist must personally reassess the patient before discharge, or rely on a protocol with a physician order to discharge the patient when criteria are met, is governed by both regulatory agencies and local institutional policy and procedures.

The key components of scores like these include the following parameters: hemodynamic stability, respiratory sufficiency, neurological baseline, ability to maintain and protect the airway, absence of excessive bleeding, normothermia, minimal pain (patients should be observed for at least 30 min after the last dose of opioid), ability to ambulate if appropriate, and absence of excessive vomiting. The ability to drink clear liquids prior to discharge is not a discharge criterion, and forced ingestion of liquids is actually associated with a higher incidence of postoperative nausea and vomiting (PONV) [29].

Patient age is also a critical factor. Although actively debated, it is suggested that preterm infants should reach a minimum number of weeks postconceptual age (PCA) to be considered for outpatient surgery due to risks of postoperative apnea. Most institutions use conservative criteria close to 50 weeks' PCA or a very conservative 60 weeks, however 44 weeks can generally be considered the absolute minimum PCA for outpatient surgery based on when the true risk of apnea is considerable. Even in those infants who reach the minimum age criteria for discharge, an extended recovery time with observation during feeding and sleeping may be warranted [30]. Risk factors associated with apnea of prematurity are anemia, PCA, and gestational age. A separate entity known as apnea of infancy can occur in term infants but, because of its rarity, term infants are not subject to the same postoperative monitored care unless other factors warrant it [31]. It is recommended that term infants on the other hand should be a minimum of 4 weeks of age to be eligible for same-day discharge. Although the risk of apnea in a full-term infant is extremely low, case reports suggest that it is not zero [32–34].

In addition to overall discharge criteria from anesthesia, there are also procedure-specific issues that may affect the time to discharge. For example, a child who receives a spinal anesthetic should show signs of resolution of both sensory and motor blockade prior to discharge. Children undergoing adenotonsillectomy typically would stay in PACU for 2 h and show an ability to take fluids. In a study to determine the factors that may delay discharge in children undergoing tonsillectomies, it was found that PONV and oxygen desaturation were the two major factors contributing to prolonged length

Table 18.3 Modified Aldrete score. Nine or more points are required for recovery to be confirmed

Category	Score = 2	Score = 1	Score = 0
Respiration	Breathes, coughs freely	Dyspnea, shallow or limited breathing	Apnea
O_2 saturation	SpO_2 >92% in room air	Supplemental O_2 to maintain SpO_2 >92%	SpO_2 <92% with oxygen
Circulation	BP within 20 mmHg of preop	BP within 20–50 mmHg of preop	BP within 50 mmHg of preop
Consciousness	Awake and orientated	Wakes with stimulation	Non-responsive
Movement: voluntarily or on command	Four extremities	Two extremities	No extremities

Table 18.4 Post Anesthetic Discharge Scoring System (PADSS) discharge criteria table. At least nine points are required to be eligible for discharge

Category	Description of status	PADSS score
Vital signs	Within 20% range of preop	2
	Within 20–40% range of preop	1
	>40% range of preop	0
Ambulation	Steady gait/no dizziness	2
	Ambulates with assistance	1
	Not ambulating/dizziness	0
Nausea and vomiting	Minimal, treated with oral meds	2
	Moderate, treated with parenteral meds	1
	Continues after repeated treatments	0
Pain	Acceptable to patient	2
	Pain somewhat acceptable	1
	Pain not acceptable to patient	0
Surgical bleeding	Minimal: no dressing changes required	2
	Moderate bleeding: dressing change	1
	Severe bleeding: intervention required	0

of stay (LOS) [35]. The authors noted that the overall risk of prolonged LOS decreased with increasing age. Interestingly, LOS was not affected by the presence of an upper respiratory tract infection (URTI), leading the authors to suggest that patients with a URTI could be eligible for outpatient surgery.

Finally, handover of care for inpatients being discharged from the PACU to the floor or ICU needs to be as rigorous as with arrival. Full handover should include not only the intraoperative report but also the medications given and any PACU issues or special instructions. Prior to the final handover of the child to the accepting team, it should be confirmed that the intravenous infusions are placed on mechanized infusion pumps rather than free-flowing drips, a final examination of wound sites should be done, and an appropriate escort (nurse or doctor) who can give an accurate report to the accepting team needs to accompany the child for transport.

KEY POINTS: DISCHARGE CRITERIA

- The modified Aldrete score rates respiration, oxygen saturation, blood pressure, level of consciousness, and movement
- The Post Anesthetic Discharge Scoring System for outpatients rates vital signs, ambulation, nausea/vomiting, pain, and surgical bleeding for discharge home
- Age of the child and specific criteria for discharge according to the surgical procedure are important considerations

Potential postanesthesia problems and complications

Respiratory

Children are more likely to have airway-related problems than cardiovascular problems in the immediate postoperative period. Next to episodes of nausea and vomiting, the most frequent complications in the PACU are those that require airway support [36]. Maintenance of the airway following general anesthesia and sedation presents challenges due to the negative factors that occur during the perioperative period. Not only are the children still under the sedative influences of the anesthesia, but there are also risks of inadequate reversal of neuromuscular blockade, as well as diffusion hypoxia and the consequences of additional analgesic medications being administered in the PACU that can result in additional altered respiratory drive. The normal anatomy of a neonate or infant can render the airway vulnerable, and when side-effects of surgery are added, particularly surgery involving the airway, it is clear that a specialist's care and attention to detail may be required.

Although tracheal extubation occurs in the operating room in the vast majority of pediatric anesthesia programs and cases, the benefits and risks of extubation while deeply anesthetized versus "awake" continue to be debated [37]. A recent observational cohort study of 880 children 1–18 years of age undergoing tonsillectomy demonstrated no difference in airway complications between those whose trachea was extubated while deeply anesthetized (n = 577) versus those extubated awake (n = 303), with both groups experiencing a rate of about 18%, which included all minor and major complications [38].

The patient whose trachea has been extubated while deeply anesthetized will often be at increased risk of airway obstruction from airway muscle laxity, or emerging from anesthesia with increased risk for laryngospasm, during the early period after admission to PACU, and so extra vigilance is required in this situation. In a minority of pediatric anesthesia programs, the patient is taken to the PACU with the endotracheal tube in place, in order to increase operating room efficiency. The trachea is extubated on the physician's order by protocol so that the PACU nurse can perform the extubation when criteria are met [10].

Hypoxemia is not uncommon in the pediatric patient who is recovering from anesthesia and surgery. In addition to mechanical issues that involve the airway, there are other intrinsic pulmonary events that lead to hypoxemia. The combination of a higher oxygen consumption in the presence of a relatively reduced functional residual capacity and higher closing capacity puts the younger child at greater risk of oxygen desaturation. For all these reasons, postoperative patients should receive supplemental oxygen either by mask or by blow-by devices, and children are no exception. Children can be reluctant to accept any device to provide oxygen, but *purposeful* removal of the mask or blow-by device is often a good sign that it is no longer required. As oxygen is being delivered, the basics of airway support must still continue to be employed including ensuring the airway is patent, there are clear breath sounds on auscultation with good chest excursion, no signs of respiratory distress (stridor, nasal flaring), no wheezing, and a normal respiratory pattern devoid of apneic episodes. A child may be best managed by placing him or her in the lateral recovery position and employing jaw thrust and mouth opening when airway obstruction is evident. Compared to the supine position, the lateral position will increase total airway volume by 45% in children who have been sedated for MRI, with the greatest change seen in the region between the epiglottis and vocal cords [39]. One must remember that neonates are mostly obligate nasal breathers, and the occlusion of the nares with assorted tubing or with improper mask placement can lead to a compromised airway.

Residual neuromuscular blockade

Residual neuromuscular blockade has significant clinical implications for the patient in the PACU. These implications are due to changes in pharyngeal function with increased risk of aspiration, airway muscle weakness that can lead to obstruction, and attenuation of the hypoxic ventilatory response. In adults, there is evidence that up to 40% of patients exhibit a train of four ratio of <0.9 in the recovery area [40,41]. Although evidence would suggest that children have a more complete response to neuromuscular reversal and respond to lower doses of neostigmine significantly better than adults, the complications that can result from incomplete reversal can be devastating in a very young child [42,43]. When a child is admitted to the recovery area and exhibits the typical signs of incomplete reversal such as weakness, or floppiness with the "fish out of water" appearance, neuromuscular blockade must be considered a cause and treated promptly before

respiratory decompensation ensues. Administering additional neuromuscular blocking reversal is not necessarily the treatment of choice and should only be used if the maximum dose of neostigmine (0.07 mg/kg) has not already been administered as that dose should not be exceeded. Larger doses of neostigmine will lead to further muscular weakness and possible cholinergic crisis. Instead, care should be supportive, including reintubation if respiratory compromise is significant.

Residual neuromuscular blockade may become less of an issue with the advent of sugammadex, a novel agent that encapsulates rocuronium or vecuronium providing rapid and complete recovery even from profound neuromuscular blockade. At the time of writing, it has not received approval from the US Food and Drug Administration (FDA) in children but its successful anecdotal use is well reported [44]. Sugammadex as a rescue medication in the pediatric PACU seems intuitive.

Postextubation stridor or croup

One complication that is typically not seen until the PACU course is postextubation stridor (also known as postintubation croup). Forty years ago the incidence of postextubation croup after anesthesia was reported at 1.6–6% [45]. Although these data are old, there is little evidence that the incidence has changed despite trends toward the use of cuffed endotracheal tubes. An editorial on the subject outlined the changes that have occurred over the last several decades based on published literature, and how these changes have supported the use of cuffed endotracheal tubes in children [46]. It remains unclear what the overall outcome will be with changes in practice, and whether eventually there will be a significant difference in the incidence of stridor in the PACU based on preference of endotracheal tube. Postextubation stridor often may not need immediate treatment beyond humidified oxygen. However, if there are any signs of respiratory distress, nebulized racemic epinephrine (0.5 mL of 2.25% solution in 3 mL normal saline for children over 6 months of age, 0.25 mL if less than 6 months) provides a rapid response. The mechanism of action of racemic epinephrine is through its stimulation of α receptors resulting in vasoconstriction and secondary reduction in mucosal and submucosal edema. Due to the rebound effect of racemic epinephrine that may occur up until 2 h after administration, the child must remain in the PACU or in a monitored setting until this risk is no longer present, as readministration may be necessary. Although it may take at least an hour to see results, a single dose of dexamethasone (0.15–0.6 mg/kg) can be administered for reduction of airway edema, and the duration significantly outlasts racemic epinephrine with a half-life of over 30 h [47–49]. Despite the long half-life, dexamethasone dosing should be repeated every 6–12 h until resolution. In cases of significant respiratory distress, the child should be admitted to a monitored setting where heliox (60–80% helium:20–40% oxygen mixture) can be delivered [50]. Although heliox has no anti-inflammatory or bronchodilatory properties, its low density allows improved oxygen delivery and carbon dioxide elimination. In extreme cases, reintubation with an endotracheal tube at least 0.5–1 mm smaller than the original tube may be needed.

Laryngospasm

Laryngospasm, an event typically associated with intraoperative care, remains a potential complication in the PACU. Neonates and infants are at greatest risk, with the relative risk decreasing by 11% for each yearly increase in age [51]. Laryngospasm may occur due to irritation of the vocal cords, commonly from either saliva or blood, or simply from the child still being at risk while emerging from anesthesia with Stage II being exhibited. Laryngospasm is the forceful closure of the vocal cords, resulting in total obstruction of the airway, and if untreated can be catastrophic. The first step must be the administration of oxygen by positive pressure mask with jaw thrust. In addition to simple jaw thrust, pressure applied to the "laryngospasm notch," located behind the lobule of the pinna of each ear, is anecdotally effective [52]. If the patient exhibits full airway obstruction without evidence of air movement, or if significant desaturations or bradycardia occur, succinylcholine is to be administered (or another rapid-acting muscle relaxant if succinylcholine is contraindicated). When laryngospasm occurs in the PACU, intubation is typically not necessary, and all that is needed for relaxation of the vocal cords is a small dose of intravenous succinylcholine (0.1–0.5 mg/kg). Small doses of propofol have also been reported for the treatment of laryngospasm in children [53]. The child will require bag/mask ventilation until good spontaneous respirations are restored. Atropine should be available in the event that either the succinylcholine or episode of hypoxia during the laryngospasm causes bradycardia.

Apnea

Although apnea may occur for many reasons in the PACU, apnea in the ex-premature infant requires careful consideration during the preoperative work-up to guarantee that the appropriate postoperative destination is secured. With increasing survival of prematurely born infants, an increasing number of these patients appear on the operating schedule and so require care in the PACU. Typically, if the child is still in the intensive care nursery, then postoperative care will continue on the neonatal intensive care unit. However, if the child is on the ward or is an outpatient, individual consideration for the unique pathophysiology of a premature infant must be given to determine the postoperative disposition and level of monitoring. Apnea is defined as cessation of airflow for more than 20 s, or the cessation of breathing for less than 20 s if it is accompanied by bradycardia or oxygen (O_2) desaturation [54]. The frequency is inversely related to gestational age and the actual cause of apnea of prematurity is unknown, although it is likely multifactorial [55]. Depression or immaturity of the respiratory central generator located in the brainstem is most likely, in addition to vulnerability to inhibitory influences such as hypoxia and temperature changes [56].

Beyond considerations that exist for infants with apnea of prematurity, the presence of obstructive sleep apnea (OSA) in any child presents a significant risk in the postoperative period and is responsible for considerable morbidity with a complication rate of up to 27% [57]. In fact, in 60% of children with severe OSA, nursing intervention in the postoperative period was required to treat complications that included desaturation to SpO_2 <90% [58]. The children also demonstrated signs of increased work of breathing and/or new radiographic findings of pulmonary

edema, effusion, infiltrate, pneumothorax, or pneumomediastinum. Because of the potential complications that exist in this population, the American Society of Anesthesiologists in 2006 published practice guidelines for perioperative management that suggested that children with a history of OSA having adenotonsillectomy should be admitted for overnight stay if they are less than 3 years of age or if they have contributing medical conditions such as obesity [59]. If an otherwise well child greater than 3 years of age has mild to moderate OSA with an apnea–hypopnea index <10, same-day discharge may be considered. If the decision is made to discharge the child the same day as the procedure, it is best if the case is performed earlier in the day and the child discharged after a minimum PACU stay of 2 h [60].

Due to the chronic hypoxemia exhibited by children with OSA and its effects on respiratory drive, it is important to be cautious when ordering pain medication postoperatively. Children with a history of OSA have a higher incidence of apnea after administration of a typical 0.5 μg/kg dose of fentanyl when compared to children without OSA [61]. As a reference, children with sleep apnea who demonstrated an oxygen saturation <85% on polysomnography required only half the morphine dose to have the same analgesic effect as a child who did not have the same degree of desaturation [62].

When an infant or child is showing signs of OSA in the PACU, immediate maneuvers to stimulate the patient and open the airway are to be performed. These maneuvers include repositioning with a shoulder roll or to lateral position, performance of jaw thrust or insertion of a nasal or oral airway, and occasionally the administration of positive pressure by mask. If these measures are unsuccessful, the child may require intubation until he or she is fully recovered and able to maintain their own airway. In addition, the child who requires nasal continuous positive airway pressure (nCPAP) or bi-level positive airway pressure (BiPAP) by mask at home during sleep may benefit from its application in the PACU.

Pulmonary edema

Pulmonary edema is rarely seen in children, but must be considered as a cause in the postoperative differential diagnosis of hypoxemia with desaturations in the PACU [63]. Causes of pulmonary edema may be related simply to the delivery of a large volume of fluid or blood products in the operating room with or without significant fluid shifts, or to negative pressure (NPPE). The clinical presentation is the same between these, but history will help delineate the cause. A history of forceful respirations against a closed airway such as laryngospasm, biting on the endotracheal tube, or even long-standing history of upper airway obstruction from enlarged tonsils or epiglottis that has now been relieved with surgery, can lead to NPPE. The pathogenesis of NPPE from negative intrathoracic pressure causes decreased pulmonary capillary perivascular pressure, favoring hydrostatic transudation of fluid into the interstitial tissue. Although normal pleural inspiratory pressures are -2 to -5 cmH_2O, negative pressures from -50 to -100 cmH_2O are possible, particularly in young muscular males. After the obstruction is relieved, there is a sudden increase in venous return and a redistribution of blood volume from peripheral to central circulation with a resulting increase in pulmonary hydrostatic pressure that is compounded by capillary leak [64]. In any of these scenarios, if significant pulmonary edema is present, the child will exhibit lower pulse oximetry readings, tachycardia, and tachypnea. Rales will be heard on chest auscultation and occasionally the child may exhibit pink frothy sputum. If the child is otherwise stable and saturations are kept within normal range with supplemental oxygen, this is all that may be required. However, depending on the degree of pulmonary edema and respiratory distress, intubation with delivery of positive end-expiratory pressure (PEEP) may be necessary along with diuresis (furosemide 0.1 mg/kg with a maximum of 5 mg) to assist with the shift of fluid out of the lungs. In the case of negative pressure pulmonary edema, the use of PEEP is supported, but whether the delivery of diuretics is of benefit remains unclear [65].

Pulmonary aspiration

The risk of pulmonary aspiration in the perioperative period in children is low at approximately 0.1%, but it is not negligible and is at least two times higher than the risk in adults [66]. Particularly after airway surgery, the increased amount of secretions and blood puts a child at risk for aspirating these fluids during recovery from the sedative effects of anesthesia or pain medications. If aspiration is suspected, examination of the lungs and a chest radiograph may help determine the diagnosis if significant rhonchi or coarse breath sounds are heard unilaterally, particularly on the right side. Treatment is supportive as sequelae are typically mild, although incidence and severity may correlate with the underlying medical condition of the child [66]. Pharmacological intervention with steroids or antibiotics for presumed aspiration is unwarranted.

Pneumothorax

Another cause of hypoxemia in the PACU is pneumothorax. Many surgical procedures such as central line placement, ventriculoperitoneal shunts, and any thoracic procedure put the child at risk for intraoperative pneumothorax that may not exhibit until the postoperative period. A thorough examination and chest radiograph will help determine the diagnosis. In the event that the pneumothorax is significant and causing respiratory compromise, a chest tube will need to be inserted and the child sent to the appropriate postoperative setting. Lesser degrees of pneumothorax may be treated with 100% oxygen by non-rebreathing facemask to hasten resolution by displacing nitrogen and allowing for faster resorption of the pneumothorax.

KEY POINTS: RESPIRATORY COMPLICATIONS

- Hypoxemia must be rapidly investigated and treated; supplemental oxygen by blow-by device or facemask is important in early recovery for prevention
- Postextubation stridor or croup is treated with humidified oxygen if mild; if it is severe, dexamethasone, racemic epinephrine, and longer PACU observation or admission are indicated
- Laryngospasm is treated with positive pressure and jaw thrust; if it does not resolve quickly, low-dose succinylcholine, or propofol, is indicated
- Apnea in former premature infants up to 50–60 weeks' postconceptional age requires vigilance, often a longer PACU stay, and inpatient admission for monitoring in patients with significant risk factors

Cardiovascular

Although respiratory complications far outweigh hemodynamic issues in the typical recovering pediatric patient, children can decompensate rapidly and cardiovascular depression is a late and ominous sign. In an analysis of the American Heart Association Get With The Guidelines–Resuscitation registry, a higher mortality was noted following cardiac/hemodynamic causes of cardiopulmonary arrest. Non-survival was also associated with older age, weekends, non-pediatric environments, and at night [67].

Hypotension

Hypotension in the PACU, particularly in the presence of tachycardia, narrow pulse pressure, poor capillary refill (>3 s), and low urine output (<0.5 mL/kg/h), is typically the result of hypovolemia. Depending on the nature of the procedure, the cause of the hypovolemia needs to be quickly determined in order to decide whether to administer fluid or blood products. Attention to any blood accumulation in surgical drains allows for a rapid assessment. Isotonic crystalloid fluid boluses (normal saline, lactated Ringer's solution, or Plasmalyte®) should be administered in 5–10 mL/kg increments depending on the degree of hypotension and ongoing losses with critical assessment of changes in blood pressure and heart rate in response to the fluid challenge. If there is any question as to the nature of the hypotension, blood should be drawn to check for acid–base status and base deficit as well as hemoglobin and/or hematocrit. If replacing blood loss, 10–15 mL/kg of packed red blood cells will raise the hemoglobin by 2–3 g/dL if no ongoing blood loss is occurring.

Other causes of hypotension that would be extremely uncommon in the PACU would be anaphylaxis from either latex exposure or delivery of postoperative drug, early signs of perioperative sepsis, or mechanical reasons such as pneumothorax or pericardial tamponade. Sympathetic block from central neuraxial anesthesia typically does not exist in a child below the age of 5 years due to lack of significant peripheral vasodilation or venous pooling, and rarely would cause hypotension in a child older than 5 years with the typical low concentrations of local anesthetic that are used for postoperative infusions.

Hypertension

The presentation of hypertension in the postoperative period is typically the consequence of pain and is therefore usually associated with tachycardia and other outward signs of discomfort. If pain is suspected, appropriate treatment is necessary to alleviate the physiological responses in a rapid, safe manner. If not due to pain, the most common cause of hypertension may actually be the result of inaccurate readings due to a small blood pressure cuff, so this cause must be ruled out early. Hypertension is rarely due to volume overload but some children are more susceptible than others to excessive intraoperative volume resuscitation, so the possibility does exist. Hypertension may also be the result of emergence agitation or bladder distension; in patients with renal failure, rebound hypertension can occur because they have not taken their regular antihypertensive agent due to nil per os (NPO) status issues. In a child with moderate to severe hypertension in the PACU that is not attributable to pain, treatment may consist of intravenous agents such as hydralazine (0.25–0.5 mg/kg), labetalol (0.2 mg/kg), nitroprusside infusion (1–10 μg/kg/min), or nicardipine infusion (0.5–5 μg/kg/min). Clevidipine is a short-acting, intravenous calcium channel blocker that has been studied for the treatment of hypertension during the emergence from anesthesia in children. Its use in the PACU has not been reported [68]. Close hemodynamic monitoring needs to occur if any of these agents is being delivered.

Tachycardia

Tachycardia is very non-specific in the PACU. As previously mentioned, when accompanied by hypotension, the combination suggests hypovolemia that needs to be promptly managed. Tachycardia and hypertension together suggest pain, anxiety, or both. Tachycardia can also be secondary to administered drugs in the operating room such as atropine or glycopyrrolate; when no other factors are present, these causes should be considered and no further treatment is necessary. Rarely tachycardia may be due to an underlying conduction abnormality, particularly in a child with a history of cardiac disease, and these children will require a cardiology consult and/or admission to the ward to determine the significance. If an arrhythmia, i.e. supraventricular tachycardia, is suspected, it is crucial to record the abnormal rhythm, either by printout or electronically with as many leads as possible, and to record a standard 12-lead ECG, so that the consultant physicians will have adequate information.

Bradycardia

Bradycardia is often a more ominous sign than tachycardia and is often consequent to hypoxia. Indeed, the heart rate of a preterm infant will begin to fall within 30 s of onset of apnea [69]. Therefore attention should be directed toward airway management and ensuring adequate oxygenation in the face of sudden, unexpected bradycardia. Having corrected hypoxia as a cause of bradycardia, other causes such as increased intracranial pressure or simple vagal response to airway maneuvers can be entertained. If bradycardia persists and is accompanied by low cardiac output or hypotension, atropine (0.02 mg/kg) should be administered. If this is unsuccessful and the patient remains in a low-output state, resuscitation efforts should then proceed with intravenous epinephrine and standard CPR per PALS protocol.

Other than tachy- or bradyarrhythmias, arrhythmias are extremely rare in the PACU. With the reduction in the use of arrhythmogenic inhalational agents such as halothane, nodal or junctional arrhythmias are less frequent, although these may be seen when higher doses of dexmedetomidine have been administered. However, a greater number of patients with congenital heart disease are surviving and requiring surgeries unrelated to the heart. These patients may have underlying defects in their conduction pathways that may become obvious in the PACU. A rhythm strip should be run in any child who has an unexpected change in heart rate to help determine any cardiac etiologies, and a cardiologist should be consulted prior to discharge from the PACU if concern remains about significant cardiac pathology as a cause of the arrhythmia. Additionally, any hemodynamically significant arrhythmia requires basic resuscitation protocol.

KEY POINTS: CARDIOVASCULAR COMPLICATIONS

- Children can decompensate rapidly, and resuscitation training and practice is important for the rare serious PACU emergency
- Hypotension is uncommon and hypovolemia is the most common cause
- Hypertension from pain and emergence agitation is common
- Tachycardia is often non-specific and results from pain, agitation, hyperthermia, and medications
- Bradycardia can be drug induced (dexmedetomidine, neostigmine) or more rarely an ominous sign of hypoxemia or cardiovascular depression that must be emergently addressed

Hypothermia and hyperthermia

Hypothermia is defined as a core temperature of less than 36°C [70]. It is well documented that children lose heat more readily than adults, and anesthesia can further disrupt the patient's ability to thermoregulate [71]. Neonates and infants are at particular risk of developing hypothermia even during transport from the operating room to the PACU. A working group established by the American Society of Anesthesiologists (ASA)/Physician Consortium for Performance Improvement noted that anesthetic-induced impairment of thermoregulatory control is the primary cause of perioperative hypothermia [72]. Even mild hypothermia (1–2°C below normal) has been associated in randomized trials with a number of adverse consequences including increased susceptibility to infection, impaired coagulation and increased transfusion requirements, cardiovascular stress and cardiac complications, and postanesthetic shivering and thermal discomfort [73]. In addition, neonates are at risk of apnea and bradycardia when hypothermic. Beyond the physiological issues, hypothermia also has an impact on efficiency of a PACU and is associated with an increased length of stay, which has logistical and financial implications for a successful surgical unit [73].

It is therefore not surprising that perioperative temperature management is one of the five quality incentives established by the ASA as Pay-for-Performance and Anesthesiology Quality Incentive [72]. The goal is to have measured at least one body temperature that is equal to or greater than 36°C (96.8°F) within the 30 min immediately before, or the 30 min immediately after anesthesia end time, with some exceptions.

Temperature is to be measured as part of the initial assessment upon a child's arrival in the PACU. Measurements from different sites may not correlate particularly well because of compensatory mechanisms such as vasoconstriction that can change the relationship between the central and peripheral temperature. Core temperature must be estimated from peripheral sites and taken rectally, axillary, orally, or via tympanic membrane. All of these sites have issues related to reliability, accuracy, and flaws in measurement technique. Axillary temperatures in neonates and infants do correlate well with rectal temperature and thus remain the preferred method in many PACUs [74,75].

Acknowledging the importance of avoiding hypothermia has led to the practice of prewarming patients in the operating room [76,77]. When this has not occurred and the patient arrives hypothermic to the PACU, a number of measures are often employed. Simple and standard measures such as fluid warmers, warm blankets, and infrared heat lamps are first line but may not be completely effective in treating hypothermia [78]. Only active warming devices such as convection or forced-air warming devices have consistently been proven effective at treating hypothermia and are therefore recommended by the ASA for these circumstances [79].

Hyperthermia in the PACU is a very different entity. The typical cause of hyperthermia would be aggressive warming in the operating room. Although extremely rare, one must still have a high index of suspicion for a late presentation of malignant hyperthermia (MH) in a hyperthermic child, particularly if any other associated signs are present such as muscle rigidity, hyperventilation, and tachycardia. Aggressive diagnosis and treatment should then ensue if a true case is suspected.

A more common concern would be how to recover the patient who may be MH susceptible but who has received a non-triggering anesthetic. Despite the seriousness of an episode of MH, it is reasonable for a patient who is at risk for MH to be admitted to the PACU and still be able to be discharged the same day as the procedure when they have not been exposed to potent inhaled anesthetics or succinylcholine [80]. In fact, there is no advantage to keeping a patient who is MH susceptible in the PACU for a prolonged period of time if there are no other complicating factors [81]. Based on a review of over 250 MH susceptible patients, and per the Malignant Hyperthermia Association of the United States (MHAUS) website, a 1 h stay in the primary PACU with an additional 1–1.5 h in a step-down PACU, if indicated, is recommended [82].

KEY POINTS: HYPOTHERMIA AND HYPERTHERMIA

- Infants and young children are at significant risk for hypothermia in the PACU
- Even mild hypothermia (below 36°C) can have adverse consequences such as delayed emergence, apnea, and longer PACU stay
- Active warming measures such as a forced-air warming system are necessary for significant PACU hypothermia
- Hyperthermia is normally the result of aggressive operating room warming, but the remote possibility of malignant hyperthermia should be considered in some patients

Emergence agitation or delirium

It is not uncommon for children to emerge from anesthesia disoriented and frightened, resulting in negative behavior of restlessness, anxiety, and inconsolability. As part of the assessment of this behavior, careful consideration of an organic cause must be made. For example, hypoxemia, hypercarbia, hypotension, hypoglycemia, raised intracranial pressure, or untreated pain should all be ruled out. Only after this has

occurred can the phenomenon of emergence delirium (ED), also referred to as emergence agitation (EA), be considered.

In the modern era of the pediatric PACU, the issue of ED has become a popular topic of discussion. For example, a well-referenced analysis of perioperative morbidity published in 2004 failed to include ED as an adverse event as it seemingly was not considered a major issue at that time [1]. Defined as "a disturbance in a child's awareness of and attention to his/her environment with disorientation and perceptual alterations including hypersensitivity to stimuli and hyperactive motor behavior in the immediate post anesthesia period," ED can be stressful for the child, parents, and caretakers [83].

There is a range of behavioral responses following anesthesia, from crying uncontrollably after emergence for more than 3 min (mild), to uncontrollable behavior requiring physical restraint for more than 3 min (major) [83]. With such a range of presentation, it is difficult to describe the precise incidence of ED as it may be as high as 80% depending on how it is defined. The spectrum of clinical presentation has therefore led to the creation of behavioral scales such as the Pediatric Anesthesia Emergence Delirium (PAED) scale (Table 18.5). When tested in 50 children for validity, the PAED scale revealed consistency and reliability [84].

The issue of EA/ED was not truly evident until the practice of using sevoflurane instead of halothane started. The suspicion that sevoflurane resulted in more frequent episodes of ED was reviewed in a meta-analysis that confirmed sevoflurane was associated with a consistently higher incidence of agitation when compared to halothane [85]. In fact, ED is associated with both of the newer inhalational agents, desflurane and sevoflurane [85,86]. Because desflurane and sevoflurane have a greater incidence of ED compared to isoflurane or halothane, this results in the conundrum of the supposed benefit of shorter-acting agents in promoting a quicker recovery and shorter discharge times possibly being negated by the increased incidence of ED from a rapid emergence. This concern was demonstrated to be valid in a study comparing recovery and discharge criteria between halothane and sevoflurane in children undergoing myringotomy tube placement. EA was significantly higher in the sevoflurane group versus the halothane group (57% versus 27%, respectively), and discharge times were similarly prolonged with the sevoflurane group [87].

It is easy to assume then that the speed of wakefulness is directly proportional to the likelihood of ED occurring. A recent study demonstrated that the odds of ED fell by 7% for every minute the child remained asleep following general anesthesia [88]. However, it is simply not the fact that rapid emergence is responsible for ED. Delaying emergence by gradually decreasing the inhaled agent has no effect on the incidence of ED [89], and comparative anesthetics that offer quick emergence such as propofol still demonstrate that inhaled agents are associated with a greater incidence of ED [90]. This was shown in a randomized crossover study in which propofol was noted to have a zero prevalence of ED compared to sevoflurane as a maintenance agent [91]. The propofol group did have a longer recovery stay, but parental satisfaction was higher in the propofol group than in the sevoflurane group.

In order to prevent EA/ED, it is important to know the factors that predict its occurrence. First, ED may be associated with the type of surgery. An increased incidence is found after otorhinolaryngological and ophthalmological surgeries, at 26% and 28% respectively, when compared to other types of procedures [92]. In addition, there are patient factors that predict postoperative ED, such as age <5 years, increased preoperative anxiety, and a temperament that is more emotional, more impulsive, less social, and less adaptable [20]. Clearly these factors cannot necessarily be controlled preoperatively. There are also anesthesia factors, over and above what agent is used to induce and maintain anesthesia. For example, the smoothness of the induction is a predictor of emergence. Weldon et al studied 80 children <6 years of age receiving either sevoflurane or halothane [93]. All the children were premedicated with midazolam and received caudal regional anesthesia after their inhaled induction so that postoperative pain would not be a factor in their EA. Although the study was designed to compare the inhaled agents, and showed that children who received sevoflurane had a significantly higher incidence of EA than halothane at arrival to PACU (26% versus 6%), it also showed that the incidence of EA was higher in the children who had increased anxiety preoperatively per the Yale Preoperative Anxiety Scale [20,94]. In addition to an increased incidence of agitation on admission and more episodes of severe agitation, these same children also had a greater incidence of difficult mask inductions.

Early thoughts as to the cause of EA/ED included the presence of pain. Although pain may be a contributing factor to an unsatisfactory emergence period, it has not been shown to be the cause of ED. In fact, ED has been shown to have a similar incidence after non-painful procedures such as MRI [87]. In children who have undergone sevoflurane anesthesia without surgical intervention, a small dose of fentanyl (1 μg/kg) 10 min prior to emergence reduced EA from 56% to 12% with no increase in time to discharge [94]. Studies using caudal block in order to take the pain issue out of the equation of postoperative ED have shown inconsistent results as to the effectiveness of regional anesthesia in addition to sevoflurane for avoidance of EA [95].

In addition to avoiding the agents that are commonly associated with ED, such as sevoflurane and desflurane, other

Table 18.5 Pediatric Anesthesia Emergence Delirium (PAED) scale

Category	Score 4	Score 3	Score 2	Score 1	Score 0
Child makes eye contact	Not at all	Just a little	Quite a bit	Very much	Extremely
Child's actions are purposeful	Not at all	Just a little	Quite a bit	Very much	Extremely
Child is aware of surroundings	Not at all	Just a little	Quite a bit	Very much	Extremely
Child is restless	Extremely	Very much	Quite a bit	Just a little	Not at all
Child is inconsolable	Extremely	Very much	Quite a bit	Just a little	Not at all

agents have been studied to determine if using them prophylactically will reduce the incidence of ED. In a meta-analysis, midazolam and 5-hydroxytryptamine-3 receptor (5-HT3) inhibitors such as ondansetron were not found to have a protective effect against ED. Adjuncts to inhalational anesthesia such as ketamine, gabapentin, and fentanyl have been shown to be effective [96]. Transition to propofol towards the conclusion of a sevoflurane anesthetic reduces the incidence of ED and improves quality of emergence [97]. In a survey of practice amongst Canadian anesthesiologists, propofol was the most commonly used adjunct to both prevent and manage ED [98]. In the same study, α_2-adrenoceptor agonists were seldom used despite the increasing evidence of their efficacy.

The α_2-adrenoceptor agonists are an emerging group of drugs used in the management of postoperative agitation. Clonidine causes sedation, analgesia, and reduction in sympathetic tone and can be administered via many routes. An intravenous dose of 2 μg/kg after anesthetic induction has been demonstrated to significantly reduce the incidence and severity of EA in boys undergoing circumcision with penile blocks under sevoflurane anesthesia [99]. This efficacy in the management of ED with clonidine has not been consistent at a dose of 1.5 μg/kg when compared to the more efficacious tropisetron [100]. Dexmedetomidine, another α_2 agonist, has both prophylactic and treatment potential for ED. When dexmedetomidine was used as a single bolus dose immediately after inhalation induction, the incidence of EA in children who received sevoflurane with caudal block was significantly lower in a dose-dependent manner. The incidence of agitation in the group who did not receive dexmedetomidine was 37%, whereas the group receiving 0.15 μg/kg had an incidence of EA of 17%, and a group who received 0.3 μg/kg had an incidence of 10% with no differences in time to discharge. Alternatively, infusion of dexmedetomidine at a rate of 0.2 μg/kg/h after induction and continuing 15 min into PACU is effective in reducing the incidence of ED [101,102]. The incidence of EA in the children who received dexmedetomidine infusion was 26% compared to 60.8% in the sevoflurane group with no differences in time to extubation or discharge from PACU.

In addition to the expected preventative measures and agents, melatonin, a hormone secreted by the pineal gland, when administered preoperatively has been demonstrated to be efficacious in the management of ED in a dose-dependent manner of up to 0.4 mg/kg (maximum 20 mg) when compared to midazolam [103]. Although doses of melatonin at 0.05 mg/kg and 0.2 mg/kg decreased ED, a dose of 0.4 mg/kg was the most efficacious and reduced the incidence of ED to 5.4%.

Beyond pharmacological intervention, parental presence has been evaluated in terms of its effect on ED. Although there was no measurable improvement in the incidence or duration of ED, the parents themselves had greater satisfaction with being present during the recovery phase [104].

EA continues to be addressed, and additional work needs to be done to determine not only how to prevent its occurrence, but also to improve the process by which it is diagnosed and treated when it does occur. A recently published algorithm for reducing the risk of ED in pediatric patients is shown in Figure 18.5 [97]. These goals are necessary in order to make an otherwise uneventful perioperative course more pleasant for the child, family, and providers.

KEY POINTS: EMERGENCE AGITATION OR DELIRIUM

- Emergence agitation is brief and self-limited; emergence delirium is longer-lasting and associated with lack of eye contact and purposeful movement, lack of awareness of surroundings, restlessness, and inconsolability
- Emergence delirium is associated with sevoflurane, young children (1–5 years), ear, nose, and throat (ENT) or eye surgery, and anxious patient/parent temperament
- Propofol, opioids, dexmedetomidine, and regional anesthesia with less sevoflurane are effective strategies

Seizures and myoclonus

Postoperative seizures are an uncommon event in the PACU but can be indicative of a more serious underlying problem. Regardless of the etiology of the seizure, supportive measures should be immediate and include the delivery of oxygen with airway maintenance and special efforts to avoid self-harm in the child. Depending on the severity and duration of the seizure, oxygen may be delivered by facemask or positive pressure ventilation, or require endotracheal intubation. A physician should be in attendance and determine the need for immediate pharmacological intervention, also depending on the severity or duration of the epileptic activity.

Postoperative seizures have numerous causes with significant consequences. Hypoxemia may be rapidly ruled in or out and treated as necessary with appropriate oxygenation and ventilation. If this is clearly not the cause, stat laboratories to rule out hypoglycemia and other electrolyte disturbances such as hyponatremia and hypocalcemia must be sent, then rapidly interpreted and treated. A rare but potentially fatal cause of postoperative seizures is local anesthetic toxicity and the seizures may actually be a prelude to cardiovascular collapse. A thorough history of local anesthetic delivery should be assessed, including last dose and total dosing, if there is any suspicion of local anesthetic toxicity. If this is determined to be the cause, in addition to supportive measures, intravenous lipid emulsion should be delivered if cardiovascular arrest ensues [105]. PACU providers should be made aware of this possibility and be informed as to the location and delivery of lipid emulsion. See Chapters 10 and 20 for further discussion of this problem.

Beyond seizure activity, myoclonus may be observed in the PACU. Myoclonus is defined as the involuntary contraction of a muscle or muscle group and is caused by a variety of factors including some anesthetic agents such as etomidate, or occurs as a prodrome to seizure activity. After other causes of myoclonus are ruled out, the possibility of central anticholinergic syndrome (CAS) should be entertained. CAS is secondary to the central antagonism of muscarinic cholinergic receptors and may be caused by medications that cross the blood–brain barrier such as atropine or scopolamine [106]. The symptoms vary from agitation to actual coma, with myoclonus as a presenting sign. Slow delivery of physostigmine (10–30 μg/kg with a maximum of 3 mg) is the treatment of choice.

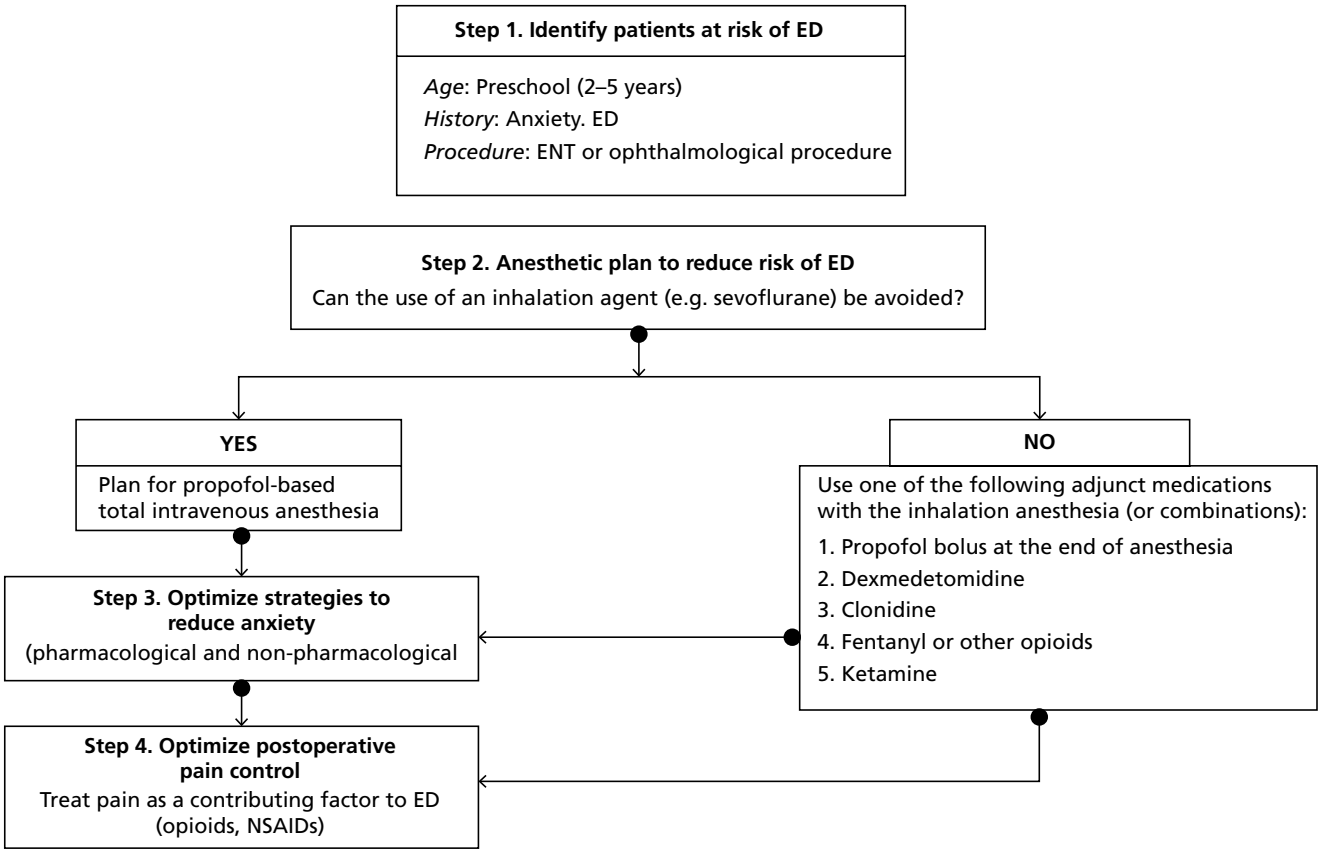

Figure 18.5 Algorithm for prevention and treatment of emergence delirium (ED). *Source*: Reproduced from Moore and Anghelescu [97] with permission of Springer Nature. ENT, ear, nose, and throat; NSAIDs, non-steroidal anti-inflammatory drugs.

Pain

Pain management does not begin in the PACU, but needs to be a consideration for the entire perioperative period, and is the responsibility of every anesthesiologist. In the PACU, the recognition of postoperative pain becomes the duty of a recovery nurse as intraoperative analgesic medications wear off and the pain becomes more intense as the patient recovers. Although a complete discussion of pain is beyond the scope of this chapter and is presented elsewhere in this book (see Chapter 37), in the PACU environment it is important to consider how to assess the pain, what analgesics are appropriate, and what potential pitfalls and complications exist.

The assessment of pain in children remains a challenge, in part because of the diversity of age range. No single assessment tool or score can possibly be applied equally to the newborn and the adolescent. Although of little benefit to children who are pre- and non-verbal, developmentally delayed, or cognitively impaired, self-reporting is probably the most important single reliable indicator of pain. Children as young as 3 years of age can reliably score their own pain [107], provided that they are trained to use the chosen score prior to surgery. There are many validated pain intensity scales including visual analogs, faces scales, and numeric ratings, which are presented elsewhere. The Oucher score utilizes photographs of a child's face exhibiting varying expressions of pain intensity alongside a numerical rating scale and allows the young child to self-report. Different ethnic versions are available and it has been validated in the 3- to 12-year-old age group, specifically in the PACU setting [108] (Fig. 18.6).

In those children unable to provide a self-report (age 3 years or less, or developmentally delayed), behavioral observational scales assist the caregiver in determining a level or degree of pain. The Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) [109], the face, leg, activity, cry, consolability scale (FLACC) [110] (Table 18.6), and the Preverbal, Early Verbal Pediatric Pain Scale (PEVPPS) [111] are all valuable tools but limited in that behavior varies significantly between individuals. These scales are not perfect as a paucity of abnormal behavior does not mean an absence of pain, and negative behavior does not necessarily indicate pain.

Finally, physiological signs such as tachycardia, tachypnea, and hypertension can be used as indicators of pain but are the least sensitive and least specific markers [112]. Particularly in a child, these physiological signs can be present due to other stresses including anxiety or fearfulness, and need to be combined with other evidence that suggests pain as a cause. With all the different types of scales available, each institution needs to determine the ones that work best for their environment for the different age groups and keep them consistent for reliability across providers.

In the clinical setting, proving the existence of pain through a validated pain score is less important than actually understanding the potential degree of pain with knowledge of the surgery and actively managing symptoms and signs of distress. The PACU nursing staff have many pain management strategies available to them, both

Figure 18.6 OUCHER pediatric pain scale for children ages 3–12 years. (A) African American version; (B) Hispanic version. *Source*: Reproduced from Beyer and Knott [108] with permission of Elsevier.

pharmacological and non-pharmacological, to ease pain and distress postoperatively [113]. Multimodal approaches are often the most effective and take advantage of non-opioid and opioid agents as well as other measures for comprehensive pain management.

Non-opioid pharmacological agents offer pain relief without some of the unfavorable side-effects such as nausea and vomiting and respiratory depression, and are therefore useful adjuncts to the postoperative pain management plan. Simple analgesics that require oral administration such as *acetaminophen* require patient cooperation and the absence of nausea and vomiting. The mode of action of acetaminophen is predominantly central by modulating dynorphin release through inhibition of cyclo-oxygenase (COX) [114], and the current understanding is that it is highly selective for COX-2 [115]. Oral dosing is 10–15 mg/kg. Intravenous acetaminophen has become a drug of choice as an adjunct to pain management in the perioperative setting [116]. A dose of 10–15 mg/kg IV every 6–8 h, with a maximum daily dose of no more than 60 mg/kg in children less than 12 years, or 3000 mg in adult-sized patients, is effective. It is crucially important to account for and report to the PACU nursing staff all acetaminophen dosing in the operating room so that maximum dose limits are not exceeded.

Other non-opioid agents such as the non-steroidal anti-inflammatory drugs (NSAIDs) can be delivered orally or intravenously. *Ibuprofen* at 10 mg/kg is given orally every 6 h, and can be alternated with acetaminophen throughout the postoperative period. Another NSAID option is intravenous *ketorolac* at 0.2–0.5 mg/kg every 6 h with a single maximum dose of 15 mg and a maximum daily dosage of 90 mg [117]. Little difference in efficacy has been noted between the NSAIDs, and the mode of action is again by COX inhibition similar to acetaminophen, but predominantly peripherally in this case [118]. NSAIDs are invaluable in the successful management of pain and have been demonstrated to have a significant opioid-sparing effect of up to 46% [119,120]. Although NSAIDs are widely used, caution should be exercised in children due to potential side-effects. Their use in neonates and infants is not currently indicated because of the risk to the developing kidneys. Their use in children also remains controversial due to the risk of bleeding from platelet dysfunction as well as the question of bone healing after certain orthopedic procedures [121,122]. *Aspirin* and other salicylates can cause Reye syndrome in children and are therefore rarely recommended in this population of patients except for

Table 18.6 The face, legs, activity, cry, consolability (FLACC) scale [110]

Categories	Scoring		
	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distractable	Difficult to console or comfort

Each of the five categories – (F) face, (L) legs, (A) activity, (C) cry, (C) consolability – is scored from 0 to 2, which results in a total score between zero and ten. *Source:* Reproduced from Willis et al [110] with permission from Jannetti Publications.

specific indications that do not include postoperative pain management [123].

Opioids continue to represent the mainstay of analgesia in the PACU. The popularity of these drugs stems from their efficacy, speed of onset, and titratability. When non-opioid agents are ineffective by themselves for pain management, the addition of an opioid analgesic is required. Often fentanyl is the opioid intravenous analgesic of choice for the initial PACU period and for outpatients. Intravenous *fentanyl* 0.5–1.0 μg/kg every 3–5 min or *morphine* 0.05–0.1 mg/kg every 10–15 min have been extensively used and studied, but caution needs to be exercised as these medications have significant adverse potential, especially in children. In particular, neonates are prone to ventilatory depression, having immature and poorly-developed responses to airway obstruction, hypercapnia, and hypoxemia [124]. Hydromorphone at 10 μg/kg every 10–15 min may also be used in the PACU setting for severe pain.

Although typically administered intravenously, opioids have good bioavailability by other routes. For example, fentanyl can be given intranasally at 2 μg/kg without an increase in vomiting, hypoxemia, or increased discharge times [125]. Short procedures such as myringotomy, when an intravenous line is not inserted, are ideally suited to this route of administration.

Opioids can also be administered through infusion devices, and patient-controlled analgesia (PCA) can be used for children typically 6 years and older [126]. Background or basal infusions should be used with caution and will require ongoing monitoring not only in the PACU but on the ward [127]. If a child is to receive PCA, it is advantageous to have this mode of analgesia started in the PACU with instructions so that it is fine-tuned and the child's pain is well under control prior to discharge to the ward.

For children who are going home from the recovery room, providing them with an oral dose of their prescribed medication prior to discharge will help the transition process from hospital to home. This allows the family additional time to get prescriptions filled and provides for a more comfortable ride home for the child. Before giving an oral medication, however, it needs to be clear that the child is alert enough to take the medication, able to secure their own airway easily, and be free of nausea or vomiting prior to discharge. In addition, any oral medication that is made of a combination of the opioid with either acetaminophen or ibuprofen must be started only after the appropriate time interval has passed to keep those agents on an every 4 or every 6 h schedule.

Non-pharmacological analgesic remedies may include physical contact through cuddling, stroking, massage, holding, and rocking. In addition, newborn infants can often be comforted with concentrated sugar water (24% dextrose 0.1–0.2 mL instilled intraorally or applied to a pacifier), perhaps due to the sucrose's release of endogenous opioids [128]. Older children may require more sophisticated methods using cognitive interventions along the lines of distraction, guided imagery, and simple delivery of information. In addition, behavioral interventions such as biofeedback, positive reinforcement, and relaxation exercises with controlled breathing can be used to help alleviate pain in the postoperative period.

KEY POINTS: PAIN MANAGEMENT IN THE PACU

- Assessment of pain in young children is challenging, but the FLACC scale for children less than 3 years, and Oucher scale for 3 years and older, are validated
- Hypertension and tachycardia are non-specific but often are signs of pain
- Non-opioid approaches such as intravenous acetaminophen or ketorolac, regional anesthesia, and sucrose for young infants can be effective
- Intravenous opioids including fentanyl and morphine are effective; adequate time is needed before repeat doses to allow the drugs to work
- Non-pharmacological means such as holding, swaddling, parental presence, rocking, feeding clear liquids, and limiting environmental stimulation are often effective

Postoperative nausea and vomiting

Postoperative nausea and vomiting (PONV) is a major cause of patient dissatisfaction in adults following anesthesia and surgery. Children have an even higher incidence of postoperative vomiting (POV) than adults [129], and nausea, which is difficult to diagnose in younger patients, is most likely underreported. Effective management is important not simply for the humanitarian aspect but because LOS in the PACU is largely determined by PONV. Each episode of vomiting can result in a 28 min delay in children after adenotonsillectomy [29] and result in being a major cause of unanticipated admission after outpatient surgery [121].

In 2014, the Consensus Guidelines for the Management of PONV were developed as an evidence-based tool for clinicians [130]. The guidelines focused on identifying patients at risk, what the risk factors for PONV/POV are, recommendations for prophylaxis, and the most effective treatment regimens. Prophylactic management of pediatric POV typically requires drug intervention that may be costly or associated with unwanted side-effects [131]. It is therefore ideal to target those children at particular risk of POV. Risk factors for children are similar to those for adults with a few differences. POV is rare under the age of 2 years but increases with age until puberty, after which it decreases. A study in children under 14 years of age noted a sharp increase in PONV at age 3 years with a 0.2–0.8% increase per year [132]. There appears to be no gender difference in preadolescent patients, and a history of PONV or motion sickness in a child's parent or sibling may be a risk factor. Certain surgical procedures are associated with a higher incidence of POV in children such as adenotonsillectomy, orchidopexy, penile surgery, hernia repair, and especially strabismus repair [133].

The revised PONV consensus guidelines included a simplified risk score to determine the degree of POV risk in children. The degree of risk is based on the number of the following risk factors that are present: (1) duration of surgery ≥30 min; (2) age ≥3 years; (3) strabismus surgery; and (4) history of POV or PONV among relatives. Risk of POV is elevated as the number of risk factors increases, with one risk factor

representing a 10% risk and four risk factors representing a 70% risk for POV [132]. Of interest, this risk assessment analysis does not include tonsillectomy (with or without adenoidectomy) as a dominant risk factor for POV, when it is described by many as a significant cause of morbidity [134].

Having determined the children who represent a risk of POV, the next step is to address factors for reducing baseline risks such as promoting the use of propofol for either total intravenous anesthesia (TIVA) or subhypnotic low-dose infusions [135]. Although not yet validated in pediatrics, in adults the avoidance of inhalation agents and nitrous oxide and the use of straight regional techniques is recommended in those patients with a high risk for PONV. This is rarely applicable to children, but a multimodal approach to pain management aimed at reducing opiate need is vital [136]. The assertion that NSAID use in tonsillectomy/adenoidectomy procedures leads to increased postoperative bleeding has been debunked in a Cochrane Database systemic review [137]. Therefore the use of NSAIDs after such procedures should be encouraged to reduce opiate need. Finally, adequate intraoperative hydration has been shown to reduce the frequency of PONV [138], although insisting that children drink prior to discharge may actually increase the incidence.

Prophylactic drug therapies can either be monotherapy or a combination of medications. The prophylactic antiemetics recommended for pediatric patients include the 5-HT3 antagonists ondansetron, dolasetron, granisetron, tropisetron, and ramosetron. Since the publication of the first guidelines, ondansetron (0.05–0.1 mg/kg up to 4 mg) has been approved for use in children as young as 1 month of age, and granisetron (40 μg/kg) and tropisetron (0.1 mg/kg) were added as therapeutic options. Ramosetron reduced the incidence of PONV to 9% in children undergoing strabismus surgery but has yet to be listed as a therapeutic option in children [139]. Because the 5-HT3 antagonists as a group have greater efficacy in the prevention of vomiting than nausea, these drugs are the first-line choice for prophylaxis in children. Newer data on pharmacokinetics of ondansetron suggest reduced clearance in children under 6 months of age. This is due in part to the immaturity of the cytochrome P450 enzymes and has led to recommendations that children younger than 4 months of age should be monitored more closely after ondansetron [140]. 5-HT3 antagonists do elongate the QT interval and caution should be exercised in using high doses, to avoid induction of cardiac dysrhythmias.

Other therapies to prevent POV include dexamethasone (0.15 mg/kg), droperidol (0.05–0.075 mg/kg up to 1.25 mg), dimenhydrinate (0.5 mg/kg), and perphenazine (0.07 mg/kg). The revised guidelines specify a revised upper limit for the dose range of dexamethasone, reduced from 8 mg to 5 mg to address concerns over unwanted side-effects such as hypoglycemia, delayed wound healing, and wound infection [141]. Dexamethasone is also associated with tumor lysis syndrome, a condition in which the destruction of tumor cell leads to a potentially catastrophic metabolic derangement. The use of dexamethasone may mask the indices used to direct oncology management and so its use must be discussed prior to administration in a newly diagnosed cancer patient. That being said, dexamethasone is a highly effective antiemetic, with timing of drug administration a key factor in successful prophylaxis. For example, dexamethasone should be administered early in the anesthetic [141] while ondansetron has been shown to be more effective when given preoperatively [142].

The 2014 consensus guidelines recommend that children who are at moderate or high risk for POV should receive combination therapy with two or three prophylactic drugs from different classes. This differs from the recommendations for adults, where combination therapy should be reserved for "high risk" patients only. The combinations recommended in the revised consensus guidelines for children are ondansetron (0.05 mg/kg) with dexamethasone (0.015 mg/kg), ondansetron (0.1 mg/kg) with droperidol (0.015 mg/kg), or tropisetron (0.1 mg/kg) with dexamethasone (0.5 mg/kg). All of these combinations require intraoperative administration, and the particular drugs, doses, and timing need to be conveyed during handover so that any breakthrough PONV/POV may be managed with that knowledge available.

The recommendations for treatment of PONV/POV when it occurs in the PACU, or when prophylaxis fails, include the use of an antiemetic chosen from a different therapeutic class than the agents used for prophylaxis. Droperidol can be used for pediatric patients who have failed all other therapies and are being admitted to the hospital, although the potential for extrapyramidal side-effects exists. The FDA issued a "black box" warning on droperidol in 2001 for its association with QT prolongation. In the doses prescribed in the US, the risk of cardiac effects from droperidol is no higher than with other available antiemetics, but this possibility may still significantly reduce the willingness of physicians to prescribe it [143]. Promethazine also has a black box warning for children less than 2 years of age due to reports of respiratory depression and death when used with opioids in the perioperative period.

Aprepitant, a neurokinin-1 receptor antagonist, has recently been approved for the management of chemotherapy-induced nausea and vomiting in children over the age of 12 years. Its use is widely reported in adults for prophylactic management of PONV although there are no data as yet in children.

Non-pharmacological therapies have undergone some investigation in pediatrics. Aromatherapy, whilst effective in adults, has been studied in children with no significant clinical benefit [144]. Acupuncture has been successfully used for POV prophylaxis in children undergoing strabismus repair, dental surgery, and tonsillectomy [145], but others have found use of this technique in children to be inconclusive [134].

With the options available and the fact that the incidence of POV is undoubtedly higher in children than in adults, a

KEY POINTS: POSTOPERATIVE NAUSEA AND VOMITING

- Risk factors for PONV in children include: age 3 years to puberty; surgery >30 min; strabismus, ENT, hernia, or orchidopexy surgery; and family history of PONV
- Propofol, regional anesthesia, use of NSAIDs, and reduction of opioid dose are effective prevention strategies for PONV
- Prophylactic antiemetics including 5-HT3 antagonists (ondansetron) and dexamethasone reduce the incidence of PONV in children
- Droperidol and promethazine (under age 2 years) have FDA black box warnings and should be avoided unless there are no other effective treatments

greater need for a better understanding and age-appropriate management of POV in children is necessary to reduce this unwanted side-effect in the perioperative period.

Medication errors

Medication errors in the PACU are a frequent occurrence, possibly as high as 5% of all orders, and have significant potential to cause harm [146]. Medication errors may occur at any point from prescription to administration and are the result of breakdowns in communication, calculation errors, decimal point errors, the use of a leading/trailing zero, and/or knowledge deficit on the part of the health professional.

Children are at increased risk because almost all medications are prescribed on a weight basis and therefore require a calculation step. In fact, error rates for children have been found to be inversely related to the weight of the patient, with the greatest errors occurring in the smallest children [147]. Analgesic medications in particular are commonly involved in medication errors because of widespread use, split dosing, and weight-based dosing regimen.

Although medication errors in children may occur at any time and for any of the previously stated reasons, most errors occur at the ordering stage and are often simply the result of poor handwriting [147,148]. For this reason, electronic prescribing systems in the PACU are becoming increasingly frequent and offer the clinician and the patient the promise of safer prescribing. The American Academy of Pediatrics has recognized that, within the hospital, computerized physician order entry (CPOE) can prevent medication errors, and this is gaining increasing support in the literature [149,150]. Particularly in children, this safeguard may be an additional layer that will prevent potentially catastrophic events in the postoperative period.

Urinary retention

Urinary retention is often difficult to assess in the pediatric patient due to a child's inability to communicate the issue clearly, and it therefore may be underdiagnosed. In the adult population, urinary retention has an approximately 16% incidence and is associated with the amount of intraoperative intravenous fluid delivery and bladder volume on admission to the PACU as well as advancing age [151]. This would suggest that straight catheterization or bladder emptying prior to emergence in the operating room should occur in patients who have received a considerable amount of intravenous fluid in the operating room without a urinary catheter present. There is no association of urinary retention in the PACU with such factors as gender, urinary symptoms, type of surgery or anesthesia, or intraoperative administration of anticholinergics or morphine. Postoperative urinary retention is not a significant factor after caudal anesthesia when compared to ilioinguinal/iliohypogastric block, and does not delay recovery [152]. However, Metzelder et al demonstrated that children who underwent distal hypospadias repair and receive penile block were significantly less likely to exhibit postoperative urinary retention when compared to a group who received caudal anesthesia (5/33 versus 15/27, respectively) [153].

Urinary retention, often forgotten as a possibility in children in the PACU, should be considered in any child who has otherwise unexplained tachycardia or signs of discomfort that cannot be attributed to the procedure.

Conclusion

The pediatric PACU environment requires careful planning and ongoing maintenance in order to provide a safe, efficient environment for the recovering pediatric patient. Despite the widespread knowledge of basic principles of postanesthetic recovery and the publication of general national standards, as this chapter indicates, specific practices are dictated by institutional experience and preference. Basic tasks such as recognizing and managing potential perioperative complications are made more complex by the nuances of taking care of pediatric patients of all ages and understanding the differences across these ages while also incorporating the parents into the experience.

CASE STUDY

The nursing staff in the pediatric PACU are notified by telephone from the operating room that a 4-year-old male has just undergone a tonsillectomy and adenoidectomy and is ready for transfer to the PACU. The operating room nurse, using a checklist to ensure that all of the important information is conveyed, gives the patient name, age, and weight, identifies the surgeon responsible, and gives a brief description of the operation. She also confirms with the anesthesia provider that there are no additional concerns or issues to be conveyed at the time of initial report. A pediatric-trained PACU nurse then prepares for the admission by establishing that the allocated bed space directly adjacent to her other patient is clean, that the monitoring is complete and working, and that there is an Ambu® bag and functioning suction.

The patient arrives in the PACU escorted by the anesthesia team and surgical resident. The patient is in the left lateral recovery position and has an oxygen mask applied that is connected to a full tank. On arrival, a rapid assessment is made by the PACU nurse and reveals a sleeping child with pink lips and patent airway. Monitors are placed and show an oxygen saturation of 100%, pulse (P) of 100, and blood pressure (BP) of 100/60. Temperature is 37°C.

Using I-SBARQ method, the nurse anesthetist introduces herself and the patient's identity is confirmed by name band with the PACU nurse. The remainder of the handover is as follows:

The patient is a 4-year-old male weighing 20 kg with a history only significant for obstructive sleep apnea who underwent adenotonsillectomy and is currently stable. He has no known drug allergies and receives no current medications. The family are in the surgical waiting room and have spoken to the surgeon. The patient has undergone general anesthesia,

with an inhalational induction of anesthesia, intravenous line placement, and the insertion of a 4.5 cuffed RAE endotracheal tube. He received fentanyl 20 μg and no muscle relaxants. For antiemetic prophylaxis he was given dexamethasone 2 mg and ondansetron 2 mg, as well as IV acetaminophen 300 mg. Fluid given was 400 mL of lactated Ringer's solution. The surgery had taken longer than anticipated due to excessive intraoperative bleeding. A deep extubation of the trachea was performed at the end of the case to avoid coughing and rebleeding. There were no drains and no labs were pending. Vital signs remained stable throughout the case with the exception of tachycardia that persisted throughout at a rate of 100–130 beats per minute. The patient's risk factors are his sleep apnea and risk of postoperative obstruction and the issue that the nurse anesthetist conveys she is concerned about is the risk of bleeding in the PACU in addition to the sleep apnea.

The nurse anesthetist has no additional specific care requirements to report, but the anesthesiologist has written postoperative orders including pain medication at a reduced dose, due to the apnea history. The IV is to be put on a pump and the family informed of the patient's arrival to PACU.

Within 10 min after arrival in the PACU, the child wakes up crying and coughing. His parents are invited into the PACU to help pacify him and aid in the assessment of anxiety versus pain. The parents are immediately concerned over the amount of blood in the saliva and ask the PACU nurse if this is normal. The PACU nurse reassesses the patient and notes that there are indeed copious blood-filled secretions from the airway which require suctioning. The vital signs are measured and noted to be as follows: SpO_2 98%, P 140, and BP 90/60. The anesthesiologist is called with a brief report of the concerns and he comes immediately to the bedside to assess.

At this time the patient vomits what appears to be a large volume of blood. The anesthesiologist immediately determines the possibility of an ongoing tonsillar bleed and so instructs the PACU nurse to administer 10 mL/kg bolus fluid and to arrange for blood products to be delivered. The child is kept in head-down position to the side and vital signs are frequently measured. The anesthesiologist communicates his concerns to the surgeon in the operating room with an updated assessment of the current situation, and a rapid plan of action is established.

During this time, other members of the PACU team bring the centrally located emergency cart with airway equipment to the bedside, along with emergency drugs for the induction of anesthesia. A second fluid bolus of 10 mL/kg is administered and a stat hemoglobin level sent for analysis, prompting the procurement of blood from the blood bank. The child is no longer vomiting and vital signs improve after the second delivery of volume, as noted by an increased BP and reduced heart rate. Resuscitation is deemed adequate and the patient is electively transported back to the operating room for re-exploration of the tonsillar bleed. The parents remain in the PACU during this time and are informed of the events as they occur. The child underwent a successful cauterization of the tonsillar bleed and made an uneventful recovery.

This case illustrates several basic points:

1. Proper handover and communication in the PACU environment are essential. The Joint Commission has made the process of handover a key element of their assessment of a medical center or unit and evidence shows that good communication reduces the incidence of adverse events.
2. The PACU is an environment of constant vigilance and attention to detail. Regular patient assessment and attention to changes in condition require rapid management. Fully functioning monitoring with frequent measurements is imperative.
3. There must be a central core of emergency equipment supply and drugs, and all team members should be familiar with what is present and available in the PACU. The ability of the PACU team to recognize the potential need for emergent airway care or volume resuscitation requires appropriate equipment and supplies that are readily available.
4. Even without issues such as pain, severe nausea and vomiting, or emergence agitation, the PACU is an environment in which a seemingly stable patient can become unstable and all team members need to act swiftly and appropriately.

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A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 19
Monitoring and Vascular Access

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Introduction

Vascular access, and monitoring of circulation, respiration, the central nervous system, and other end organs, is a central task for the pediatric anesthesiologist. The vast majority of cases will require simple peripheral venous access, and standard non-invasive monitors. Extensive surgery or significant underlying disease may necessitate invasive cardiovascular monitoring, and procedures where the brain is at risk may require central nervous system monitoring. This chapter will address peripheral venous access, and then invasive vascular access and monitoring, followed by monitoring of respiration, temperature, renal monitoring, monitoring of neuromuscular blockade, and central nervous system monitoring. Finally, point-of-care ultrasound will be reviewed.

Venous access

Peripheral veins

Any visible peripheral vein, and many that are not visible, may be utilized for peripheral venous access. One strategy in pediatric patients is to cannulate a small superficial vein on the hand or foot with a small catheter (24 or 22 gauge) before induction, or during inhalation induction of anesthesia, to facilitate the early administration of intravenous agents and provide expeditious airway management. Later, with the airway secure and with an immobile patient, larger-bore peripheral venous access can be achieved. Simple surgeries without blood loss require smaller catheters, but if significant fluid or blood administration is anticipated, larger catheter sizes should be utilized. Recommended sizes for major surgery are 22 or 24 ga 1″ catheters for infants newborn through 6 months, 22 ga 1″ or 20 ga 1.25″ catheters for 6 months to 3 years, 20–22 ga or 18 ga 1.5″ for 3–12 years, and 16 or 14 ga 2″ catheters for teenage or adult patients. Resistance to fluid flow predicted by Poiseuille's law is proportional to the length of the catheter and the viscosity of the fluid, and inversely proportional to the fourth power of the catheter radius. When rapidly infusing the more viscous colloids or packed red blood cells, it is important to use a large-bore, short catheter in a large peripheral vein.

The saphenous vein at the ankle is large and in a constant anatomical position in patients of all ages. It can usually be cannulated even if it cannot be seen or palpated. A recommended technique is to apply a tourniquet below the knee, prepare the site antiseptically, and extend the ankle at the medial malleolus with one hand while puncturing the skin at a shallow angle of 10–30° with an angiocatheter 0.5–1 cm

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

anterior and 1 cm inferior to the medial malleolus. Advance the catheter slowly in the groove between the malleolus and the tibialis tendon until blood return through the needle is established. Advance the needle and catheter together several millimeters, then advance the catheter over the needle into the vein with the index finger of the same hand that made the skin puncture, while maintaining extension of the ankle so that the saphenous vein is tethered straight in its course, to minimize the possibility of puncturing the posterior wall due to kinking of the vein. If the vein can be entered but the catheter will not advance its full length into the vein, a small flexible guidewire of 0.015″ or 0.018″ may be used to assist in cannulation of the saphenous or any other peripheral vein [1]. Other large peripheral veins may be found in infants and children on the dorsum of the hand, at the wrist superficial to the radial head, as branches of the cephalic or brachial venous system in the antecubital fossa, or on the dorsolateral aspect of the foot. The latter site is especially prominent in many newborns.

The external jugular vein is often visible in infants and children undergoing anesthesia and surgery. This site can be used in cases of difficult access. A recommended technique is to choose the larger external jugular vein, place a small rolled towel under the shoulders and place the patient in 30° Trendelenburg position, prepare the site antiseptically, and have an assistant compress the vein gently with pressure just above the clavicle to further distend it. Rotation of the head 45–90° away from the side of cannulation, and slight extension of the neck and traction of the skin over the vein with one hand will tether the vein into a straighter course to facilitate successful cannulation. The vein is punctured high in its visible course with an angiocatheter attached to a syringe filled with heparinized saline, and with the needle bent upwards 10–20° to facilitate the very flat, superficial angle of incidence necessary to cannulate the vein without puncturing its back wall. With constant, gentle aspiration of the syringe, the vein is entered and catheter advanced into the vein. Short peripheral catheters of the same size as recommended above should be used. A catheter advanced too far into the venous plexus beneath the clavicle will often exhibit resistance to the free, gravity driven, flow of fluid, and traction or withdrawal of the catheter a few millimeters may be necessary. External jugular catheters are often difficult to secure to the skin on the neck, and suturing them in place is recommended. This will enhance stability postoperatively as the patient begins moving. One advantage of using the external jugular vein for a peripheral venous catheter is that it is easily accessible under the surgical drapes, and can be frequently monitored for extravasation or kinking of the catheter, which is more common with this site than with the other commonly used peripheral veins.

Umbilical vein

The umbilical vein in the fetus is a conduit to carry oxygenated and detoxified blood from the placenta, through the abdominal wall, the liver, and patent ductus venosus to the inferior vena cava (IVC) and the right atrium [2] (Fig. 19.1). This vessel can usually be cannulated at the umbilical stump for the first 3–5 days of postnatal life. Passage into the IVC

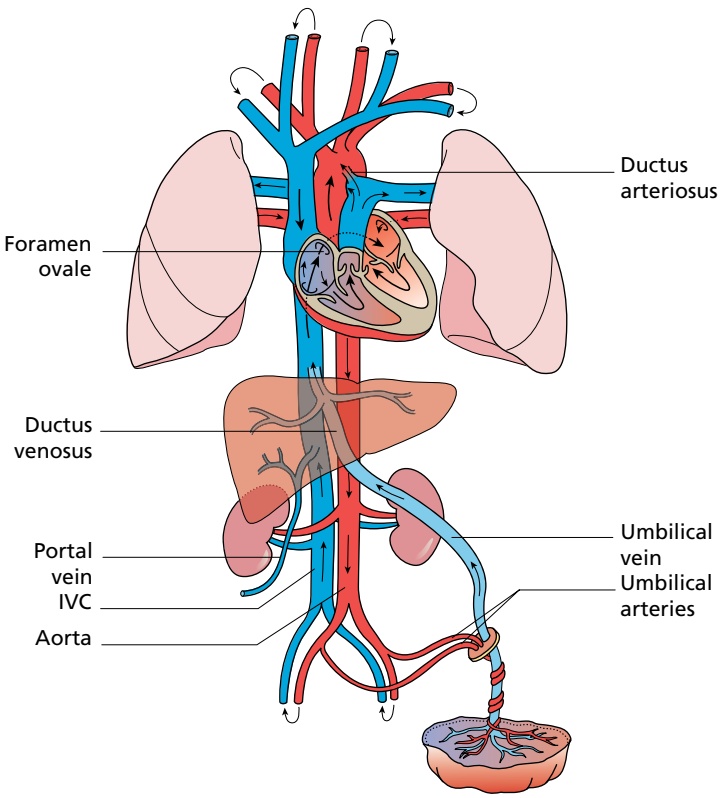


Figure 19.1 The fetal circulation. A catheter placed in the umbilical vein should have its tip through the ductus venosus into the inferior vena cava (IVC) at or near its junction with the right atrium. The tip of an umbilical artery catheter should lie at the level of the third lumbar vertebral body, between the origin of the renal arteries and the bifurcation of the aorta. *Source*: Reproduced from Parellada and Guest [2] with permission of William and Wilking (CCC) Wolters Kluwer Health.

depends on the patency of the ductus venosus, which often exists for the first few days, just as the ductus arteriosus. Sterile technique without a guidewire is used to pass the catheter blindly a premeasured distance. If no resistance to passage is met and free blood return is achieved, the catheter tip is usually in the high IVC or right atrium, and functions as a central venous catheter. Catheter tip position must be determined by radiography as soon as possible to determine if it is through the ductus venosus into the IVC or the right atrium. Often, the ductus venosus is not patent, and the catheter tip passes into branches of the hepatic veins and is visible in the liver radiographically. In this location the catheter must not be used except for emergencies. Central venous pressure monitoring is inaccurate in this position, and portal vein thrombosis, liver and intestinal necrosis can occur with the infusion of hyperosmolar or vasoactive drugs such as sodium bicarbonate and dopamine. An alternative site for central access must be chosen.

KEY POINTS: PERIPHERAL AND UMBILICAL VENOUS ACCESS

- The saphenous vein at the ankle often provides reliable large peripheral vein access in infants and small children
- The external jugular vein can be used as an emergency peripheral intravenous access site
- The umbilical vein can be used for a catheter that passes through the ductus venosus into the IVC for the first 3–5 days of postnatal life

Percutaneous central venous access

Percutaneous central venous access can be utilized for several indications:

- difficult peripheral venous access or need for prolonged vascular access
- need to monitor central venous pressure, i.e. large fluid shifts or blood loss, or cardiovascular surgery
- need for vasoactive infusions [3].

Precise indications will vary according to the practitioner. A double-lumen central catheter of the smallest acceptable size is recommended for percutaneous central venous catheter placement. For all sites, either audio Doppler or two-dimensional ultrasound can be used to facilitate insertion. The larger distal lumen is used for central venous pressure monitoring and drug injection, and the smaller proximal lumen for vasoactive and other infusions. The smallest available double-lumen catheter is currently 4 Fr in size. Superior vena cava (SVC) catheters should be used with caution or not at all in patients weighing less than 4 kg because of the increased risk of thrombosis (see section "Complications of vascular access"). Recommended sizes and lengths are shown in Table 19.1.

Sterile technique using preprocedure scrubbing, cap, mask, gloves, gown, and wide draping leads to a "cleaner" insertion technique with fewer infectious complications [4]. In cardiac patients, the left side SVC lines should generally be avoided. The risk of erosion/perforation is greater, and 5–15% of patients with congenital cardiac disease have a persistent left SVC, which most often drains either to the coronary sinus or left atrium, neither of which is a desirable location for a catheter tip. So, if left-sided line placement is contemplated, ascertain by echo/cath report the presence of the left SVC. If this is not known in a patient with congenital heart disease, choose an alternative site, i.e. femoral vein.

Table 19.1 Recommended central venous catheter sizes and lengths according to weight

Patient weight	IJ/subclavian vein	Femoral vein
<10 kg	4 Fr, 2 lumen, 8 cm	4 Fr, 2 lumen, 12 cm
10–30 kg	4 Fr, 2 lumen, 12 cm	4 Fr, 2 lumen, 12–15 cm
30–50 kg	5 Fr, 2 lumen, 12–15 cm	5 Fr, 2 lumen, 15 cm
50–70 kg	7 Fr, 2 lumen, 15 cm	7 Fr, 2 lumen, 20 cm
>70 kg	8 Fr, 2 lumen, 16 cm	8 Fr, 2 lumen, 20 cm

IJ, internal jugular.

The following general discussion of the Seldinger technique in pediatric patients can be applied to all percutaneous vascular access sites, either venous or arterial. The Seldinger technique is used for all percutaneous central venous cannulations. A central line insertion and maintenance "bundle" will reduce infection rates and should be followed, including a checklist to ensure all steps are followed [5] (Box 19.1). After wide sterile skin preparation with iodine or chlorhexidine-based solution, wide draping is carried out, preferably with a clear, fluid-impermeable adhesive aperture drape so that the underlying anatomy is clearly visible. Slow, controlled, careful needle manipulation, especially in small infants, must be emphasized. The slight movement in or out of only 1 mm or less may be enough to prevent passage of the guidewire. It is very important to have the guidewire prepared to insert and immediately accessible when the vein is entered, so the anesthesiologist does not have to look away from the puncture site to reach for the wire on a distant tray, often resulting in enough movement of the needle to prevent successful guidewire passage. After the desired vein is entered, the needle position is fixed by stabilizing it against the patient's body with the heel of the nondominant hand, and the guidewire is carefully advanced into the right atrium. The resistance to wire passage should be minimal. Experienced operators learn to recognize the "feel" of a guidewire passing successfully. If any resistance is encountered, the wire must be carefully withdrawn and another approach made if the needle is still in the vessel, ascertained by free aspiration of blood. Forcing a guidewire in the face of resistance can lead to significant complications. The electrocardiogram should be carefully observed as the guidewire is slowly advanced. Premature atrial contractions (PAC) are usually observed as the first guidewire-induced dysrhythmia, signifying atrial location. If no PAC are observed, the operator should suspect that the guidewire is not in the atrium. If ventricular extrasystoles are the first observed dysrhythmia, especially if they are multifocal in nature, the wire is very likely in an artery, and the left ventricle has been entered retrograde. After guidewire passage, a very small skin incision with a #11 scalpel is made. Finally, careful dilation and catheter passage follows. The dilators in the prepackaged central venous catheter kits are often one size larger than the catheter, i.e. 5 Fr

Box 19.1: Central line catheter care bundles

Insertion bundle

- Wash hands before the procedure
- For all children aged ≥2 months, use chlorhexidine gluconate to scrub the insertion site for 30 s for all areas except the groin, which should be scrubbed for 2 min. Scrubbing should be followed by 30–60 s of air drying
- No iodine skin prep or ointment is used at the insertion site
- Use a sterilized prepackaged tray with catheter that contains all necessary equipment and supplies, including full sterile barriers
- Create an insertion checklist, which empowers staff to stop a non-emergent procedure if it does not follow sterile insertion practices
- Use only polyurethane or Teflon catheters[a]
- Conduct insertion training for all care providers, including sides and video

Maintenance bundle

- Assess daily whether catheter is needed
- Catheter-site care
  - No iodine ointment
  - Use a chlorhexidine gluconate scrub to sites for dressing changes (30-s scrub, 30-s air-dry)
  - Change gauze dressings every 2 days unless they are soiled, dampened, or loosened[a]
  - Change clear dressings every 7 days unless they are soiled, dampened, or loosened[a]
  - Use a prepackaged dressing-change kit or supply area
- Catheter hub, cap, and tubing care
  - Replace administration sets, including add-on devices, no more frequently than every 72 h unless they are soiled or suspected to be infected
  - Replace tubing that is used to administer blood, blood products, or lipids within 24 h of initiating infusion[a]
  - Change caps no more often than 72 h (or according to manufacturer recommendations); however, caps should be replaced when the administration set is changed[a]
  - The prepackaged cap-change kit, or supply area elements to be designated by the local institution

[a] These procedures are according to the Centers for Disease Control and Prevention (CDC) recommendations.

dilator for 4 Fr catheter. This may be undesirable for small infants, and either passage of the catheter without dilation, or use of a dilator the same size as the catheter is preferable to make the smallest possible hole in the vein to minimize bleeding and trauma to the vessel wall, both of which may lead to an increased incidence of thrombosis or vascular insufficiency. Meticulous attention must be paid to blood loss in small infants during catheterization procedures, with direct compression of bleeding puncture sites using the heel of the non-dominant hand while threading dilators, catheters, etc. Use of an assistant may be necessary in difficult catheterizations. After passage of the catheter to the desired depth, it is secured with sutures and a dressing. If more than 1 cm of catheter is outside the patient, additional suturing or catheter-holding devices are necessary,

Internal jugular vein

The right internal jugular (IJ) vein is the most common site chosen for central venous access in pediatric cardiac surgery, and is often an excellent choice for other major surgery. It is large, and runs in close proximity superficial to the carotid artery along most of its length. The primary advantage of using the internal jugular vein is that it provides a direct route to the right atrium, and thus a high rate of optimal catheter positioning if the vessel can be cannulated. Various studies report only a 0–2% incidence of catheter tip outside the thorax, in contrast to 5–10% for the subclavian route [6,7]. The primary disadvantage comes from difficulty in cannulation in small infants, who have large heads and short necks, and thus it is difficult to obtain the shallow angle of approach necessary to access the vessel. Also some series report a 10–15% incidence of carotid artery puncture in infants and ultrasound studies of neck vessel anatomy reveal the partial or complete overlap of the internal jugular vein anterior to the carotid artery [7]. This site is also not comfortable for some awake infants, and tip migration may be significant with turning the head or flexion/extension of the neck [8]. All insertion techniques involve placing a small roll under the shoulders, using steep Trendelenburg position, and rotating the head no more than 45° to the left. Greater rotation will produce more overlap of the internal jugular vein and carotid artery, and increase the risk of carotid puncture [9]. Recent studies have demonstrated that liver compression and simulated Valsalva maneuver increase the diameter of the internal jugular vein, possibly increasing the success rate of cannulation [10].

There are numerous approaches to the internal jugular vein, some of which are described here (Fig. 19.2).

- Muscular "triangle" method: puncture at the top of the junction where the sternal and clavicular heads of the sternomastoid muscle meet, lateral to the carotid impulse, directing the needle at the ipsilateral nipple. These landmarks are often not well defined in infants.
- Puncture exactly halfway along a line between the mastoid process and the sternal notch, just lateral to the carotid impulse.
- Use the cricoid ring as a landmark, and puncture just lateral to the carotid impulse.
- Jugular notch technique: puncture just lateral to the carotid impulse, just above the jugular notch on the medial clavicle – a low approach.

An ultrasound technique should be used to identify clearly the course of the vessel and detect any significant overlap with the carotid artery. There is no need to use a finder needle for small catheters where the access needle is 20 ga or smaller. Surface landmarks are often inaccurate for estimating the correct depth of insertion for SVC lines, i.e. locating the tip midway between the sternal notch and nipple. See section "Ascertainment of correct position of central venous catheters" for method to ascertain the correct placement for all sites. See Video clip 19.1.

Subclavian vein

The subclavian vein is positioned immediately behind the medial third of the clavicle [11,12]. Advantages of this route include the subclavian vein's relatively constant position in all ages in reference to surface landmarks, stability, and less tip migration with patient movement, and comfort for the

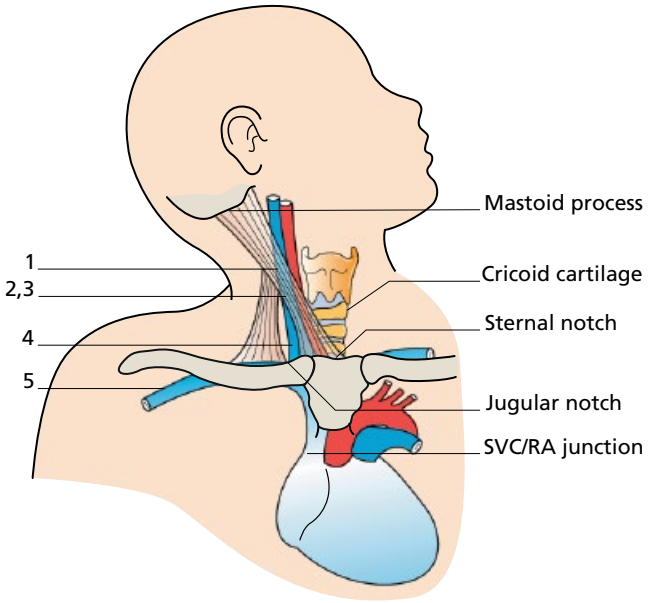


Figure 19.2 Sites for central venous cannulation of the superior vena cava. 1: high approach, midway between mastoid process and sternal notch; 2, 3: middle approach using apex of muscular triangle or cricoid cartilage; 4: low approach using jugular notch; 5: lateral approach to subclavian venipuncture. *Source*: Reproduced from Andropoulos et al [31] with permission of Wolters Kluwer. RA, right atrium; SVC, superior vena cava.

awake patient [13,14]. Disadvantages include an incidence of pneumothorax, especially with an inexperienced operator, and an occasional inability to dilate the space between the clavicle and first rib. Also, in 5–20% of patients, subclavian catheters will enter the contralateral brachiocephalic vein or ipsilateral internal jugular vein instead of the SVC [15].

Technique: A small rolled towel is positioned vertically between the scapulae, steep Trendelenburg position is used, and the arms are restrained in neutral position at the patient's sides. This position maximizes the length of subclavian vein overlapping the clavicle, and moves the vein anterior, bringing it in close proximity to the posterior surface of the clavicle [11]. The right subclavian vein should always be the first choice (see section "Ascertainment of correct position of central venous catheters"). Turn the head toward the side being punctured (i.e. toward the right for a right-sided line). This position will compress the internal jugular vein on that side and prevent the guidewire from entering it, especially in infants [16], which may lead to complications such as dural sinus thrombosis [17]. It will not, however, prevent the guidewire from crossing the midline and entering the contralateral brachiocephalic vein [16]. The needle is bent upwards in midshaft at a 10–20° angle to ensure a very shallow course. In our experience the puncture site that is most successful is 1–2 cm lateral to the midpoint of the clavicle [11], directly lateral from the sternal notch, with the needle directed at the sternal notch. Contact the clavicle first to ensure a shallow angle of incidence to minimize the risk of pneumothorax. Then, the needle is "walked" carefully underneath the clavicle and advanced slowly with constant aspiration until blood return is achieved. Advancing the needle only during expiration is recommended to minimize the risk of pneumothorax. Having an assistant manually ventilate the patient will facilitate this process. If not successful, the needle is withdrawn slowly with gentle aspiration, because about 50% of infant subclavian veins are cannulated during withdrawal due to compression or kinking of the vein during needle advancement. Slow, controlled, careful needle manipulation, especially in small infants, must be emphasized. After the vein is entered, advance the guidewire; there should be no resistance. Look for PAC, sometimes only one or two, as a sign that the wire is in the heart. If no dysrhythmias are seen, withdraw the wire, rotate it 90° clockwise, and advance it again until PAC are seen. Use a dilator (be very careful not to advance it too far – only far enough to expand the space between the clavicle and first rib) and pass the catheter to the desired depth using one of the guidelines noted in section "Height- and weight- based formulae".

Complications during subclavian catheterization occur when a needle angle of incidence is too cephalad, resulting in arterial puncture, or too posterior, resulting in pneumothorax. If the needle course remains shallow, just underneath the clavicle, and directed straight horizontally at the sternal notch, complications are rare. Advancing the needle too far in infants may result in puncture of the trachea.

External jugular vein

Advantages of this approach are its superficial location and thus low risk of arterial puncture. The disadvantage is that the younger the patient, the less likely it is that the guidewire will pass into the atrium; the success rate is less than 50% if the patient is less than 1 year of age, and only 59% in patients less than 5 years [18,19]. Positioning is the same as for the internal jugular approach, the vein is punctured high in its course, and the guidewire is passed. Often it can be observed turning medially toward the SVC. If no resistance is felt, and PAC are seen, or the guidewire is visualized on the transesophageal echocardiogram (TEE), then passage has been successful. Because of the low success rate of central cannulation from the external jugular vein approach, our practice is to use the internal jugular vein first in all patients.

Femoral vein

The femoral vein has long been used for central venous catheterization in pediatric patients, with no greater infection or other complication rate compared to other sites [20,21].

Technique: The patient is positioned with a rolled towel under the hips for moderate extension. The puncture site should be 1–2 cm inferior to the inguinal ligament (line from the anterior superior iliac spine to the symphysis pubis), and 0.5–1 cm medial to the femoral artery impulse, with the needle directed at the umbilicus. Ultrasound guidance (see section "Ultrasound guidance for vascular access") is important for the greatest chance for first-pass, atraumatic placement. The guidewire is passed, ensuring no resistance. A vessel dilator is used, and then the catheter is passed all the way to the hub to position the tip in the mid IVC. It is important to puncture the vessel well below the inguinal ligament, to minimize the risk of unrecognized retroperitoneal bleeding. Bleeding below the inguinal ligament is easily recognized and treated with direct pressure.

Several studies have conclusively demonstrated that in the absence of increased intra-abdominal pressure or IVC obstruction, mean central venous pressure as measured in the IVC below the diaphragm is identical to that measured in the right atrium in patients with and without congenital heart disease [22–26]. The only caveat is in the patient with an interrupted

IVC with azygous vein continuation into the SVC, a condition commonly encountered in patients with the heterotaxy syndromes. The equivalence of IVC and right atrial pressures under these conditions has not been evaluated, but the catheter can be used as any other central line for infusion of drugs and fluids. See Video clip 19.2.

Ascertainment of correct position of central venous catheters

Correct placement of central venous catheters (CVC) is essential to prevent complications (see section "Complications of vascular access") and to give accurate intravascular pressure information. The tip of a central venous catheter should lie in the SVC, parallel to the vein wall, to minimize the perforation risk. Many authorities recommend placement in the upper half of the SVC, where the tip will be above the pericardial reflection in most patients, thus minimizing the risk of tamponade if perforation occurs [27]. In small patients the SVC is often short, i.e. 4–5 cm total length, and the pericardium is usually opened during cardiac surgery in these patients, providing drainage in case of perforation. In addition, the risk of arrhythmias is present with a catheter positioned in the right atrium. Various methods to determine correct placement are discussed as follows.

Radiography and echocardiography

The chest radiograph is considered the gold standard for correct placement, but obtaining and processing a chest radiograph is time consuming, costly, and usually not necessary in the operating room. A chest radiograph should be obtained immediately postoperatively (Fig. 19.3), position of intravascular catheters ascertained, and adjustments made by the anesthesiologist if necessary. It is important to note that an anteroposterior radiograph may miss malposition in one of several ways. The most common is for an SVC catheter to be directed posteriorly down the azygous vein, which may not be detected by anteroposterior radiograph alone. Ideally, the tip of the catheter should be parallel to the SVC wall, in the mid SVC, but in any case it should be above the SVC–RA junction. The position of the pericardial reflection is variable in infants and young children, and radiographic landmarks such as the carina to ascertain tip placement above the pericardial reflection are not reliable [28].

If TEE is utilized for cardiac surgery, the tip of the central catheter can usually be visualized in the region of the SVC–RA junction; this is easily done before surgery starts and is a very accurate method of ascertaining correct position [15] (Fig. 19.4).

Electrocardiographically-guided placement

The intravascular electrocardiogram (ECG) may be used in children to guide correct CVC placement [29,30]. Either a 0.9% or 3% saline-filled lumen with special ECG adaptor, or a guidewire within the lumen attached to a sterile alligator clip and leadwire substituted for the right arm surface ECG lead may be used. Entry of the catheter tip into the right atrium is signified by the sudden appearance of a P atriale, an exaggerated, large, upright P wave. The catheter tip is then pulled back 1–2 cm into the desired position in the SVC. The success rate for proper placement in the reported studies has been 80–90%, but there have been no controlled studies in children comparing this method to other methods. This method also requires special equipment that is not always available.

Height- and weight-based formulae

A large study of CVC placement in infants and children undergoing congenital heart surgery developed formulae for correct insertion depth based on height and weight [31] (Table 19.2). CVC were inserted in the right internal jugular or subclavian vein and postoperative radiograph studies were used to determine the tip position in reference to the SVC–RA junction. The

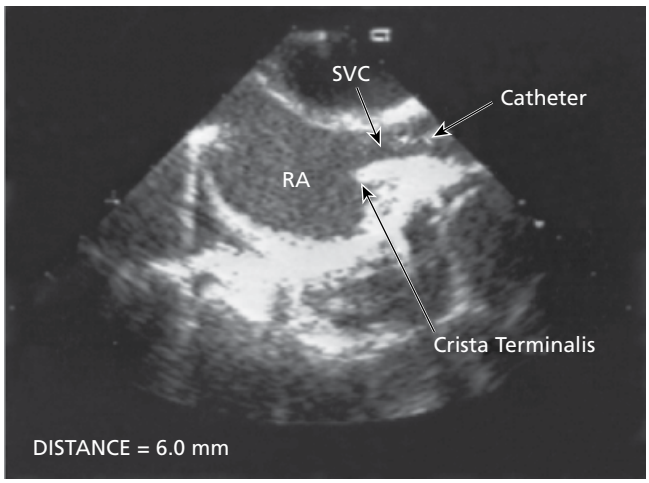


Figure 19.4 Transesophageal echocardiographic image of the superior vena cava (SVC)–right atrial (RA) junction in the sagittal plane in an infant. The tip of the right internal jugular catheter is in the SVC, 6 mm above the RA. *Source:* Reproduced with permission from Andropoulos et al [15] with permission of Wolters Kluwer.

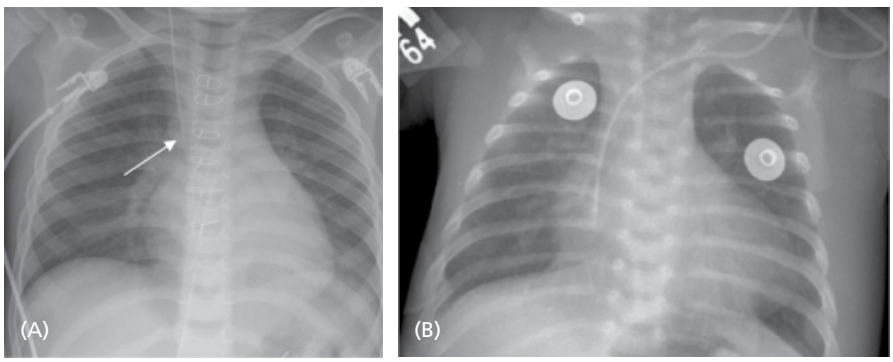


Figure 19.3 (A) Postoperative chest radiograph with the tip of a right internal jugular vein catheter in proper position in the mid superior vena cava. (B) Tip of catheter malpositioned, deep in the right atrium.

length of catheter inside the patient was added to this distance to determine the position of the SVC–RA junction, and formulae developed that would predict placement above the RA, in the SVC, 97.5% of the time (95% confidence interval 96–99%). All catheter tips predicted to be in the atrium using these data would be high in the RA within 1 cm of the SVC–RA junction, minimizing any perforation risk. The formulae are simple and easily implemented because weight and height can be easily measured in all patients undergoing surgery.

For patients with height less than 100 cm:

$$(\text{Height} \div 10) - 1\,\text{cm}$$

is the correct insertion distance, i.e. a 75 cm patient would have the catheter secured at 6.5 cm for either the right internal jugular or the subclavian route.

For patients with height 100 cm or greater:

$$(\text{Height} \div 10) - 2\,\text{cm}$$

is the correct distance. The caveats to this seemingly useful technique are that for the internal jugular vein, the puncture site is high, exactly midway between the mastoid process and the sternal notch; and for the subclavian, the puncture site 1–2 cm is lateral to the midpoint of the clavicle. If different puncture sites are utilized, the operator must adjust the formulae accordingly. Also, the formulae have not yet been evaluated for accuracy in a prospective fashion.

Percutaneously inserted central catheters

Percutaneously inserted central catheters (PICC) have been utilized in the neonatal nursery for more than a decade, and have become standard practice for ill newborns expected to require prolonged venous access. The complication rate for these catheters is very low, and they are usually relatively easy to insert into the central circulation via the antecubital, saphenous, scalp, hand, axillary, or wrist veins, when placed by experienced, skilled personnel. Such personnel include nurses [32] or physicians placing them at the bedside, or in the interventional radiology suite [33] with ultrasound and fluoroscopic guidance. The key to successful placement is early access, before all large visible superficial veins are injured from attempts at peripheral intravenous placements. For this reason, the PICC line is optimally placed in the critically ill newborn in the first 12–24 h after admission. Like all CVC, PICC occasionally cause complications such as perforation of the atrium, or embolization of a portion of the catheter [34]. The infection rate is very low.

Technique: A suitable vein should be identified. The branches of the basilic vein on the medial half of the antecubital fossa offer the highest success rate because of their large size and direct continuation with the axillary and subclavian veins. The cephalic vein tributaries can also be used, but are less likely to pass into the axillary vein. Other sites, e.g. the saphenous, hand, and scalp veins, are cannulated as for a peripheral intravenous catheter. The site is prepared and draped, and appropriate local anesthesia and/or intravenous analgesia are administered. The vein is entered using a large break-away needle or angiocatheter, and a 2 Fr non-styletted silicone catheter flushed with heparinized saline is passed with forceps a distance measured from the entry site to the SVC–RA junction. Continued easy passage without resistance, and continuous ability to aspirate blood signify proper placement. A radiograph, with injection of diluted contrast if needed, should be obtained prior to use. Proper catheter tip position is in the SVC or IVC, not in the right atrium. Occasionally the PICC line will not pass centrally, i.e. into the intrathoracic portion of the subclavian vein or further, or into the IVC. In this case it should be considered no differently than a peripheral venous line. For central PICC lines, any centrally delivered medication or fluid may be used, i.e. parenteral nutrition, dopamine, CaCl, etc. The 2 Fr PICC lines are too small for rapid fluid boluses or blood products, therefore inadequate as the sole prebypass access for cardiac surgery, or for other major surgery. Recently, 3.5–4 Fr soft polyurethane double-lumen PICC lines, with two 22 ga lumens, have become available, and can be placed using modified Seldinger technique with a central vein placement rate of 66% [35]. Alternatively, 3 Fr PICC lines, placed with the aid of ultrasound and fluoroscopic guidance with a guidewire in the interventional radiology suite, may be used in newborns with caution, especially in the SVC position, because of the risk of thrombosis [36]. In older infants and children these larger catheters are preferred. Tan et al [37] reported a series of 124 such catheters in cardiac surgical neonates, noting a low thrombosis rate of 1.6%, and a low infection rate of 3.6 per 1000 catheter days, with a median onset of 37 days; thus these catheters can be extremely useful in this population.

Table 19.2 Recommended length of superior vena cava central venous catheter (CVC) insertion in pediatric patients based on weight: right internal jugular or subclavian veins

Patient weight (kg)	Length of CVC insertion (cm)
2–2.9	4
3–4.9	5
5–6.9	6
7–9.9	7
10–12.9	8
13–19.9	9
20–29.9	10
30–39.9	11
40–49.9	12
50–59.9	13
60–69.9	14
70–79.9	15
80 and above	16

KEY POINTS: CENTRAL VENOUS ACCESS

- Indications include monitoring central venous pressure (CVP), administering vasoactive infusions, and securing access for cases with large fluid shifts or blood loss
- The right internal jugular vein is the most direct route to the SVC, and the tip is properly positioned more often than subclavian vein catheters
- Femoral venous catheters measure CVP in the IVC and are accurate reflections of intrathoracic CVP in the absence of increased intra-abdominal pressure
- Height- and weight-based formulae, ultrasound, and radiography are used to place the tip of a CVP catheter in the SVC and not the right atrium

Arterial access

Tables 19.3 and 19.4 display recommended catheter sizes for arterial access based on site and patient weight.

Radial artery

This is the preferred location in the newborn if an umbilical artery line is not possible or needs to be replaced, and in virtually all other patients. Placement on the same side as an existing or planned systemic-to-pulmonary artery shunt is avoided, e.g. a right-sided modified Blalock–Taussig shunt.

Technique: The wrist is extended slightly with rolled gauze, and the fingers taped loosely to an armboard, with the thumb taped separately in extension to tether the skin surface over the radial artery (Fig. 19.5). An angiocatheter flushed with heparinized saline is used as a "liquid stylet" to increase the rapidity of flashback of blood into the hub of the needle after aseptic preparation. The skin is punctured at a 15–20° angle at the proximal wrist crease at the point of maximal impulse of the artery. Palpation is the usual method of identifying the artery, but audio Doppler localization can be helpful if the pulse is weak. Lighter planes of anesthesia provide stronger pulses and increase the success rate of cannulation. The first attempt, before any hematoma formation or partial dissection of the artery, always yields the greatest chance for success, so the operator should optimize conditions, e.g. positioning, lighting, and identification of the vessel. Puncture of the artery with the needle is signified by brisk flashback. The needle and catheter are then advanced 1–2 mm into the artery, and an attempt is made to thread the catheter primarily over the needle its full length into the artery. Threading should have minimal resistance and is signified by the continuing flow of blood into the hub of the needle. If threading is not successful, the needle is replaced carefully in the angiocatheter, and the needle and catheter can be passed through the back wall of the artery. Then the needle is removed, and a 0.015″ guidewire with flexible tip can be used to assist threading of the catheter. The catheter is pulled back very slowly, and when vigorous arterial backflow occurs, the guidewire is passed, and the catheter threaded over the guidewire into the artery [38]. Minimal resistance signifies successful threading. If threading is unsuccessful, further attempts may be made at the same site or at slightly more proximal sites to avoid areas of arterial spasm, thrombosis, or dissection. The circulation distal to the catheter should be assessed by inspection of color and capillary refill time of fingertips and nailbeds, and quality of signal from a pulse oximeter probe. A recommended technique for securing the catheter is with a clear adhesive dressing and transparent tape so that the insertion site and hub of the catheter are visible at all times. See Video clip 19.3.

Table 19.3 Recommended arterial catheter sizes: radial, dorsalis pedis, posterior tibial, brachial arteries

Weight	Radial/DP/PT arteries	Brachial artery
<2 kg	24 ga	Not recommended
2–5 kg	22 ga	24 ga
5–30 kg	22 ga	22 ga
>30 kg	20 ga	22 ga

DP, dorsalis pedis; PT, posterior tibial.

Table 19.4 Recommended arterial catheter sizes: femoral, axillary arteries

Weight	Femoral/axillary arteries
<10 kg	2.5 Fr, 5 cm long
10–50 kg	3 Fr, 8 cm long
>50 kg	4 Fr, 12 cm long

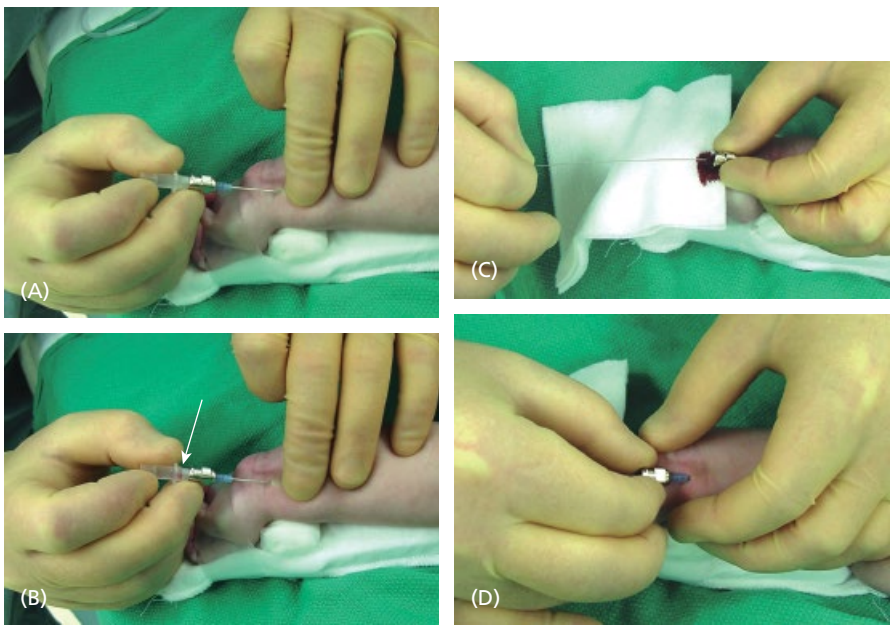


Figure 19.5 Insertion of a radial arterial catheter in an infant. (A) The radial artery is approached with a saline-filled angiocatheter, at the proximal wrist crease. (B) Rapid flashback of arterial blood (*arrow*) is noted with arterial puncture using liquid stylet technique. (C) A 0.015″ guidewire is inserted and threaded into the artery. (D) The angiocatheter is threaded over the guidewire.

Femoral artery

The superficial femoral artery is a large vessel that is easily accessible in almost all patients [39] and is a logical second choice for cardiac surgery when radial arterial access is not available. In infants, especially patients with trisomy 21, transient arterial insufficiency develops in up to 25% of patients after arterial catheterization when 20 ga (3 Fr) catheters are used [39]. For this reason, in the author's institution the smallest commercially available catheter, 2.5 Fr (equal to 21 ga), is used in patients weighing less than 10 kg (see Table 19.4).

Technique: A small towel is placed under the patient's hips to extend the leg slightly to neutral position. Slight external rotation, with the knees restrained by taping to the operating room bed, fixes adequate position. After sterile preparation and draping, the course of the superficial femoral artery is palpated and punctured 1–2 cm inferior to the inguinal ligament, to avoid puncturing the artery above the pelvic rim where a retroperitoneal hematoma could develop. If the pulse is weak, as in the case of aortic arch obstruction, use of audio Doppler effectively identifies the course of the vessel. The puncture technique varies and may include direct puncture with an angiocatheter, or Seldinger technique using the needle in the commercially supplied kit, or a 21 ga butterfly needle with the extension tubing removed. All of the above are flushed with heparinized normal saline to increase the rapidity of flashback. A small flexible guidewire, 0.015″ or 0.018″, is used. It is normally possible to thread a polyethylene catheter over the guidewire without making a skin incision; under no circumstances is dilating the tract and artery with a dilator recommended, which could cause arterial spasm, dissection, or bleeding around the catheter if the puncture site is large. The catheter is secured by suturing around the entry site of the catheter and wings around the hub. Distal perfusion is immediately assessed, and a pulse oximeter probe is placed on the foot for continuous monitoring and early warning of arterial perfusion problems.

Brachial artery

The brachial artery has been successfully used for monitoring for cardiac surgery in children, but using this site for arterial monitoring should generally be avoided because it has poor collateral circulation compared to the radial, femoral, and axillary arteries. Theoretically, there should be a higher incidence of arterial insufficiency with this site, but a study by Schindler et al, of 386 brachial artery catheters in infants and children undergoing cardiac surgery, documented no permanent ischemic damage, and only three temporary arterial occlusions, when 22 and 24 ga catheters were used [40]. This site should only be used in situations when there are limited other options, e.g. a right upper extremity arterial line is required to monitor pressure during cross-clamping for repair of coarctation of the aorta, or during bypass for aortic arch hypoplasia or interruption.

Technique: A 24 ga catheter should be used in patients under 5 kg. The arm is restrained in neutral position on an armboard, and the arterial impulse is palpated above the elbow crease, well above the bifurcation into radial and ulnar arteries. Cannulation proceeds as for the radial artery. Meticulous attention to distal perfusion must be paid at all times, and the catheter removed for any signs of ischemia. Pulse oximeter monitoring of distal pulses will provide early detection of perfusion problems. The catheter should be removed or replaced with a catheter in a site with better collateral circulation as soon as possible after the repair.

Axillary artery

The axillary artery is large and well collateralized, and several series in critically ill children have demonstrated this to be a viable option with a low complication rate when other sites are not accessible [41,42]. However, given the potential morbidity of an ischemic arm and hand, and the theoretical problem of intrathoracic bleeding, this puncture site should be considered a site of last resort when there are limited options.

Technique: The arm is abducted 90° and extended slightly at the shoulder to expose the artery. The artery is palpated high in the axilla and punctured using an angiocatheter, which is then exchanged over a guidewire for a longer catheter, or by primary Seldinger technique. A catheter that is too short (e.g. 22 ga 1″ long) will often be pulled out of the vessel with shoulder extension. Therefore, the shortest recommended catheter is 5 cm long (see Table 19.4). Careful attention must be paid to distal perfusion, as with the brachial artery. Tip position should be ascertained by chest radiograph, and should not lie deeper than the first rib. The proximity to the brachiocephalic vessels makes it imperative that the catheter be flushed very gently by hand after blood draws, and that no air bubbles or clots ever be introduced, because of the risk of retrograde cerebral embolization.

Umbilical artery

The umbilical artery is accessible for the first few days of life, and is the site of choice for newborns requiring surgery in the first week of life (see Fig. 19.1). The complication rate is lower with the catheter tip placed in the high position, i.e. above the diaphragm, versus the low position, i.e. at the level of the third lumbar vertebra [43]. The catheter can be left in place for 7–10 days. A relationship to intestinal ischemia and necrotizing colitis has been demonstrated [44], and enteral feeding with an umbilical artery catheter in place is controversial [45]. Umbilical catheters are most commonly inserted by the neonatal staff in the delivery room or neonatal ICU shortly after birth. The technique involves cutting off the umbilical stump with an umbilical tape encircling the base to provide hemostasis, dilating the umbilical artery, and blindly passing a 3.5 Fr catheter a distance based on weight, then assessing position as soon as possible radiographically. Lower extremity emboli, vascular insufficiency, and renal artery thrombosis have all been described [46]; however the overall risk is low and this site is highly desirable because it is a large central artery yielding accurate pressure monitoring [47] during all phases of neonatal surgery, and preserves access for future interventions.

Temporal artery

The superficial temporal artery at the level just above the zygomatic arch is large and easily accessible in newborns, particularly the premature infant. It was widely used in the 1970s in neonatal nurseries [48] but rapidly fell out of favor with the realization that significant complications, e.g. retrograde

cerebral emboli, were disturbingly common [49,50]. It should only be used when a brachiocephalic pressure must be measured for the surgery in the face of an aberrant subclavian artery, so that the only way to measure pressure during cross-clamping or on bypass is via direct aortic pressure, or temporal artery pressure [51]. Examples are coarctation of the aorta, aortic arch interruption, or hypoplasia, with an aberrant right subclavian artery that arises distal to the area of aortic obstruction [52]. The catheter must be used only during the case, blood drawing and flushing should be minimized, and it must be removed as soon as possible after the repair.

Technique: A 24 ga catheter is used for newborns. The artery is palpated just anterosuperior to the tragus of the ear, just superior to the zygomatic arch. A very superficial angle of approach, i.e. 10–15°, is used, and the artery is cannulated as described for the radial artery.

Dorsalis pedis/posterior tibial arteries

These arteries are often easily cannulated and quite useful for monitoring and blood sampling during surgery when radial arteries are not available. Superficial foot arteries should not be used for cardiopulmonary bypass cases, because of the well-known peripheral vasoconstriction, and vasomotor instability in the early postbypass period, which is more pronounced with these arteries than with the radial artery.

Technique: Dorsalis pedis – the foot is plantar flexed slightly to straighten the course of the artery, which is palpated between the second and third metatarsal. A superficial course is taken and the artery cannulated. Posterior tibial – the foot is dorsiflexed to expose the artery between the medial malleolus and the Achilles tendon. The artery is often deep to the puncture site, so a steeper angle of incidence is required.

A recent study assessed the suitability of the posterior tibial and dorsalis pedis arteries, versus the radial artery, in patients with a median age of 13 months [53]. The first phase of the study measured the diameter and cross-sectional areas of the arteries by ultrasound, and the second was the randomized trial in 275 subjects. The posterior tibial artery was similar in size to the radial artery (1.4 ± 0.3 versus 1.3 ± 0.3 mm) but larger than the dorsalis pedis artery (1.0 ± 0.2, $p < 0.001$). First-attempt success rate with the posterior tibial artery was similar to the radial artery (75% versus 83%), but higher than the dorsalis pedis artery (45%, $p < 0.001$). The posterior tibial artery would appear to be the artery of choice for a pedal arterial line if other arteries are not available.

Ulnar artery

The ulnar artery should only be used as a last resort when other options are not available, because its use is usually only considered when radial artery attempts have been unsuccessful or thrombosed by past interventions. There is a high risk of ischemia of the hand if both the radial and ulnar artery perfusion is significantly compromised. Despite this, one series of 18 ulnar artery catheters in critically ill infants and children had an ischemia rate not different from radial and femoral artery catheters of 5.6% [54]. With the increasing use of high-resolution ultrasound for arterial catheter placement (see section "Ultrasound guidance for vascular access"), it is evident that at times the ulnar artery appears to be of larger diameter than the radial artery in some patients, particularly in Down syndrome. If this is the case, some anesthesiologists will attempt the ulnar artery as the first cannulation attempt site.

Arterial cutdown

Cutdown of the radial artery is a reliable and often efficient method to establish access for congenital heart surgery, and other major surgery when other arterial access has failed or is not available. Despite the speed and ease of access for a cutdown, available literature indicates a higher rate of bleeding at the site, infection, failure, distal ischemia, and long-term vessel occlusion compared to percutaneous techniques [55,56].

Technique: The arm is positioned as for percutaneous radial catheterization. After surgical preparation and draping, an incision is made at the proximal wrist crease between the styloid process and the flexor carpi radialis tendon, either parallel or perpendicular to the artery. Sharp and blunt dissection is carried out until the artery is identified, and it is isolated with a heavy silk suture, vessel loop, or right-angle forceps. It is no longer considered necessary to ligate the artery distally to prevent bleeding, and in fact the artery may remain patent after a cutdown if not ligated distally. The simplest and very effective technique is to cannulate the exposed artery directly with an angiocatheter, in the same manner as for percutaneous radial artery catheter placement. The catheter is then sutured to the skin at its hub, and the incision closed with nylon sutures on either side of the catheter. Removal entails cutting the suture at the hub of the catheter, removing the catheter, and applying pressure for a few minutes until any bleeding stops. The remaining skin sutures can be removed at a later date.

KEY POINTS: ARTERIAL ACCESS

- Indications include beat-to-beat blood pressure monitoring in cases with potential for hemodynamic instability, and need for frequent blood testing for arterial blood gases, hemoglobin, or other testing
- The radial artery is the preferred site for most arterial cannulations
- The femoral artery is a large vessel that is often second choice if the radial arteries are not available
- The posterior tibial artery is larger and more reliable than the dorsalis pedis artery
- The ulnar, brachial, axillary, and temporal arteries should only be utilized if other sites are not available, and the catheter should be removed as soon as possible

Percutaneous pulmonary artery catheterization

Percutaneous pulmonary artery (PA) catheterization has a limited role in pediatric anesthesia for several reasons. The small size of many patients precludes placement of adequate sized sheaths and catheters, and many patients in whom PA catheter monitoring would be desirable have intracardiac shunting, invalidating results of standard thermodilution cardiac output measurements and confusing mixed venous oxygen saturation (SvO_2) measurements. In addition, the frequent need for

right-sided intracardiac surgery makes PA catheterization undesirable. Thus, when PA pressure or SvO_2 monitoring is indicated, transthoracic PA lines are the most common method in congenital heart surgery. The availability of continuous central venous oxygen saturation catheters, and the perception that the risk:benefit ratio for PA catheter placement is most often unfavorable, limit the indications for this technique.

The most common indications for percutaneous PA catheterization in pediatric anesthesia are in patients over 6 months of age able to accept a 5 or 6 Fr introducer sheath in the femoral or internal jugular vein. Patients having surgery on left heart structures who do not have intracardiac shunting, who are at risk for left ventricular dysfunction or pulmonary hypertension, may benefit from the information available. Examples include aortic surgery, aortic valve repair or replacement, subaortic resection or myomectomy for hypertrophic cardiomyopathy, and mitral valve repair or replacement. In addition, major surgery, i.e. liver transplant in larger patients, may be an indication for percutaneous PA catheterization.

Technique [57]: An oximetric catheter is recommended. Commercially available models are 5.5 Fr, or 8.5 Fr, and thus require a 6 Fr or 9 Fr sheath, respectively. The 5.5 Fr catheter should be used in patients under 50 kg, and the 8.5 Fr in patients over 50 kg. The sheath is placed into the internal jugular, femoral, or subclavian veins as described above. The preferred sites of insertion are the right internal jugular, left subclavian, or femoral vein because of the direct path and curvature of the catheter. If an oximetric catheter is used, it is calibrated prior to insertion. The balloon integrity should be tested before insertion by inflating the recommended volume of air or CO_2, and the sterility sleeve is inserted before placement. The PA and CVP ports are connected, flushed, and calibrated before insertion. The PA catheter is inserted 10–15 cm with the balloon deflated, depending on patient size. The balloon is inflated, and the catheter advanced slowly toward the tricuspid valve, whose position is indicated by enlarging V waves on the CVP trace. The catheter is advanced through the tricuspid valve by advancing during diastole until the characteristic right ventricular trace is visible, with no dicrotic notch, and a diastolic pressure of 0–5 mmHg. Then, the catheter is advanced carefully through the pulmonary valve during systole, until the characteristic PA tracing is visible, with a dicrotic notch and higher diastolic pressure. The catheter is then advanced gently until the pulmonary capillary wedge pressure tracing is obtained, at which time the balloon is deflated so the PA tracing rapidly returns. Difficulty with advancing through the pulmonary valve may be assisted by counterclockwise rotation of the catheter while advancing, positioning the patient right side down, and giving a fluid bolus, or by using TEE to visualize the tip and guide subsequent attempts [58]. The catheter must not be left in the wedge position except for brief periods because of the risk of pulmonary artery rupture and lung ischemia distal to the catheter. During bypass, the catheter can be pulled back several centimeters to reduce the risk of perforation on bypass.

Information obtainable with a PA catheter includes right atrial pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure (PCWP). In the absence of mitral valve stenosis or pulmonary venous or arterial hypertension, PA diastolic ~ PCWP ~ LAP ~ left ventricular end-diastolic pressure, which is proportional to left ventricular end-diastolic volume, the classic measure of preload [59]. Despite the presence of pulmonary hypertension or residual mitral stenosis (diagnosed with postoperative TEE), information from the PA catheter can still be used to direct therapy.

Cardiac index may be measured by standard thermodilution methods, with care taken to input the correct calculation constant into the monitor software according to the catheter size and length, and volume and temperature of injectate. The average of three consecutive injections made in rapid succession at the same point in the respiratory cycle, i.e. expiration, will optimize conditions to achieve an accurate measurement during steady-state conditions. Vascular resistances and stroke volume can also be calculated, using the formulae in Table 19.5 [59,60].

Hemodynamic data represent only half of the information available from an oximetric PA catheter. The other half consists of oxygen delivery and consumption measurements and calculations, which may also be used to guide therapy in the critically ill patient with low cardiac output syndrome [59,60] (Table 19.6). They require either measurement of mixed venous

Table 19.5 Derived hemodynamic parameters

Formula	Normal values		
	Adult	**Infant**	**Child**
$CI = \frac{CO}{BSA}$	2.8–4.2 L/min/m^2	2–4	3–4
$SVI = \frac{SV}{BSA}$	30–65 mL/beat/m^2	40–75	40–70
$LVSWI = \frac{1.36 \cdot (MAP - PCWP) \cdot SVI}{100}$	45–60 g · m/m^2	2–40	30–50
$RVSWI = \frac{1.36 \cdot (PAP - CVP) \cdot SI}{100}$	5–10 g · m/m^2	5–11	5–10
$SVRI = \frac{(MAP - CVP) \cdot 80}{CI}$	1500–2400 dyne · s · cm^{-5} · m^2	900–1200	1300–1800
$PVRI = \frac{(PAP - PCWP) \cdot 80}{CI}$	250–400 dyne · s · cm^{-5} · m^2	<200	<200

BSA, body surface area; CI, cardiac index; CO, thermodilution cardiac output; CVP, central venous pressure; LVSWI, left ventricular stroke work index; MAP, mean arterial pressure; PAP, pulmonary arterial pressure; PVRI, pulmonary vascular resistance index; RVSWI, right ventricular stroke work index; SVRI, systemic vascular resistance index; SV, stroke volume; SVI, stroke volume index.

Table 19.6 Derived oxygen delivery/consumption parameters

Formula	Normal values		
	Adult	**Infant**	**Child**
Arterial O_2 content $CaO_2 = (1.39 \cdot Hb \cdot SaO_2) + (0.0031 \cdot PaO_2)$	18–20 mL/dL	15–18	16–18
Mixed venous O_2 content $CvO_2 = 1.39 \cdot Hb \cdot SvO_2 + 0.0031 \cdot PvO_2$	13–16 mL/dL	11–14	12–14
Arteriovenous O_2 content difference $avDO_2 = CaO_2 - CvO_2$	4–5.5 mL/dL	4–7	4–6
Pulmonary capillary O_2 content $CcO_2 = 1.39 \cdot Hb \cdot ScO_2 + 0.0031 \cdot PcO_2$	19–21 mL/dL	16–19	17–19
Pulmonary shunt fraction $Q_s/Q_t = 100 \cdot (CcO_2 - CaO_2)/(CcO_2 - CvO_2)$	2–8%	2–8	2–8
O_2 delivery index $DO_2I = 10 \cdot CO \cdot CaO_2/BSA$	450–640 mL/min/m^2	450–750	450–700
O_2 consumption index $VO_2I = 10 \cdot CO \cdot (CaO_2 - CvO_2)$	85–170 mL/min/m^2	150–200	140–190

Hb, hemoglobin; PaO_2, partial pressure of oxygen in arterial blood; PvO_2, partial pressure of oxygen in mixed venous blood; PcO_2, partial pressure of oxygen in pulmonary capillary blood; Q_s, pulmonary shunt blood flow; Q_t, total pulmonary blood flow; SaO_2, measured arterial oxygen saturation; ScO_2, measured pulmonary capillary oxygen saturation; SvO_2, measured mixed venous oxygen saturation.

and systemic arterial saturations from blood samples from the tip of the PA catheter and arterial line (measured by co-oximetry, not calculated), or substitution of these values with SvO_2 from the oximetric catheter (a valid assumption if properly calibrated), and pulse oximeter value instead of measured systemic saturation. There are data from adult and pediatric critical care literature suggesting that the ability to increase and maximize both oxygen delivery and consumption may improve outcome and is a predictor of survival from critical illness, including postoperative cardiac surgery [61–64].

Ultrasound guidance for vascular access

Numerous studies demonstrate that ultrasound guidance, either two-dimensional visual ultrasound [65], or audio Doppler ultrasound, improves the outcome of central venous cannulation, in both children and adults [66,67]. Use of these methods leads to fewer attempts, decreased insertion time, fewer unintended arterial punctures, and fewer unintended arterial catheter placements. The consensus of many experts in the field of vascular access is that use of these guidance techniques should be considered standard of care. A recent meta-analysis of eight controlled trials of two-dimensional ultrasound guidance versus landmark method for internal jugular or subclavian vein access in children combined data from 760 patients [68]. With ultrasound the relative odds of successful placement was 1.32 ($p = 0.003$), the number of attempts was lower by -1.26 ($p < 0.001$), and there was a trend toward lower risk of arterial puncture and time to cannulation.

In recent years ultrasound for arterial cannulation has been the subject of an increasing number of case series and several controlled trials, and has also increasingly become standard practice. Finally, peripheral venous access with ultrasound guidance has been the subject of numerous recent reports and clearly offers advantages over landmark or blind techniques when venous access is difficult, including lower number of punctures and time to cannulation [69,70] (Fig. 19.6).

A 9.2 MHz pencil-thin audio Doppler probe can be gas sterilized and reused. The probe is applied to the site, and the course of the artery and vein are ascertained by their characteristic audio profiles: high-pitched, intermittent, systolic flow for the artery, and low-pitched, continuous venous hum for the vein. The probe is centered over the loudest signal, perpendicular to the skin surface, and the vessel is punctured

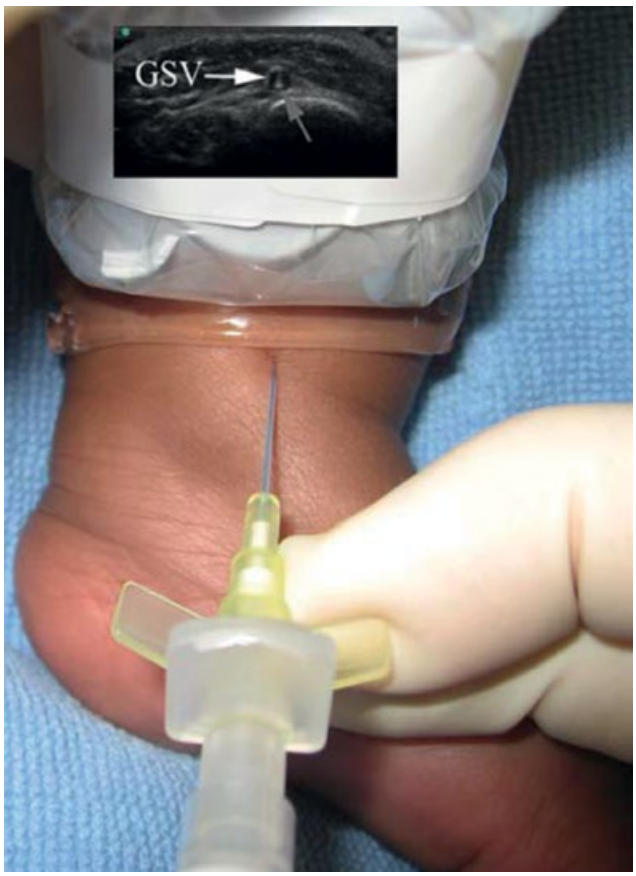


Figure 19.6 Greater saphenous vein (GSV) peripheral access using ultrasound guidance. The ultrasound image is a short-axis view of the tip of the IV catheter inside the vein. *Source:* Reproduced from Triffterer et al [69] with permission of Elsevier.

exactly in the axis of the center of the probe. A "pop" followed by the continuous sound of blood aspiration can often be heard when the vessel is entered. The guidewire, dilator, and catheter are then passed as described previously. A variation of the audio Doppler technique is a device with the Doppler probe within the needle [71]. However, these needles are expensive, direct comparison has not shown them to be superior to visual ultrasound for cannulation, and because the lumen of the needle is partially occluded by the Doppler probe, flashback of blood is slow and unreliable.

Two-dimensional ultrasound, either in the form of commercially available devices for CVC cannulation only (Sonosite®), or surface probes on standard echocardiography machines, can be used to image large vessels (Fig. 19.7A). The color Doppler feature on the latter may be particularly useful to identify desired vessels during difficult vascular access. The internal jugular vein is the most frequently accessed vessel with ultrasound, and it is visualized superficial to and lateral to the carotid artery. The internal jugular vein is also easily compressible with the probe and is gently pulsatile, while the carotid artery is round, difficult to compress with probe pressure, and very pulsatile (Fig. 19.7B). The probe is held directly over the desired vessel, with the goal of puncturing it exactly in the midline. The needle can be seen indenting and then puncturing the vessel during correct placement (Fig. 19.7C).

Two-dimensional ultrasound is particularly useful to clarify the anatomy after several previous attempts have been made. One can identify the vessel in the midst of a hematoma that has formed, or recognize overlap of the artery and vein. Once the vessel has been punctured and the guidewire passed, ultrasound can be used to visualize the guidewire in the lumen of the vessel by scanning closer to the heart. Ultrasound methods are described most often for the internal jugular vein, but are also useful for the femoral and subclavian veins. It should also be noted that real-time ultrasonographic visualization of needle insertion, vessel puncture, and guidewire passage of the internal jugular vein in infants results in fewer attempts and faster cannulation than merely marking the skin after ultrasound visualization followed by blind puncture of the vessel [72]. Several case series of central venous cannulation in very small infants have been published in which two-dimensional ultrasound safely guided catheter placement even in premature neonates down to weights of 1.0 kg or lower [73].

Audio Doppler can be used to assist in the cannulation of any artery, and is particularly useful when pulses are diminished from previous attempts, hypotension, or vasospasm. Two-dimensional ultrasound can also be used to cannulate radial arteries: Schwemmer et al found that this technique resulted in a 100% success rate, versus 80% for the traditional palpation method, and also resulted in a higher success rate on the first attempt and lower number of attempts [74]. Two-dimensional ultrasound was also demonstrated to be superior to audio Doppler for radial artery cannulation in patients <12 kg when used by anesthesia residents or fellows with no or little experience with ultrasound-guided cannulation [75]. The overall success rate in this randomized study was 65% in the ultrasound group and 46% in the audio Doppler group ($p = 0.048$).

The technique for arterial cannulation with ultrasound involves visualizing the artery in short-axis cross-sectional area, and inserting the needle tip until it can be seen puncturing the arterial wall and resting within the lumen. The artery can be seen as pulsatile, and color-flow Doppler can also aid in its identification. A newer approach involves the longitudinal view of the artery, which allows a longer length of the needle to be visualized to ensure that is within the artery lumen and not puncturing the back wall of the artery [53] (Fig. 19.8). A controlled study of short- versus long-axis imaging for radial artery cannulation in 97 infants and children revealed no difference in success rate (94% short axis versus 98% long axis), time to successful cannulation, or complications [76]. The posterior artery wall puncture rate was much higher in the short-axis group (96% versus 18%, $p < 0.001$); the clinical significance of this is unclear.

KEY POINTS: ULTRASOUND GUIDANCE FOR VASCULAR ACCESS

- Accumulating data suggest that two-dimensional ultrasound for central venous access increases success rate, decreases number of attempts, and may decrease arterial puncture rate and time to cannulation
- Arterial access, particularly in infants and small children, can be facilitated with ultrasound, and both short- and long-axis views may be helpful
- Peripheral venous access, especially where no vein is visible, can be significantly facilitated by two-dimensional ultrasound

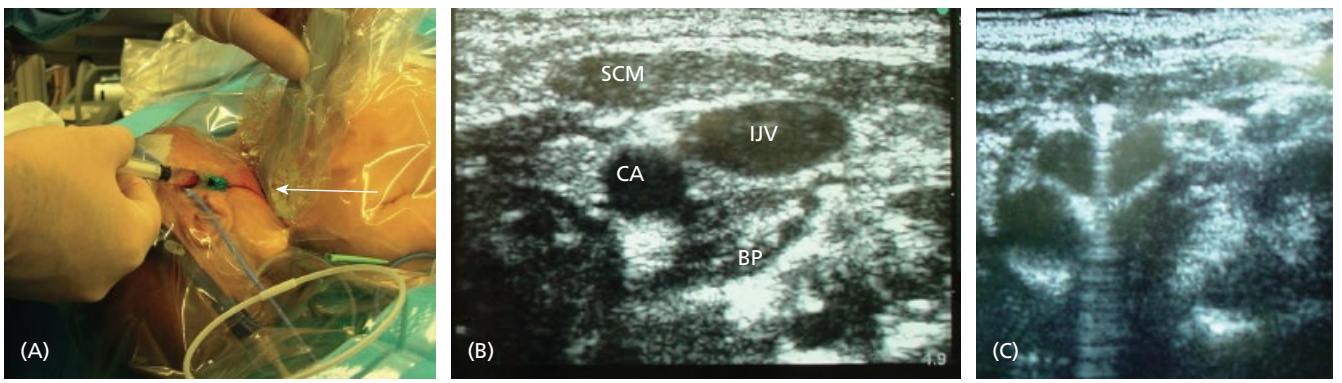
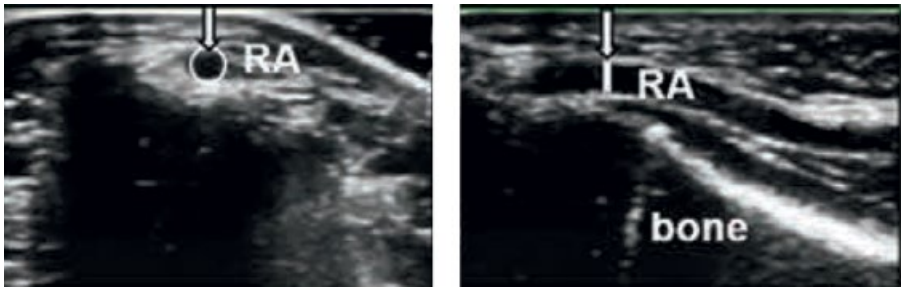


Figure 19.7 (A) Ultrasound-guided puncture of the internal jugular vein in an infant. The arrow denotes a 13 MHz pediatric probe. (B) Two-dimensional ultrasound view of the right internal jugular vein and carotid artery in an infant. CA, carotid artery; IJV, internal jugular vein; SCM, sternocleidomastoid muscle; BP, brachial plexus. (C) Needle just prior to puncture of the right internal jugular vein.



(A) (B)

Figure 19.8 (A) Radial artery in short-axis view. (B) Radial artery in long-axis view. *Source:* Reproduced from Kim et al [53] with permission of Wolters Kluwer.

Interpretation of intravascular pressure waveforms

Arterial waveforms

The normal systemic arterial pressure waveform changes with progression distally from the central arterial circulation, e.g. ascending aorta, distally to abdominal aorta and femoral arteries, and then to the peripheral arteries such as the radial and dorsalis pedis/posterior tibial arteries [59] (Fig. 19.9). In general, the more central sites will produce less peaked systolic pressure waves with slightly lower systolic pressure readings. The dicrotic notch is pronounced in the central arteries. With distal progression, pulse wave amplification will produce a higher peaked systolic pressure wave with a slightly higher systolic pressure. This is most pronounced in the arteries of the foot, where the systolic pressure may be 5–15 mmHg higher than in the ascending aorta. The mean and diastolic pressures change very little with progression. This concept is very important in interpreting arterial pressure tracings. The postbypass arterial tracing is frequently dampened with catheters in small distal arteries, e.g. radial or foot arteries [77]. This usually resolves within a few minutes after bypass. For particularly long and difficult operations with long bypass and cross-clamp times, or in major non-cardiac cases with substantial blood loss and hemodynamic instability, it may be useful to place catheters in larger arteries, e.g. femoral or umbilical, or to measure the pressure directly in the aortic root immediately after bypass to ascertain an accurate arterial pressure.

The arterial pressure tracing can yield more information than simply the systolic and diastolic blood pressures [78,79]. The slope of the upstroke of the pressure wave may be an indicator of systemic ventricular contractility, i.e. the steeper the upslope, the better the contractility. Significant reductions in contractility flatten the upslope. The position of the dicrotic notch may give an indication of peripheral vascular resistance. In infants, the normal dicrotic notch is in the upper half of the pressure wave. With low peripheral resistance, as in arterial runoff through a patent ductus arteriosus, the dicrotic notch is lower on the descending limb of the waveform, due to diastolic runoff into the pulmonary artery, resulting in a relatively longer period of ventricular systole. The area under the curve of the systolic portion of the arterial tracing increases with increased stroke volume. Finally, a hypovolemic patient will often exhibit more pronounced respiratory variation during positive pressure ventilation, as the stroke volume decreases when positive pressure impedes an already limited venous return (Fig. 19.10). Computerized pulse-contour

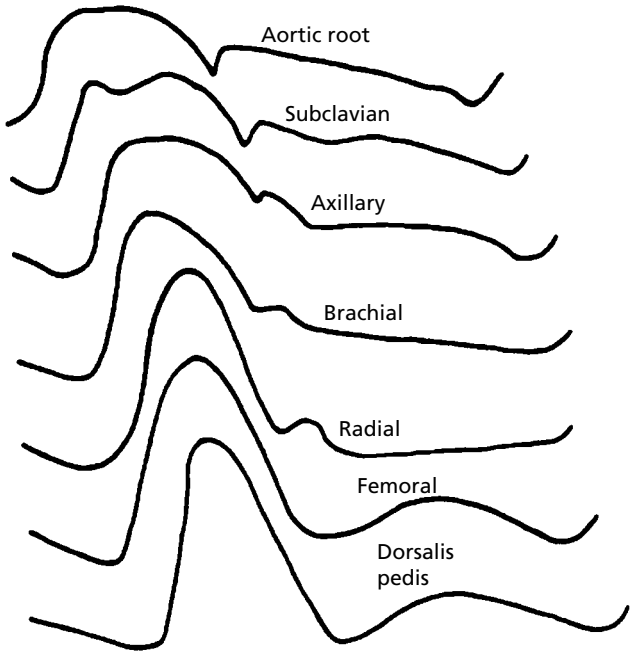


Figure 19.9 Progression of the arterial pressure tracing from the root of the aorta to more peripheral arteries. Pulse wave amplification produces a higher systolic peak and slightly lower diastolic pressure in the smaller distal arteries, especially the dorsalis pedis. *Source:* Reproduced with permission from Reich et al [59] with permission of Elsevier.

analysis of the arterial pressure waveform has been used to measure stroke volume (see section "New techniques in pediatric intravascular monitoring").

Mechanical and electronic components of the intravascular pressure measurement system are important considerations when interpreting waveforms [59]. The shortest possible large-bore, stiff plastic tubing should be used. Minimizing the number of stopcocks and connections will also improve the fidelity of the transmitted pressure wave. Thorough flushing before use to produce a bubble- and clot-free fluid path is critical. Periodic recalibration at the right atrial level is important to account for "drift" in the transducer setting. When ringing or overdamping is recognized, some monitor models offer adjustment of electronic filter frequency. The routine setting should be 12 Hz. If the arterial tracing is underdamped, e.g. overshoot producing an artificially high spike as the systolic pressure, filter frequency may be decreased as low as 3 Hz to compensate. Conversely, if overdamped, the filter frequency may be increased to as high as 40 Hz. Mechanical devices (ROSE®, accudynamic®) may also be inserted to

change the resonance frequency and/or damping factor of the system. Under no circumstances should a bubble be intentionally introduced into the system to produce increased damping effect. Appropriateness of resonance frequency may be tested by flushing the system from a pressurized bag of heparinized saline, stopping suddenly, and observing the number and amplitude of oscillations required to return to baseline waveform. Proper damping is signified by one oscillation below, and one above the mean before return to normal waveform [80,81].

Failure of arterial pressure monitoring systems is always possible during surgery, due to mechanical problems such as kinking or clotting of the catheter. Spasm of the artery is more common than in adults, and the artery may be compressed, such as aberrant right subclavian compression from a TEE probe, or compression of an axillary artery from a sternal retractor. A back-up oscillometric blood pressure cuff should always be present, preferably placed on a different extremity than the arterial catheter.

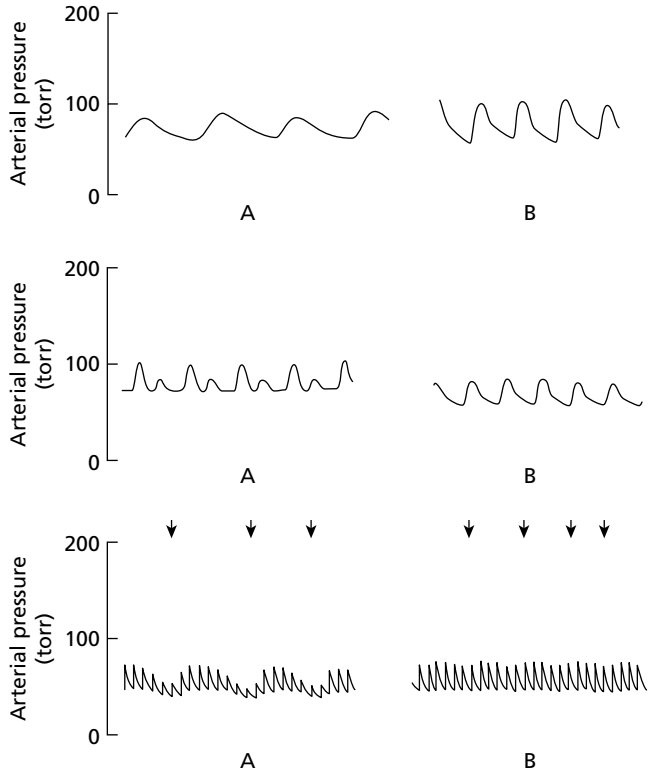


Figure 19.10 (*Top panel*) The arterial pressure tracing with depressed (A) and normal (B) myocardial contractility. (*Middle panel*) Low (A) and normal (B) systemic vascular resistance. (*Lower panel*) Hypovolemia (A) and normovolemia (B) – arrows represent positive pressure ventilations. *Source:* Reproduced with permission from Gregory [78] with permission of Elsevier.

Central venous, right and left atrial waveforms

Normal atrial (i.e. central venous) pressure waveforms consist of the A, C, and V waves corresponding to atrial contraction, closure of the tricuspid or mitral valves, and ventricular contraction. Normal right atrial A wave pressure is lower than V wave pressure, which is usually less than 10 mmHg. Changes from the normal tracing can give important information about the hemodynamic status and cardiac rhythm of the patient. For example, when atrioventricular synchrony is lost, as in junctional ectopic tachycardia or supraventricular tachycardia, the A wave disappears and the V wave enlarges considerably, reflecting backwards transmission of ventricular pressure through an ineffectively emptied atrium (Fig. 19.11). Determining the cardiac rhythm from the ECG is often difficult at rapid heart rates because the P wave of the ECG is indiscernible. The left or right atrial waveform can give crucial added information in this situation, clearly retaining the A wave in cases of sinus tachycardia. Competency of the AV valves can also be assessed from the atrial tracing. Mitral or tricuspid regurgitation will produce a large V wave on the left atrial tracing. It is often very useful to record the vascular pressure tracings in sinus rhythm at baseline for later comparison.

New techniques in pediatric intravascular monitoring

Cardiac output monitoring

Because traditional percutaneous, balloon-tipped pulmonary artery catheterization is limited in small children and those with intracardiac shunting, several other recent methods to measure cardiac output and oxygen delivery in patients with congenital heart disease have been applied. Lithium dilution cardiac output (LiDCO) uses a standard central line in the SVC or even a peripheral intravenous catheter, and a special

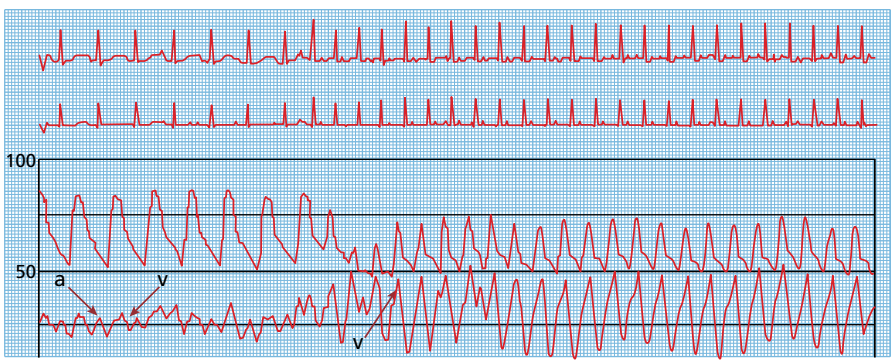


Figure 19.11 ECG demonstrating normal sinus rhythm in the first third of the panel, with onset of supraventricular tachycardia. Note the arterial pressure tracing with a 12–15 torr decrease in systolic pressure, and the loss of the A wave on the central venous pressure tracing, with the appearance of large V waves with a systolic pressure increase from 10 to 16 mmHg.

femoral artery catheter equipped with a lithium-detecting electrode. A dilute solution of lithium chloride is injected into the vein, and arterial blood is withdrawn into the lithium electrode. The cardiac index is related to the area under the curve of the change of lithium concentration. This method has been demonstrated to have reasonable correlation with thermodilution cardiac output in children after congenital heart surgery. In a study of 48 measurements in 17 patients 2.6–34 kg, correlation between LiDCO and thermodilution cardiac output was good ($r^2 = 0.96$, mean bias -0.1 ± 0.31 L/min [82].

Transpulmonary thermodilution cardiac output uses a similar principle as LiDCO, with temperature as the indicator instead of lithium concentration. Cold saline is injected into a CVC, and via a thermistor placed in a femoral artery, a time temperature curve is derived that correlates reasonably well with standard thermodilution cardiac output as measured by a standard pulmonary artery catheter [83]. Lithium and thermodilution methods are limited to patients without any intracardiac shunting, significantly restricting their use in congenital heart disease. A recent systematic review of 14 adult studies and two pediatric studies assessing the reproducibility of transpulmonary thermodilution with three injections determined that the reproducibility was within 6.1 ± 2.0% in adults and 3.9 ± 2.9% in children [84]. This method would appear to be suitable to follow trends in cardiac output in critically ill children.

Yet another newer method is pulse-contour analysis of the arterial waveform (PiCCO), which relates the contour and area under the curve to the stroke volume, and thus the cardiac output. This continuous method is periodically calibrated using the transpulmonary thermodilution cardiac output as described previously (again making the method invalid with intracardiac shunting), and demonstrated a good correlation with transpulmonary thermodilution in a study of 24 pediatric patients after cardiac surgery ($r^2 = 0.86$, mean bias 0.05 ± 0.4 L/min/m^2) [85].

A related measure is pulse pressure variation, noted previously under interpretation of arterial pressure waveforms. During positive pressure ventilation, variation in pulse pressure derived from the arterial line has been reported to be proportional to the degree of hypovolemia and fluid responsiveness in adults [86]. Commercial systems are available to quantify this variation, and in one study of acute normovolemic hemodilution in children undergoing cranial vault surgery the increase in pulse pressure variation correlated well with the estimated blood volume during the blood removal phase [87].

Attempts have been made to relate pulse pressure variation to pulse oximeter plethysmographic variation, which depends on variability to light absorption over the cardiac cycle in response to positive pressure ventilation and is a feature built into new pulse oximeters [88] (Fig. 19.12). One study in 45 ventilated critically ill children demonstrated strong correlation ($r = 0.84$, $p < 0.0001$) and close agreement (bias +1.44 ± 6.4) in variation of the two indices [88]. However, another study in adolescent scoliosis surgery patients found a small bias of −0.56% in measurements, but a very wide range of limits of agreement of >20%. Neither study assessed fluid responsiveness to this measure. More data are required before recommending this parameter for pediatric patients.

Central venous oxygen saturation monitoring

Monitoring of intravascular oxyhemoglobin saturation using reflectance catheters has been used in the umbilical artery, pulmonary artery, and adult-sized central venous catheters for a number of years, but only recently have standard pediatric sized 4 and 5 Fr, double- and triple-lumen central venous catheters become available for routine use to measure central venous oxygen saturation ($ScvO_2$) in pediatric patients. In 16 pediatric patients undergoing cardiac surgery, Liakopoulos

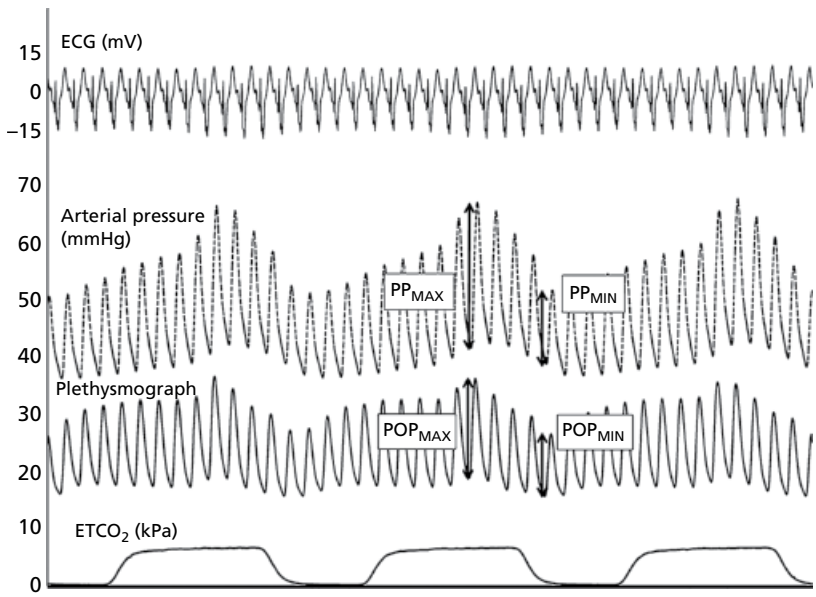


Figure 19.12 Plethysmographic signal variation versus pulse pressure variation to assess volume status. Simultaneous display of waveforms; plethysmograph is from pulse oximeter signal. ECG, electrocardiogram; $ETCO_2$, end-tidal carbon dioxide; POP, plethysmographic variation; PP, pulse pressure. *Source:* Reproduced from Chandler et al [88] with permission of Springer Nature.

et al demonstrated good correlation between $ScvO_2$ as measured with the catheter, versus blood co-oximetry (r^2 = 0.88, bias −0.03 ± 4.72%) [89] (Fig. 19.13). The advantage of this method is that it is an accurate measure of oxygen delivery that is independent of intracardiac shunting and thus may have better utility in the congenital heart disease patient. Two subsequent studies in a total of 28 pediatric cardiac surgery patients yielded mixed results: one showed minimal bias and narrow variability, and the other demonstrated a small bias but a wide 95% limit of variability of over 15% [90,91]. More outcome data are needed for this technique, but it may be useful as an adjunct for continuous monitoring of oxygen delivery in major cases.

Emergency vascular access

Intraosseous access to the venous circulation has been described for use during a crisis when no other venous access is available, e.g. during cardiopulmonary resuscitation or shock [92]. Rarely, it may be required for emergency resuscitation in the operating room or intensive care unit, and it is therefore necessary for the pediatric anesthesiologist to be familiar with the technique. Normally this procedure is used only in small children, and the flat surface of the proximal tibia is used. Commercially available 14 or 16 ga intraosseous needles, or 16 ga bone marrow aspiration needles may be used. The site is aseptically prepared, the skin is punctured, and the outer bony cortex is contacted. With a boring motion, the needle is advanced through the outer cortex into the marrow space, heralded by a sudden loss of resistance. Infants have active marrow production in long bones, and when the stylet is removed and the needle aspirated, bone marrow should appear in the hub. Rapid infusion of 10 mL normal saline without extravasation confirms proper placement, and emergency drugs and fluids may be administered. They reach the central circulation via the bone marrow sinusoids, which connect to the emissary veins from the bony cortex, and then to the larger veins draining into the central circulation. Drugs injected intraosseously, e.g. epinephrine, reach the heart slightly more slowly than when injected into a central vein, but the peak drug levels are not different [92]. Intraosseous needles should be available for the rare crisis in the operating room or intensive care unit. Intraosseous needles should be replaced as soon as possible with conventional peripheral or central venous access.

Newer intraosseous access systems are now available with a drill-like driver that inserts a premeasured length needle into the intraosseous space and has a custom connector and fixation dressing (Fig. 19.14) [93]. Complications of intraosseous access can be severe and mostly involve extravasation of caustic substances like calcium chloride when the needle is malpositioned or dislodged. These include compartment syndrome with need for fasciotomies, and amputation [94,95]. Intraosseous access should be used for life-threatening emergencies only, requires constant checking for proper needle position, and should be removed as soon as possible after standard vascular access is obtained.

KEY POINTS: NEW TECHNIQUES IN PEDIATRIC INTRAVASCULAR MONITORING

- Lithium dilution, transpulmonary thermodilution, pulse contour analysis, and pulse pressure variation can be used to monitor cardiac output but have limited and mixed data in pediatrics
- Continuous central venous oxygen saturation monitoring correlates moderately well with co-oximetry and can be used as a trend monitor of oxygen delivery and consumption
- Intraosseous access in the flat surface of the tibia of infants and small children can be used in life-threatening emergencies to infuse emergency drugs and fluids

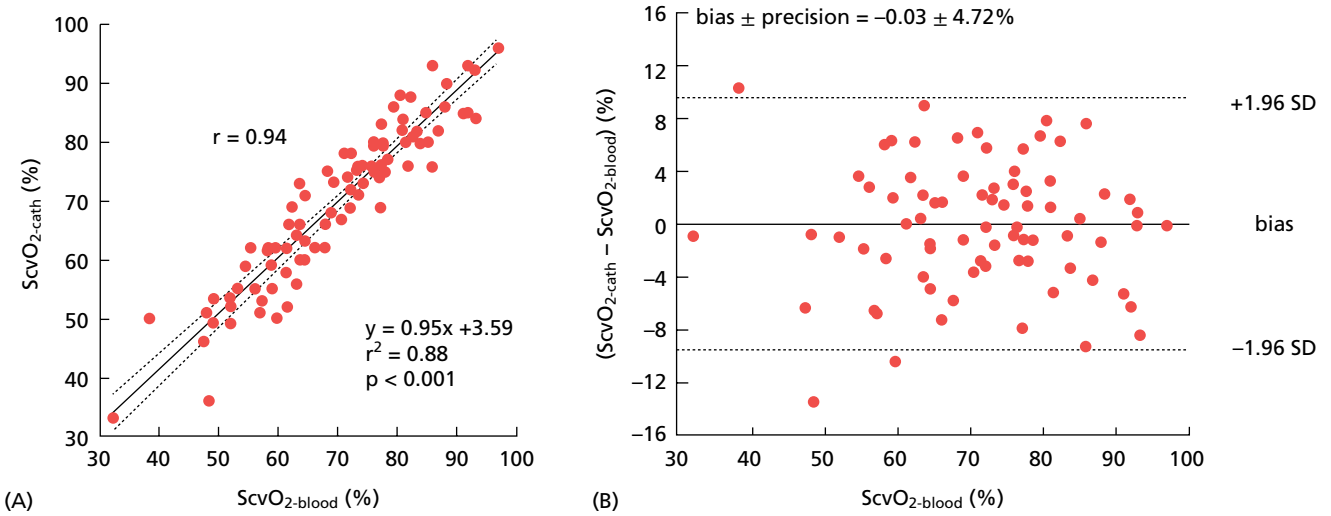


Figure 19.13 Central venous oxyhemoglobin saturation ($ScvO_2$) in the superior vena cava, comparing blood co-oximetry to fiberoptic reflectance spectroscopy. (A) Correlation between catheter ($ScvO_2$-cath %) and blood co-oximetry ($ScvO_2$-blood %). (B) Bland–Altman plot of bias and precision between the two methods. *Source:* Reproduced with permission from Liakopoulos et al [89] with permission with permission of Springer Nature.

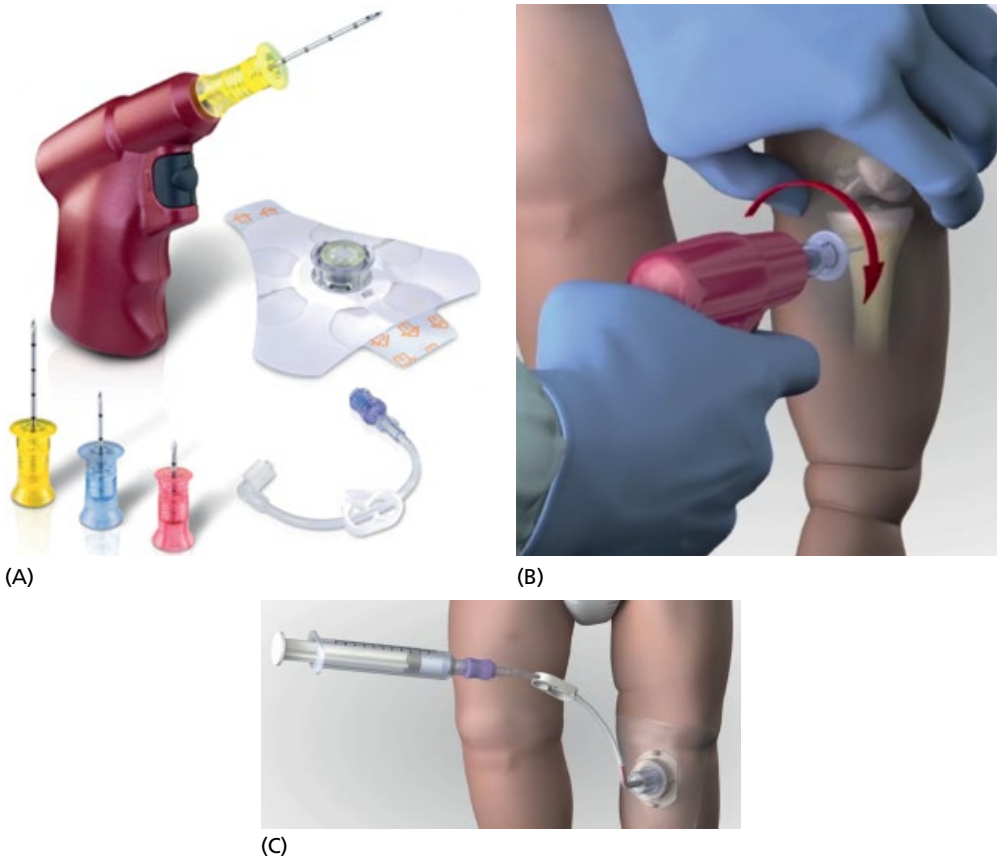


Figure 19.14 EZ IO® intraosseous infusion system. (A) Driver, needle selection, tubing, and fixation device. (B) Insertion into the flat surface of the proximal tibia in an infant. (C) Fixation device and connection tubing; aspiration of blood/bone marrow is seen in distal tubing. *Source*: Courtesy of Teleflex Corp., Morrisville, NC, USA.

Complications of vascular access

Thrombosis

Thrombosis is the single most frequent complication, especially among infants. Central venous thrombosis secondary to vascular access develops in 5.8% of neonatal patients, which is ten times that of older patients, and accounts for 40–50% of central venous thromboses after congenital heart surgery [96]. The frequency significantly decreases in patients over 6 months of age. Factors that contribute to the risk of thrombosis include: (1) large-bore catheters in small vessels, i.e. larger than 4 Fr in small infants; (2) duration of cannulation exceeding 7 days; (3) venous stasis due to extreme fluid restriction or low cardiac output; (4) infusion of high-osmolarity fluids, i.e. concentrated dextrose in parenteral nutrition fluids; and (5) hypercoagulable states [97]. Other risk factors for thrombosis include protein C resistance due to factor V Leiden mutation, prothrombin mutations, methylenetetrahydrofolate reductase mutations [98], elevated preoperative C-reactive protein [99], and arterial catheterization with the use of vasoconstrictors such as norepinephrine, vasopressin, or terlipressin [100]. Immediate consequences of SVC thrombosis include SVC syndrome [101] with increased intracranial pressure and chylothorax from ineffective drainage of the thoracic duct into the SVC. IVC thrombus leads to ascites, renal, and intestinal dysfunction, and edema of the lower abdomen and extremities. The patient must be assessed carefully for signs of thrombosis, and suspicion of thrombosis should be evaluated by ultrasound examination. Treatment modalities include removing the catheter, heparinization, thrombolytic agents such as tissue plasminogen activator and urokinase [102–104], antithrombin III replacement [105], and surgical thrombectomy. Mortality from SVC thrombosis is reported to be as high as 33% and it is therefore critical to try to prevent this complication, preferably by avoiding SVC catheters in patients under 4 kg. Thrombosis also leads to a higher rate of infection [106,107]. Heparin-bonded catheters may decrease the rate of thrombosis and do not increase risk of bleeding [106,108]. They may also lead to a lower rate of catheter colonization and infection [109]. However, it is currently not possible to bond both heparin and antibiotics to the same catheter. In patients with occlusion of central veins from previous catheters, magnetic resonance venography may be useful in identifying patent veins for future interventions [110].

Thrombosis or dissection of an artery is a serious complication that must be treated immediately. Immediately after arterial catheter placement it is important to inspect the extremity distal to the catheter, comparing it to the other extremity, and palpate distal pulses. Absence of a pulse, pallor, slow capillary refill, cool temperature, and no flow by color Doppler examination are all signs of arterial compromise. Placement of a pulse oximeter probe distal to the catheter serves as a continuous monitor and provides early warning of vascular insufficiency. Transient compromise to perfusion immediately after catheter placement due to arterial spasm or during low-output states may be observed. However, when extremity

perfusion is significantly compromised, treatment by removal of the catheter, use of vasodilators, warming the extremity, heparin, thrombolytics, surgical consultation for thrombectomy, fasciotomies, or surgical reconstruction is indicated. Modern high-resolution Duplex ultrasound scanning can quickly and accurately diagnose the location, size, and consequences to blood flow of an arterial thrombus and should be obtained if this is suspected [111].

Malposition/perforation

Central venous catheter tips should not lie in the right atrium. Adult and pediatric studies have consistently demonstrated a higher rate of heart and great vessel perforation with associated cardiac tamponade when catheter tips are in the atrium [27,112–116]. Perforation is also less common with right-sided lines, e.g. right internal jugular or subclavian, because the catheter tip is parallel to the vein wall. The catheter tips of left-sided lines are frequently at a 45–90° angle of incidence to the SVC or atrium, and mechanical models demonstrate that this position is more likely to lead to great vessel perforation [117]. Finally, 5–10% of patients with congenital heart disease have a left SVC [116], which most often drains into the coronary sinus or left atrium, and both of these sites are undesirable locations for a catheter tip [118]. Thus the ideal position of a CVC is in the mid SVC with the tip parallel to the vein wall (see Fig. 19.3). Soft polyurethane or silicone catheters are also much less likely to perforate than stiffer polyethylene catheters [117]. Perforation is recognized by inability to consistently aspirate blood, an abnormal waveform, and signs and symptoms of pericardial tamponade or hemothorax. Treatment involves aspiration of all the blood possible through the catheter and establishing alternative access, intravascular volume replacement, and drainage of the pericardial or pleural blood, by needle, tube, or surgical exploration.

Many authorities recommend positioning the tip of the catheter in the superior half of the SVC, above the pericardial reflection. This recommendation is based on the theoretical concept that if there is a perforation, cardiac tamponade will not be produced, and also the catheter tip will be above the SVC bypass cannula and thus yield accurate CVP measurements on cardiopulmonary bypass [119]. There are several problems with this approach in pediatric anesthesia and surgery, particularly in small patients. First, the SVC is often only 4–5 cm long, leaving little room for error in placement. It is preferable to have the catheter slightly too deep in the SVC, because this will lead to accurate pressure measurements and proper infusions of drugs and fluids. When a multilumen catheter is positioned too high, a proximal port may not be intravascular, leading to extravasation of important or caustic drugs and fluids [120]. In addition, the pericardium is usually opened in congenital heart surgery, and drained postoperatively, rendering placement above the pericardial reflection unnecessary. Many series of catheter placements in children document that the internal jugular route results in tip placement in the SVC or RA 98–100% of the time, whereas the subclavian route has a 5–15% incidence of catheter malposition, i.e. across the midline in the contralateral brachiocephalic vein or up the ipsilateral internal jugular vein. A recently published randomized trial of internal jugular versus subclavian catheters in pediatric cardiac surgery confirmed this, with 17 of 128 (13.2%) subclavian catheters malpositioned versus 2 of 139 IJV catheters (1.4%), $p < 0.001$ [121].

Despite numerous previous reports of cardiac perforation by central venous catheters, and the publication of studies documenting height- and weight-based formulae for depth of insertion of SVC catheters in infants [31], reports of cardiac perforation resulting in death or necessitating surgical exploration by sternotomy continue to occur [122].

When IVC catheters are used, accurate CVP measurements are usually obtained whether the tip of the catheter is above or below the diaphragm. Umbilical venous catheters should be above the level of the diaphragm at the IVC–RA junction, but not in the RA [123] to ensure passage through the ductus venosus and parallel position to the IVC wall [124]. In a series of 128 portal vein thromboses in neonates, 73% of them had an umbilical venous catheter and in half of them it was malpositioned; this constituted a major risk factor for poor outcome [125].

A recently described complication of femoral venous catheters is inadvertent placement in the lumbar venous plexus, which may result in paraplegia from epidural hematoma or infusion of vasoconstrictive substances [126,127]. Catheterization of the lumbar venous plexus usually occurs when there is partial or total occlusion of the IVC from previous interventions, and the guidewire passes posteriorly through collateral circulation into the lumbar plexus. This malposition may be suspected during insertion when resistance to catheter passage is encountered, or the catheter will not thread its entire length. An anteroposterior radiograph reveals an abnormal catheter course, often appearing to be more lateral than normal. A lateral radiograph will definitely diagnose such malposition where the catheter tip passes posterior to the vertebral bodies. The catheter must be removed immediately and the patient assessed for neurological deficit if this malposition is discovered. Retroperitoneal hematoma from perforation of the femoroiliac vessels by the catheter or guidewire can also occur [128].

Inadvertent arterial puncture can usually be prevented by the use of an ultrasound guidance system for CVC placement as described in the section "Ultrasound guidance for vascular access." However, if this complication occurs, the following general principles are useful. After needle puncture, if there is any question about whether the vessel is an artery, remove the needle immediately, elevate the area, and maintain firm pressure for 5–10 min. A small-bore needle puncture of the carotid or femoral artery, e.g. 20 ga or smaller, is not usually an indication to cancel surgery. If a larger hole is created in the artery, i.e. a dilator and the catheter have been placed, pressure transduction can be used to confirm the location. In this case, a discussion with the surgeon must ensue. Normally, the catheter can be removed, and pressure held without consequences unless a very large catheter was used, e.g. introducer sheath or large-bore CVP catheter, in which case surgical exploration and repair should be undertaken. In most cases of elective cardiac surgery, it is prudent to postpone the case if a large hole has been made in the artery. The case can usually be safely performed 24 h later if no bleeding has occurred. In emergency or urgent cases which must proceed despite a large hole in the artery, the neck or groin should be prepped into the field for exploration if excessive bleeding or hematoma formation occurs.

Pneumothorax

This complication is most frequent with the subclavian approach, but also may occur with the internal jugular approach, especially with the low puncture sites, e.g. jugular notch approach. To avoid this complication with the subclavian approach it is important to advance the needle only during expiration. A very shallow approach, with the needle directed just posterior to the clavicle and at the sternal notch, is also important. For the internal jugular vein a higher puncture site, and limiting the caudad advancement of the needle to stop above the clavicle will usually prevent this complication [129].

Continuous aspiration should be performed as the needle is advanced using a saline-filled syringe. If air is aspirated as the needle advances, attempts at venipuncture should stop immediately, and careful monitoring for compromise of ventilation and hemodynamics should ensue. A chest radiograph should be obtained to make the diagnosis if the start of surgery is not imminent, and pleural drainage by needle, catheter, or tube should be undertaken if indicated. The pleura can be opened on that side after sternotomy if pneumothorax is diagnosed or suspected.

Infection

Catheter-related sepsis results in significant morbidity, some mortality, prolongation of ICU stay, and increased expense. The incidence of arterial catheter related infection is low. A study of 340 arterial catheters in children revealed a 2.3% incidence of local site infection, and 0.6% catheter sepsis [130]. However, CVC-associated bloodstream infection is a major problem. There is strong evidence that several strategies may be employed to reduce this complication [131]. The first is the use of full barrier precautions, e.g. sterile gown, mask, gloves, and careful septic technique, during insertion [5]. Second, chlorhexidine has been shown to be superior to other antiseptic solutions. Finally, antibiotic bonding to the resin of the catheter will reduce infection [132]. This can be done in several ways, i.e. antibiotics already embedded in the resin (minocycline/rifampin or chlorhexidine/silver sulfadiazine) or applied at the time of insertion by soaking the outer and inner surfaces of the catheter in a negatively charged antibiotic at 100 mg/mL concentration such as vancomycin, cefazolin, or other cephalosporins. Antibiotic is slowly released from the catheter, delaying and reducing colonization and reducing the incidence of catheter sepsis. The increased cost per catheter is about $20, but one episode of catheter sepsis is estimated to cost $14,000 in 1995 dollars [132]. In a study of antibiotic-impregnated catheters in 225 critically ill children, minocycline–rifampin-coated catheters delayed the onset of infection in those patients who were infected to 18 days, from 5 days in non-antibiotic catheters [133]. Central venous catheters indwelling for more than 5–7 days have an increased incidence of colonization and sepsis [134] as well as vessel thrombosis. Suspicion of catheter sepsis should be followed by peripheral blood culture, and blood culture from the central line. The catheter should be removed when possible and the tip cultured. Institute antibiotic therapy empirically tailored to the most common institution-specific pathogens, and provide coverage for *Staphylococcus epidermidis*, which continues to be a common pathogen in catheter-related sepsis. A comprehensive, systematic intervention program to prevent central line-associated bloodstream infections in a very busy cardiac ICU, including insertion, access, and maintenance protocols, and a protocol for timely removal of central lines, reduced the infection rate from 7.8 infections per 1000 catheter days to 2.3 infections per 1000 catheter days [135]. A recommended central line insertion bundle is displayed in Box 19.1.

Arrhythmias

Other complications associated with vascular access procedures include arrhythmias. Ectopic atrial tachycardia, in particular, has been associated with a catheter tip in the right atrium [136,137]. Atrial fibrillation has also been associated with CVC placement [138]. More commonly, arrhythmias occur with the passage of the guidewire [139] and include isolated PAC, supraventricular tachycardia, and, if the guidewire is advanced into the right ventricle, premature ventricular contractions and even ventricular tachycardia or fibrillation. Complete heart block has also been described during guidewire passage in small infants [140]. Great care must be taken when passing the guidewire to stop advancing it when significant arrhythmias are encountered, and when advancing the catheter over the wire to retract the wire as the catheter is advanced. Patients particularly at risk for significant arrhythmia are those with a known history of arrhythmia and also those with significant right ventricular hypertrophy.

Systemic air embolus

Systemic air embolus is a constant threat for patients with central or peripheral venous catheters and intracardiac shunting [141], particularly two-ventricle patients with right-to-left shunting, and single-ventricle patients in infancy who have obligate mixing of systemic and pulmonary venous return in the systemic ventricle. Air may lodge in the coronary arteries (especially the right), pulmonary artery, or cerebral vessels, leading to potentially serious complications. Observation of the TEE, or transcranial Doppler ultrasound as used for neurological monitoring, reveals rapid passage of any introduced systemic venous air into the aorta and cerebral circulation. For this reason, meticulous attention must be paid to prevent introduction of air into the systemic venous circulation as much as possible. Precautions include thorough de-airing of all intravenous infusions before connection to the patient, de-airing of continuous flush central venous lines, air filters on continuous infusions, and careful technique when injecting drugs and fluids. The latter involves holding any syringe upright, flushing fluid from the proximal intravenous tubing into it, and aspirating and tapping the syringe first before injecting so that any air is trapped at the superior aspect of the syringe. Constant vigilance of all infusions, and use of TEE as a monitor for intracardiac air and the transcranial Doppler for systemic arterial air, may reduce the risk of significant air embolus.

Other complications

Thoracic duct injury, chylothorax [142], brachial plexus injury, cervical dural puncture [143], phrenic nerve injury [144], vertebral arteriovenous fistula [145], Horner syndrome [146], and tracheal puncture have also been described. These

complications can essentially be eliminated with skilled personnel using ultrasound-guided techniques to accurately identify the location of the vessel.

Finally, embolization of catheter or guidewire fragments sheared off during difficult insertion procedures occurs occasionally [17]. Never withdraw a guidewire or catheter through a needle if any resistance is encountered. If resistance is encountered, the guidewire and needle, or catheter and needle, must be withdrawn completely from the vessel together as a unit.

KEY POINTS: COMPLICATIONS OF VASCULAR ACCESS

- Thrombosis is the most common complication of venous and arterial access; arterial thrombosis must be promptly diagnosed and treated
- Malposition and perforation are more common in small infants, and with left-sided intrathoracic central venous catheters
- Infection of central catheters can be reduced using an insertion and maintenance bundle of care

Respiratory monitoring

The continuous monitoring of ventilation in the anesthetized patient is the standard of care for pediatric anesthesia [147]. Inadequate ventilation is one of the most frequent causes of patient injury in the American Society of Anesthesiologists' Closed Claims database [148], including in pediatric patients. This section will review methods of respiratory monitoring, including inspection and auscultation, pulse oximetry, capnography and anesthetic gas monitoring, and the monitoring of ventilation volumes and pressures.

Inspection and auscultation

Although not often emphasized due to the proliferation of technology to monitor ventilation, inspection of the patient for adequate and symmetrical chest rise, lack of signs of inspiratory or expiratory obstruction, and lack of cyanosis or pallor representing inadequate oxygenation is an important monitoring technique for every anesthetized patient. The precordial or esophageal stethoscope, although used less frequently in recent years [149], is still very useful for continuous auscultatory monitoring of respiration and heart tones, and serves as an adjunct to the electronic devices used for every case. A standard stethoscope is essential equipment to have available at all times to assess ventilation, as equipment failures occur.

Pulse oximetry

Pulse oximetry uses the unique light absorption characteristics of oxy- and deoxyhemoglobin to estimate the arterial oxygen saturation (SpO_2). In standard pulse oximetry, two wavelengths, 660 and 930 nm are used, transmitted through tissue to a detector that uses an algorithm to measure only the pulsating, arterial portion of oxyhemoglobin and filters out absorption due to non-pulsating capillaries, veins, and bone and soft tissue [150]. The widespread clinical availability of pulse oximetry since the mid 1980s has done more to change anesthetic and critical care practice in the past three decades than any other single monitor. Despite the obvious intuitive value of measuring SpO_2 to prevent arterial desaturation episodes, to date there are only four published large controlled trials of pulse oximetry and outcome, all in adults, and although these trials demonstrated reduced incidence of perioperative hypoxemia, they did not demonstrate a difference in outcomes [151].

The utility of pulse oximetry in pediatric anesthesia was conclusively shown by Coté et al in two studies [152,153]. The first was a single-blind study of 152 patients where all had pulse oximetry but in half the data were not available to practitioners whereas in the other half the monitor and alarms were available. Major desaturation (<85% for >30 s) occurred more frequently in the blinded group (35 versus 11, $p = 0.021$). The pulse oximeter diagnosed hypoxemia before cyanosis and bradycardia were evident. In a second single-blind study of pulse oximetry and capnography in 402 patients, 260 ventilation problems were detected in 153 patients; blinding the oximeter data increased the number of patients experiencing major desaturation events (31 versus 12, $p = 0.003$), blinding the capnograph data had less effect, with only five of 59 major desaturation events first diagnosed by the capnograph, versus 41 by the oximeter and 13 by the anesthesiologist. These studies firmly established the utility of the pulse oximeter in preventing and diagnosing major desaturation events, and were the cornerstone of the current requirement for pulse oximetry in all pediatric anesthetic and sedation cases.

Pitfalls, problems, and artifacts of pulse oximetry

There are a variety of manufacturers of pulse oximeters, and the instructions for each should be followed carefully, particularly the proper disposable or reusable probe size for each patient. In small infants less than 3 kg it is often desirable to wrap the disposable probe around the hand or foot, as these will allow light transmission but are often more secure than their tiny digits. Bright ambient light should be shielded by covering the probe. Despite the ubiquitous use of pulse oximetry, it should be remembered that there are a myriad of manufacturers and proprietary algorithms for signal acquisition and averaging, and that in the normal arterial oxygen saturation ranges >90%, pulse oximetry is accurate to ± 2%, with potentially less accuracy at SpO_2 <90% [150].

Cyanotic congenital heart disease (CHD) is common in pediatric anesthesia, and several studies have compared SpO_2 to measured blood arterial oxyhemoglobin saturations in cyanotic CHD using co-oximetry. Schmitt et al [154] studied 56 children with cyanotic CHD undergoing cardiac surgery with two simultaneous steady-state measurements comparing SpO_2 to co-oximeter measured arterial blood oxygen saturation (SaO_2) in each patient. The linear regression between SpO_2 and SaO_2 was 0.91; however, using Bland–Altman analysis, the bias and precision between the two methods was very close when SpO_2 was >80%, but much worse when SpO_2 was <80%, with the pulse oximeter overestimating the measured arterial saturation by 5.8%, and two standard deviations of precision being only 10%. In a more recent study using two modern generation pulse oximeters, Torres et al [155] made 122 paired

observations in 46 children with acyanotic and cyanotic CHD after cardiopulmonary bypass, and found that in patients with SpO_2 <90%, the bias was 3–6%, with the oximeter reading higher than the measured blood saturation, with precision 5–6%. Thus, although the pulse oximeter is an excellent trend monitor in cyanotic CHD, it will consistently overestimate the true arterial saturation, especially with SpO_2 <80%.

Poor peripheral perfusion states are common in pediatric anesthesia due to hypothermia, hypovolemia, cardiogenic shock, and many other etiologies. Since pulse oximetry relies on adequate perfusion of the digits so the device can detect oxyhemoglobin saturation in pulsating tissue, vasoconstriction that accompanies these conditions can prevent detection of minimal levels of arterial pulsation and prevent the pulse oximeter from functioning. Villanueva et al [156] studied 19 children 2–60 kg requiring arterial catheters for surgery, and measured the accuracy and functioning of two older generation pulse oximeters in response to low perfusion states induced both by inflation of a blood pressure cuff and by clinical conditions, using seven perfusion variables (age, weight, core and skin temperature, hemoglobin, pulse pressure, and laser Doppler blood flow). They compared bias in 94 paired measurements between SpO_2 and measured arterial hemoglobin saturation. Overall, bias was within ±2%. Factors increasing bias included decreased weight, decreased pulse pressure, decreased core temperature, and decreased laser Doppler flow. The strongest predictor of inaccurate readings was skin temperature <30°C. In the six instances of oximeter failure to function, low skin temperature was present in all. Pulse oximetry can also serve as a perfusion monitor in an extremity or digit distal to an arterial catheter, i.e. radial or femoral; if an adequate pulse oximeter plethysmograph signal is present, it is a sign of adequate perfusion.

Intravascular dyes that absorb light in the same range as hemoglobin predictably will affect SpO_2. Among the commonly used dyes, methylene blue produces a significant, short-lived, artifactual desaturation. Indocyanine green produces a less profound desaturation effect, and indigo carmine's effect is even less profound [157]. Although the light absorption spectrum of bilirubin has some overlap with hemoglobin, hyperbilirubinemia has been shown to have little effect on the accuracy of pulse oximetry [158]. Fetal hemoglobin also has little effect on the accuracy of pulse oximetry [159].

The usual sites on the extremities for pulse oximetry occasionally are unavailable due to burns, trauma, surgery on the extremities, or congenital malformations. In these cases, conventional pulse oximeter probes have been placed on the earlobe, bridge of nose, buccal mucosa, tongue, and penis [160–162]. More central locations (buccal mucosa, tongue, nose) will experience desaturation and resaturation changes significantly earlier than the distal sites on the hand or foot [163]. In cases where major vascular structures may be occluded during surgery or where access to the extremities is limited (cardiac surgery), it is often helpful to place two or more pulse oximeter probes, on both upper and lower extremities, in case of failure of one site to function.

Newer developments in pulse oximetry

Newer generation pulse oximeters developed over the past 10–15 years (Masimo Signal Extraction and Rainbow Technologies, Masimo Corp. Mission Viejo, CA, and Nellcor N-395 and N-595, Nellcor-Puritan Bennett Corp, Pleasanton, CA), have been designed to address some of the limitations of the older technology, and to extend the capabilities of pulse oximetry to measure new parameters, such as total hemoglobin, and perfusion by quantifying the plethysmographic signal. The new technologies incorporate more sensitive electronic filtering designed to detect true arterial pulsation during motion, or poor peripheral perfusion. In a study of 75 children monitored in the postanesthesia care unit where motion artifact is a frequent problem, Malviya et al [164] studied the new versus the old technology and determined that the new technology correctly determined the 27 true desaturation events of SpO_2 <90% 100% of the time, whereas the older technology was successful only 59% of the time. In addition, false alarms were reduced by 50% with the new technology.

The newer technologies use up to eight wavelengths of light, and are capable of determining accurate SpO_{2in} the presence of abnormal hemoglobins, including carboxyhemoglobin and methemoglobin [165]. With increasing concentrations of either of these abnormal hemoglobins, conventional two-wavelength pulse oximetry reads an SpO_2 that converges toward 85%, the isosbestic point for normal hemoglobin. However, because both of these substances have higher affinity for hemoglobin than oxygen, the true oxygen saturation is significantly lower. The additional wavelengths will detect these abnormal hemoglobins and also measure a true SpO_2, and thus are important additions if the patient is at risk for these conditions. Despite this technological advance, unless the patient is at risk for carbon monoxide inhalation such as after a burn injury, or methemoglobinemia such as with high-concentration nitric oxide inhalation, its utility in routine pediatric anesthesia is limited. Another novel use of the new technology is to measure total hemoglobin; this is proportional to the total absorption of light in the light path, but depends on a constant SpO_2 and blood volume, i.e. changes in the amount of hemoglobin in the light path due to changes in intravascular volume can be confused with changes in absolute hemoglobin concentration. With these caveats, this non-invasive estimation of hemoglobin concentration has reasonable accuracy and could find clinical utility as a trend monitor [165]. Finally, despite these advances in technology, Robertson and Hoffman [166] found that two different late generation pulse oximeters performed significantly differently under adverse clinical conditions in terms of rejection of data, and that as SpO_2 decreased, particularly to <70%, there was significant disagreement, with a bias of 3–7% at these low saturations.

Pulse oximetry can serve as a more objective index of peripheral perfusion by converting the pulsatile component of the light absorption signal into an electric signal that represents the plethysmograph at that particular location. Displaying this signal continuously can serve as a useful estimate of tissue perfusion in that location, i.e. a strong beat-to-beat signal variation represents adequate tissue perfusion. In addition, the degree of respiratory variation of arterial pulse pressure with positive pressure variation can be an important measure of fluid status, i.e. the greater the respiratory variation in the pulse pressure, the greater the relative hypovolemia; intravascular fluid administration will often reduce this respiratory variation [167]. Because the plethysmograph

derived from pulse oximetry is derived from arterial pulsations, it is now being used as a non-invasive monitor of volume status. As noted above, the variation in the plethysmographic waveform amplitude of the pulse oximeter has been shown to correlate well with variation in arterial pulse pressure intraoperatively and in the ICU in adult patients; pediatric data are sparse and the correlation with arterial pulse pressure variation not as strong. Future study will be required to determine whether this modality could be used clinically.

All of these cited data suggest that pulse oximeter values, particularly under challenging clinical conditions, should always be interpreted in light of the clinical condition of the patient and other respiratory and circulatory parameters.

Capnography

Monitoring of end-tidal carbon dioxide (CO_2) is a requirement for all general anesthetics, both to confirm the initial correct placement of endotracheal tubes and other airway devices, and also to continuously monitor adequacy of ventilation [147]. Most capnographs utilize infrared light to quantify CO_{2in} the exhaled gas, and there are two major configurations: mainstream and sidestream. Mainstream capnography uses an in-line detector in the breathing circuit near the connector of the endotracheal tube. It requires disposable cuvettes and frequent calibration. Advantages are rapid response time, and no aspiration of gas from the breathing circuit. Disadvantages include a bulky apparatus that may place tension on the endotracheal tube. Sidestream capnographs aspirate gas from the breathing circuit at the elbow distal to the Y-piece. Advantages include lightweight small-bore tubing for aspiration and automatic calibration. Disadvantages include a relatively slower response time and potential for aspiration of large volumes of gas up to 200 mL/min, which may be problematic with small infants and low fresh gas flows. Microstream capnography uses lower gas aspiration volumes of 50 mL/min or less [168].

After direct laryngoscopy to visualize an endotracheal tube through the vocal cords into the trachea, capnography is the gold standard to confirm correct placement of the endotracheal tube. However this method is certainly not foolproof, and false-positive detection of CO_2 with a waveform may be seen with esophageal intubation and detection of CO_2 introduced into the stomach with mask ventilation – this yields low values of end-tidal CO_2 which disappear within 5–6 breaths. A tube seated at or just above the larynx can detect CO_2 but be at risk for dislodgement. Falsely negative CO_2 detection with correct endotracheal tube placement may be seen in cardiac arrest or very low cardiac output states where pulmonary blood flow is insufficient. It may also be seen with severe bronchospasm preventing gas exchange.

A normal end-tidal CO_2 tracing has a rapid upslope, a long flat plateau with minimal upslope, rapid return to baseline of zero without rebreathing, and immediate transition into the next inspiration (Fig. 19.15A). Common findings include separation between end-expiratory and the next inspiration with a large endotracheal tube leak (Fig. 19.15B). If the exhaled CO_2 does not return to baseline of zero, rebreathing may be occurring, often caused by a faulty expiratory valve or by increased deadspace in the breathing system, i.e. by a condenser humidifier too large for the patient's tidal volumes (Fig. 19.15C).

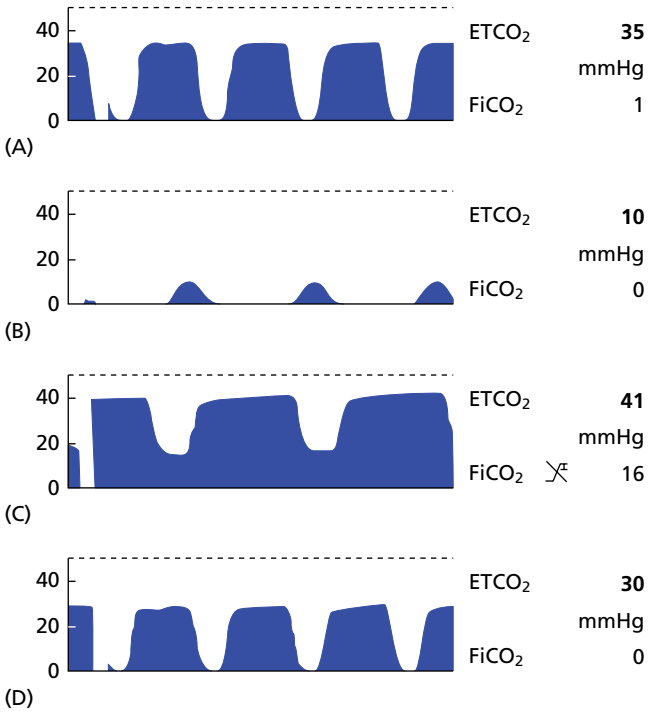
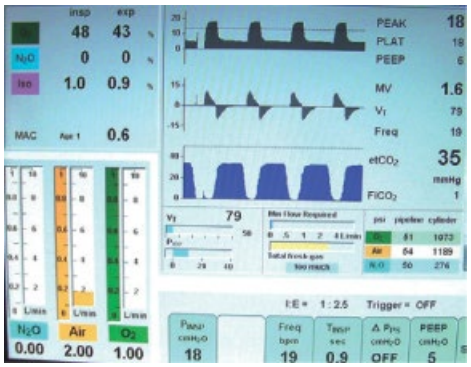


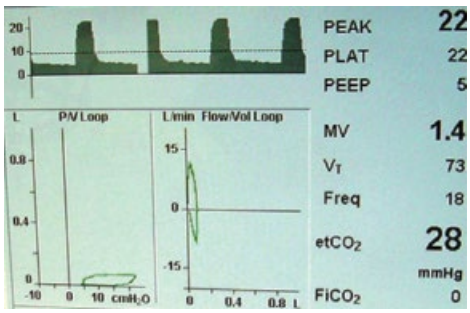
Figure 19.15 Common capnography variants. (A) Normal: note rapid upslope and flat plateau with minimal inspired CO_2. (B) Large leak: causes include large endotracheal tube leak, or partial disconnection of sampling line. (C) Rebreathing CO_2: causes include increased anatomical deadspace in patient or circuit, exhausted CO_2 absorber, addition of inspired CO_2. (D) Large $ETCO_2$–$PaCO_2$ gap: $PaCO_2$ was 40 mmHg in this patient with cyanotic heart disease.

A steep expiratory upslope often signifies expiratory obstruction, most often from bronchospasm. Oscillations of the $ETCO_2$ values during the plateau phase usually signify minimal ventilator volumes caused by displacement of the lungs by the cardiac stroke volume.

Besides monitoring the adequacy of ventilation, the purpose of capnography is to estimate, as accurately as possible, the patient's arterial CO_2 tension to avoid hypercapnea and its undesirable effects on pulmonary artery and intracranial pressure, and hypocapnea and its undesirable effects in decreasing cerebral blood flow. The difference between end-tidal and arterial CO_{2in} patients with normal heart and lungs, and no increase in anatomical or physiological deadspace, is less than 3–5 mmHg. In pediatric anesthesia, the gap is often larger, and there are several causes. Deadspace in the breathing circuit (an extension of the anatomical deadspace where there is flow of gas, but no gas exchange, thereby diluting the exhaled CO_2) is a common cause, especially in small patients. The deadspace volume in endotracheal tubes, endotracheal tube connectors, condenser humidifiers, Y-pieces and elbows, and mainstream capnographs will often cause a significant underestimation of the arterial CO_2. Generally, the smaller the patient, the greater the effect. Premature infants less than 1.5 kg in weight are especially affected [169]. Using small-volume endotracheal tube connectors, placing condenser humidifiers proximal to the CO_2 sampling line, or using special endotracheal tubes with a CO_2 sampling lumen that extends to the tip of the endotracheal tube have all been used to increase the accuracy of capnography in small patients [170–172] (Fig. 19.16C). Cyanotic CHD is another common cause in



(A)



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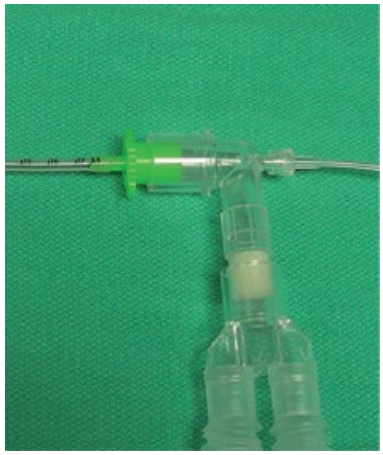

(C)

Figure 19.16 Respiratory monitoring. (A) Standard modern anesthesia machine monitoring screen with compliance-compensated tidal volume, pressures, flows, inspiratory time, anesthetic gas concentration. (B) Respiratory loops: flow–volume and pressure–volume loops. (C) Configuration to minimize deadspace: pediatric circle system; small infant condenser humidifier proximal to sampling line; minimum deadspace (0.5 mL) connector.

pediatrics. Right-to-left intracardiac shunting causes blood to bypass the lungs, reducing pulmonary blood flow and thus the volume of blood relinquishing CO_2 to the exhaled gas. The end-tidal to arterial CO_2 gap may be 15–20 mmHg or greater with significant cyanosis [173] (Fig. 19.15D). The relationship varies with each patient, but in general the more cyanotic the patient (greater reduction in pulmonary blood flow), the greater the CO_2 gap. Improving pulmonary blood flow, such as by the placement of a systemic to pulmonary artery shunt, will decrease the end-tidal to arterial gap. Patients with significant pulmonary hypertension with or without intracardiac shunt will often have a large gap. A decreasing end-tidal to arterial CO_2 gap often signifies increased pulmonary blood flow, accompanied by improvement in pulmonary hypertension or cardiac output. Finally, intrapulmonary shunting, such as that caused by lobar consolidation from pneumonia or atelectasis, causes a variable increase in end-tidal to arterial CO_2 difference, depending on the accompanying degree of hypoxic pulmonary vasoconstriction.

Capnography is useful for monitoring of ventilation in patients without an endotracheal tube. Although the deadspace is increased under a facemask, capnography is effective to monitor the adequacy of tidal volumes with spontaneous or assisted mask ventilation. Similarly, the deadspace is slightly increased with the larger-bore airway of the laryngeal mask airway, but monitoring of CO_2 is essential when this device is used. Finally, monitoring ventilation with a divided, CO_2 sampling nasal cannula during spontaneous ventilation with a natural airway during sedation and monitored anesthesia cases is now common practice and is especially useful when there is not direct proximity to the patient, i.e. MRI scanner [174].

As with any monitor using a mechanical–electrical interface, spurious capnograms and end-tidal CO_2 values can be caused by equipment malfunction or failure. A partially disconnected CO_2 sampling line or cracked connector can entrain room air and artificially lower end-tidal CO_2 values. A CO_2 sampling line occluded by exhaled moisture or secretions will read little or no end-tidal CO_2. Automatic machine calibration at inopportune times, i.e. immediately after intubation, as well as other malfunctions make it necessary to possess adequate clinical skills of auscultation by precordial, esophageal, or standard stethoscope.

Anesthetic agent monitoring

Most modern anesthetic gas concentration monitors are sidestream units combined with capnography, and use polychromatic infrared analyzers that detect each of the halogenated agents individually, as well as CO_2, N_2O, and O_2. These units are easy to use and calibrate, economical to operate, reliable, and reasonably accurate. Mass spectroscopy has greater accuracy and also can measure nitrogen concentration, which is important in the diagnosis of pulmonary embolus. However these units are more expensive and have largely been superseded by the infrared monitors. Although the modern units are fairly accurate, deviations as high as 5–11% relative value are seen with infrared when compared to the gold standard gas chromatography [175]. Thus, although it is important to measure inspired and end-tidal anesthetic concentrations, assessment of the relative anesthetic depth of the individual patient is critical. As with capnography, newer microstream technology that minimizes deadspace will both improve response times and allow for aspiration of smaller volumes of gas from the breathing circuit for sampling, which is important in the care of small infants [176].

Ventilatory volumes and pressures

Modern anesthesia machines have the capability to measure airway pressures, volumes, and flows using spirometry combined with pneumotachygraph technology; however, in most cases these parameters are not measured at the patient airway but at some point proximal to all the connections of the circle breathing system. This configuration introduces the potential for significant error in measurement of pressures and tidal volumes, particularly in small patients weighing less than 5–10 kg with tidal volumes <100 mL, because of the compression volume of the circle system. In other words, the average plastic disposable circle system has a compliance volume loss

of 1–3 mL per cmH_2O of pressure during inspiration; as much as 60 mL tidal volume is delivered not to the patient but rather to the circle system, with peak pressures of 20 cmH_2O above end-expiratory pressure (Fig. 19.16 A–C). Badgwell et al [177] determined that with a standard disposable pediatric circle system and standard adult anesthesia bellows the total compliance volume of the system is about 190 mL, with a peak inspiratory pressure of 20. It is obvious that with small infants the anesthesia machine readout may be very inaccurate. There are two potential solutions to this problem. First, newer generation modern anesthesia machines can calculate an exact breathing circuit compression volume during a preanesthesia machine check; during volume ventilation, additional volume is added to each breath equal to the compliance compensation volume [178]. This is only accurate if the circle system configuration is not changed after the machine check, i.e. if a distensible breathing circuit is extended to its full length, the compliance volume changes. Also, some systems will limit the extent of compliance compensation allowed for small tidal volumes less than 100–200 mL as a safety measure, so that sudden large inappropriate tidal volumes are not delivered to small patients in the event of a change in compression volume. The second method to solve this issue is to use a spirometry system that is attached to the proximal end of the endotracheal tube so that volumes and pressures are measured at the airway; this is possible with a variety of systems, whether integrated into the anesthesia delivery system or as standalone units made for infants.

KEY POINTS: RESPIRATORY MONITORING

- Pulse oximetry is a mandatory monitor and is accurate over a wide range of arterial saturations and perfusion states
- Capnography is an essential monitor and can be used to aid in diagnosis of expiratory obstruction, disconnection, inadequate ventilation, and inadequate cardiac output
- Modern anesthetic machines can more accurately measure small tidal volumes and flows using microprocessor-controlled compliance compensation techniques

Temperature monitoring

Accurate monitoring of temperature during general anesthesia is an accepted standard of care in pediatric patients, because changes in body temperature are anticipated in these patients for a variety of reasons. The physiology of maintenance of body temperature, methods of achieving this, and complications of temperature homeostasis are discussed in Chapter 45. Measurement of temperature has been simplified by easy availability of thermocouple standalone probes, or with esophageal stethoscopes, bladder catheters, skin temperature probes, tympanic membrane probes, or pulmonary artery catheters with incorporated thermistors. Central core temperature is best measured in the esophagus, rectum, or nasopharynx. These sites are generally accepted to be the most accurate, and will be equivalent if the probes are placed properly. This means in the mid-esophagus, at least 2–5 cm into the rectum, and in the case of nasopharyngeal temperature, with the probe inserted to a depth equal to the distance from the nares to the tragus of the ear, placing the tip of the probe under the cribriform plate and thus in closest proximity to the brain. Axillary temperature is often simple and convenient, especially in short pediatric cases, but several minutes may be required for temperature equilibration, and readings will be about 1°C lower. For major intra-abdominal, intrathoracic, or intracranial cases, or surgery in small infants, a core temperature site should be chosen. For monitored anesthesia care or sedation cases, temperature monitoring should be readily available and used if temperature change is anticipated. If the brain is particularly at risk, i.e. intracranial or cardiopulmonary bypass cases, actual brain temperature may be up to 2°C above rectal temperature [179]. Measurement of skin temperature, i.e. sole of the foot, versus core temperature may provide added information to assess the degree of heat loss or peripheral vasoconstriction during major surgery. With thermal homeostasis and adequate peripheral perfusion, skin temperature at the sole of the foot should be no more than 5°C below core temperature.

Urinary monitoring

Monitoring of urine output with a bladder catheter is important for major surgery, where significant blood loss, fluid shifts, or hemodynamic change are anticipated. Although influenced by a multitude of factors, a urine output of 1 mL/kg/h or greater is generally assumed to indicate adequate intravascular volume status and perfusion to the kidneys. Low or absent urine output can be due to mechanical obstruction of the tubing, hypovolemia, or antidiuretic hormone secretion, with hypovolemia by far the most frequent cause. Although it is possible, measurement of urinary sodium and osmolarity is rarely performed intraoperatively. Excessive urine output can be caused by hypervolemia, hyperosmolarity of the urine as seen in hyperglycemia (renal glucose threshold approximately 180 mg/dL in infants and children, may be lower in neonates), osmotic agents such as mannitol, or diuretics such as furosemide. The color of the urine may provide important information: hematuria can be seen with hemolysis from cardiopulmonary bypass or a transfusion reaction, tea-colored urine from myoglobinuria during malignant hyperthermia or significant muscle crush injury. Cloudy urine may be from calcium oxalate crystals, proteinuria with concentrated urine, or urinary tract infection.

Blood gas and other point-of-care testing

Rapid point-of-care testing, either in the operating room or in close proximity with rapid turnaround time, has made real-time monitoring of multiple parameters possible, especially for major surgery associated with significant blood loss, or in unstable patients in whom frequent assessment of blood gas values, hemoglobin, and other parameters is important to guide patient care. There are a variety of machines available, but among the most useful is the point-of-care blood gas machine that also measures electrolytes, hematocrit, glucose, ionized calcium, measured oxygen saturation, and lactate values (Fig. 19.17). Modern machines can make all of these

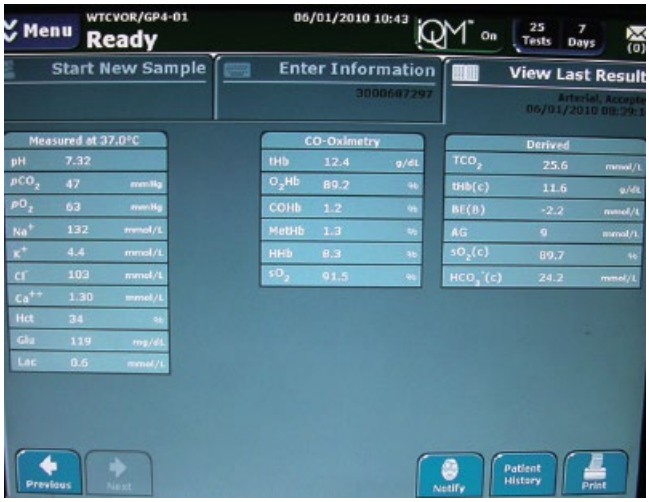

Figure 19.17 Point-of-care monitor for blood gases, electrolytes, hematocrit, ionized calcium, glucose, lactate, co-oximetry. 0.5 mL heparinized blood sample, 80 s measurement time, temperature correction.

measurements on 0.5 mL or less of heparinized whole blood, with results available in less than 2 min. Temperature correction algorithms and electronic recording of values make these machines suitable for electronic medical records. In cardiac surgery, major trauma, neonatal, spine surgery, thoracic surgery, and other major surgical cases, measuring these parameters at regular intervals may provide rapid early warning of major changes in the patient's condition, e.g. metabolic acidosis, or significant anemia or worsening A-aO_2 gradient, that are not evident from standard monitoring, and are available significantly sooner than sending the sample out to the hospital's regular clinical laboratories. Other rapid tests available as point-of-care tests include rapid coagulation assessment with partial thromboplastin time, thromboelastography, or rapid platelet function tests, potentially directing specific therapy to improve coagulation in the individual patient. For all new modalities, an analysis of the cost:benefit ratio and careful assessment of the potential to improve outcomes is important. See Chapter 12 for further discussion of coagulation monitoring.

Neuromuscular transmission monitoring

Accurate assessment of the status of neuromuscular blockade in children is important when non-depolarizing neuromuscular blocking agents are utilized, because simply relying on an estimate of the half-life of the drugs is notoriously inaccurate [180]. Standard nerve-stimulating devices utilize a current of 30–80 mA, and the most common method is to utilize the train-of-four scheme. The most common and standard placement for leads is to use small ECG leads placed over the ulnar nerve so that thumb adduction via the activation of the adductor pollicis brevis nerve can be observed. Any "fade" in the amplitude of contraction, observed visually, indicates residual neuromuscular blockade. The absence of any contraction with the train of four, or contraction only after a tetanic stimulus of 50 or 100 MHz, indicates dense neuromuscular blockade and that reversal with neostigmine or other anticholinesterase agents should not be attempted. Other sites, such as the peroneal nerve or facial nerve, may also be utilized, the latter with caution because direct muscle contraction may be observed, causing an underestimation of the degree of blockade.

Central nervous system and somatic monitoring

Near-infrared spectroscopy

Near-infrared spectroscopy (NIRS) is used to measure both cerebral and somatic oxyhemoglobin saturation. Since its now classic description in 1977 by Jobsis [181], this technology has been the subject of over 1000 publications, and because of its non-invasive compact, portable nature, and potential to measure tissue oxygenation in the brain and other organ systems during surgery and critical illness, is gaining more widespread clinical use. This section will examine the technical aspects of NIRS, parameters measured, and clinical uses in adult and pediatric cardiac and non-cardiac surgery and critical care, evidence for effectiveness in improving clinical outcomes, and pitfalls and complications of NIRS usage.

Technical concepts of near-infrared spectroscopy

NIRS is a non-invasive optical technique used to monitor brain tissue oxygenation. Most devices utilize two to four wavelengths of infrared light at 700–1000 nm, where oxygenated and deoxygenated hemoglobin have distinct absorption spectra [182–184] (Fig. 19.18). Commercially available devices measure the concentration of oxy- and deoxyhemoglobin, using variants of the Beer–Lambert equation:

$$\log\left(\frac{I}{I_0}\right) = \varepsilon_\lambda LC$$

where I_0 is the intensity of light before passing through the tissue, I is the intensity of light after passing through the tissue, and the ratio of I/I_0 is absorption. Absorption of the near-infrared light depends on the optical path length (L), the concentration of the chromophore in that path (C), and

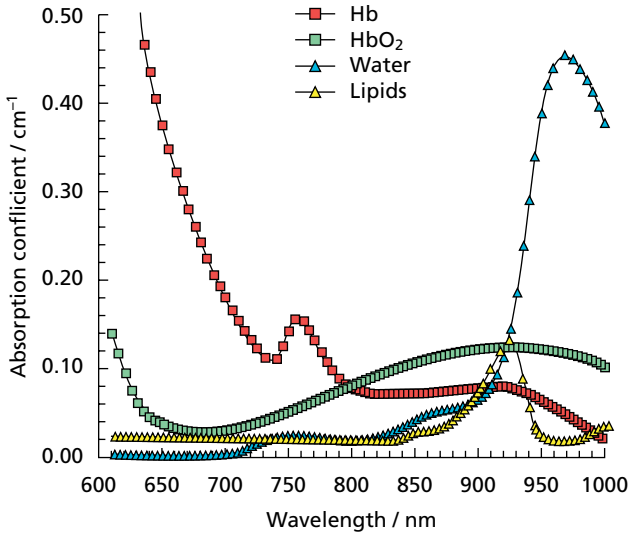

Figure 19.18 Absorption spectrum of oxyhemoglobin, deoxyhemoglobin, water, and lipids. *Source*: Courtesy of Somanetics Corporation.

the molar absorptivity of the chromophore at the specific wavelength used (ε_λ).

Cerebral oximetry assumes that 75% of the cerebral blood volume in the light path is venous, and 25% is arterial. This 75:25 ratio is derived from theoretical anatomical models. Watzman et al [185] attempted to verify this index in children with CHD by measuring jugular venous bulb saturation and arterial saturation, and comparing it to cerebral saturation measured with frequency-domain NIRS. The actual ratio in patients varied widely, but averaged 85:15.

In the various models of cerebral oximeters currently on the market, the sensor electrode is placed on the forehead (Fig. 19.19A) below the hairline. A light-emitting diode (LED) or laser emits infrared light that passes through a "banana-shaped" tissue volume in the frontal cerebral cortex to two or three detectors placed 3–5 cm from the emitter. The screen displays regional cerebral oxygen saturation (rSO_2) and trend over time (Fig. 19.19B). By using different sensing optodes and multiple wavelengths, extracranial and intracranial Hb absorption can be separated. Narrow arcs of light travel across skin and skull but do not penetrate the cerebral cortex. Deep arcs of light cross skin, skull, dura, and cortex (Fig. 19.20). Subtracting the two absorptions measured, shallow from deep, leaves absorption that is due to intracerebral chromophores, and this processing renders the cerebral specificity of the oximeter (Fig. 19.21). However, the accuracy of NIRS is confounded by the light scattering that alters the optical path length; the available commercial clinical devices solve this problem differently. The depth of light penetration is 2–4 cm.

There are several cerebral oximeters that are currently widely commercially available, including the INVOS 5100, NIRO 200, Foresight, and Equanox. Of these, the Somanetics INVOS system (Somanetics, Inc. Troy, MI, USA; INVOS 5100) is in common use and has disposable probes including an adult probe for patients over 40 kg, as well as a pediatric probe designed for patients 4–40 kg which uses a different algorithm that takes into account the thinner skull and extracranial tissues compared to the adult [186]. More recently a neonatal probe has become available and is easier to apply as it conforms well to the smaller forehead shape. It uses two wavelengths, 730 and 810 nm, has one LED and two detectors, spaced at 3 cm and 4 cm apart from the emitter, and uses spatially resolved spectroscopy (Fig. 19.22). The distinct absorption coefficients of oxy- and deoxyhemoglobin permit measurement of the relative signals from these compounds in the light path (Fig. 19.20), and the INVOS device reports oxyhemoglobin/total hemoglobin (oxy- + deoxyhemoglobin) × 100, as the measured regional cerebral oxygen saturation (rSO_2), in percentage. The rSO_2 is reported as a percentage on a scale from 15% to 95%. A subtraction algorithm based on probe size removes most of the transmitted shallow (3 cm detector) signal, leaving over 85% of the remaining signal derived from brain frontal cortex. This device is approved by the US Food and Drug Administration (FDA) for use in children and adults as a trend-only monitor. It is compact, noninvasive, and requires little warm-up. A signal strength indicator displays adequacy of the detected signal. The device

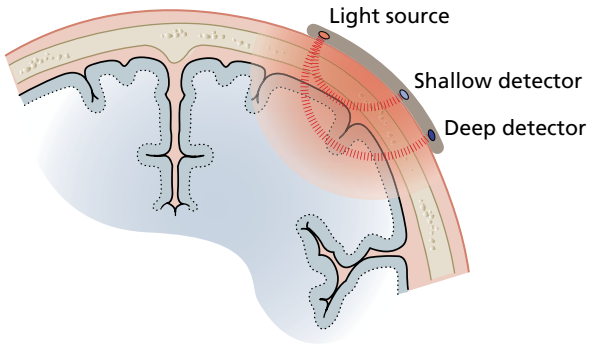

Figure 19.20 NIRS method. A light or laser-emitting diode emits light that passes through the skin, skull, meninges, and into a small portion of the frontal cerebral cortex. Some light is scattered, and some is absorbed by oxy-and deoxyhemoglobin. A portion passes through tissues and is detected by a shallow and a deep detector, 3 and 4 cm respectively from the light source. The shallow component is subtracted out, leaving mostly intracranial signal. *Source*: Courtesy of Somanetics Corporation.

Figure 19.21 Different NIRS probes for neonate cerebral 1–4 kg (*far left*), neonatal somatic 1–4 kg (*second from left*), pediatric cerebral/somatic (4–40 kg) (*second from right*), and adult >40 kg (*far right*) monitoring. *Source*: Courtesy of Somanetics Corporation.

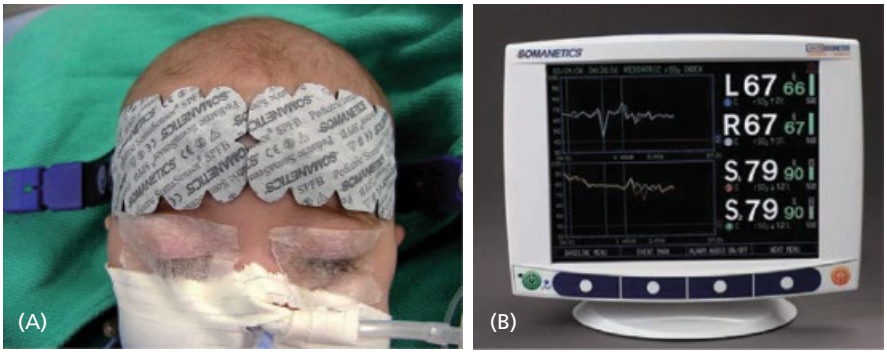

Figure 19.19 (A) Bilateral NIRS probes on an infant. (B) Four-channel NIRS monitor screen. L and R designate left and right cerebral hemispheres; S3 designates renal saturation with a probe placed on the flank at the T10–11 level; S4 designates mesenteric saturation with a probe placed in the midline between the umbilicus and symphysis pubis. See text for further explanation.

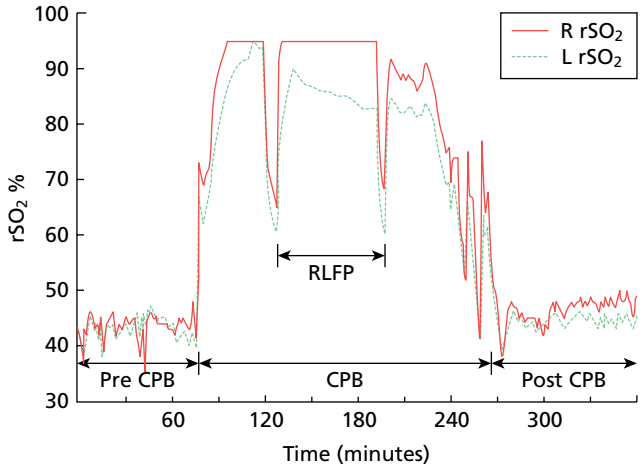

Figure 19.22 Typical changes in regional cerebral oxygen saturation (rSO_2) during cardiac surgery in a neonate with hypoplastic left heart syndrome undergoing Norwood stage I palliation, with cardiopulmonary bypass (CPB), regional cerebral low flow perfusion (RLFP), and deep hypothermic circulatory arrest (DHCA). Note precipitous decline at minute 115 with onset of DHCA for atrial septectomy, and again at minute 185 for replacement of aortic cannula.

does not depend on pulsatility like a pulse oximeter, and operates at all temperatures. Cerebral blood volume index (Crbvi) can also be calculated, representing the total hemoglobin in the light path, which may be used as an estimate of cerebral blood volume; however, this application is only FDA approved for research purposes, not for clinical use.

The NIRO 200 (Hamamatsu Photonics, Hamamatsu, Japan) uses three wavelengths of near-infrared light (775, 810, and 850 nm), emitted by a laser diode and detected by a photodiode. It uses spatially resolved spectrophotometry, and the three wavelengths allow better determination of light path length according to the Beer–Lambert law, which allows calculation of absolute concentrations of oxygenated and total hemoglobin. The NIRO 200 reports a tissue oxygenation index (TOI) as well as hemoglobin indices including changes in total hemoglobin and oxy- and deoxyhemoglobin. The probes are not disposable, but are attached with a disposable probe holder. This device may potentially be more accurate than the INVOS system due to the increased number of wavelengths of light, however it is not FDA approved for use in the USA.

A more recent FDA-approved device is the Foresight monitor (Casmed; Branford, CT). This device uses four wavelengths of light: 690, 778, 800, and 850 nm. The purpose of the additional wavelengths is to better discriminate non-hemoglobin sources of infrared absorption, which may lead to a more accurate calculation of oxygenated and total hemoglobin concentrations [187]. The Foresight monitor reports the percentage of oxygenated hemoglobin to total hemoglobin as a cerebral tissue oxygen saturation ($SCTO_2$), and is marketed as an absolute cerebral tissue oxygen saturation. Currently available probes are disposable and are appropriate only for patients 2.5–8 8 kg and >40 kg.

The Equanox device (Nonin Medical, Plymouth, MN, USA) is now also FDA approved, and uses four wavelengths from 730 to 880 nm. This monitor also utilizes a dual emitter/dual detector sensor and dynamic compensatory algorithms that effectively eliminate scalp and skull light absorption contamination. This allows greater focus on brain tissue and automatic adjustment for variations in tissue optical properties to improve accuracy over a wide range of age and physiological conditions. In 100 pediatric patients with CHD and measured cerebral oxygen saturations of 34–91%, the monitor values were compared to a weighted average of measured jugular venous bulb saturation and arterial saturation and found to have excellent correlation, with mean bias of 0.5%, precision 5.39%, and correlation coefficient of 0.88 [188].

Comparison between these commercial devices reveals differences in measured values due to the different numbers of wavelength, and subtraction algorithms, thus making direct data comparisons difficult [183]. However, regardless of the device used, it is important to remember that all devices measure combined arterial and venous blood oxygen saturation, and cannot be assumed to be identical to $SjvO_2$. Maneuvers to increase arterial oxygen saturation, i.e. increasing FiO_2, will increase cerebral oxygenation as measured by these devices, but the $SjvO_2$ may remain unchanged.

The Foresight device is still relatively new and comparison data with the INVOS are not available. However, the Foresight monitor may predict a more accurate value for the true brain saturation compared to the INVOS monitor that will make between-patient comparisons easier. The Equanox monitor also has the advantage of measuring absolute brain tissue saturation, and excellent correlation with blood oximetry.

Early attempts to validate the non-invasive measurement of cerebral oxygen saturation in children with CHD compared the $SjvO_2$ and rSO_2. In 40 infants and children [189] undergoing congenital heart surgery or cardiac catheterization, the correlation for paired measurements was inconclusive except for infants less than 1 year of age. In 30 patients undergoing cardiac catheterization, an improved correlation r = 0.93 was found [190], and there was a linear correlation between changes in arterial CO_2 and cerebral saturation.

Somatic near-infrared oximetry

Using the same principles of unique light absorption spectra of hemoglobin species, NIRS has also been used to measure tissue oxygenation in skeletal muscle, i.e. quadriceps, forearm, or thenar eminence muscle, in adults and children [191]. In addition, a probe placed over the flank at the T10–L2 level will measure tissue saturation in skeletal muscle and, in small infants, renal oxygenation, due to the small light penetrance distance needed in these small patients [192] (Fig. 19.23). Finally, mesenteric saturation has also been measured in infants with a probe placed in the midline between the umbilicus and the symphysis pubis [193].

Parameters monitored with near infrared spectroscopy

To simplify terminology, the term rSO_2, for regional oxygen saturation, will be utilized for the remainder of this chapter, regardless of the device used. Cerebral rSO_2 measurements are an estimate of venous-weighted oxyhemoglobin saturation in the sample volume illuminated by the light path, i.e. the frontal cerebral cortex in most situations. rSO_2 can be altered by any of the factors that affect cerebral oxygen supply:demand ratio and is especially affected by the unique features of the cerebral circulation, including cerebral autoregulation and alterations in cerebral blood flow according to $PaCO_2$. Any factor that decreases cerebral oxygen

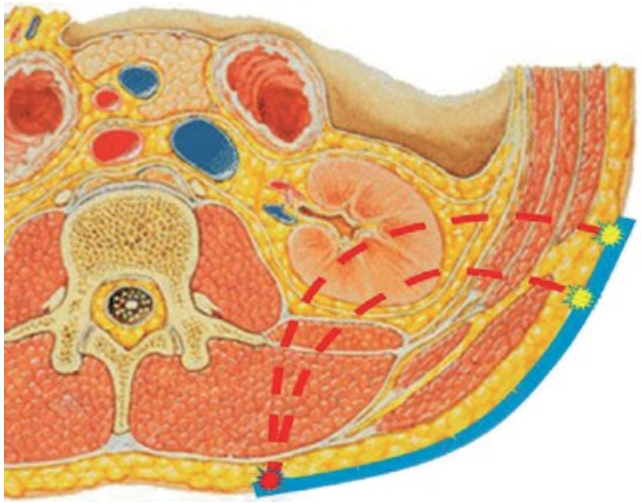

Figure 19.23 Principles of somatic NIRS. In a neonate or small infant, a NIRS probe placed on the flank over the T10–12 area measures the oxyhemoglobin saturation of the tissues in the light path, particularly muscle and renal tissue beds. *Source*: Courtesy of George Hoffman MD.

Box 19.2: Factors affecting cerebral oxygen consumption and delivery

Factors decreasing $CMRO_2$ and generally increasing rSO_2

- Hypothermia
- Increasing sedation, anesthesia, analgesia with benzodiazepines, opioids, dexmedetomidine
- Treating seizures

Factors increasing oxygen delivery to brain and generally increasing rSO_2

- Increasing $PaCO_2$
- Increasing hemoglobin
- Increasing cardiac output
- Increasing FiO_2 or other ventilatory maneuvers to increase SpO_2
- Increasing mean arterial pressure (outside limits of autoregulation, i.e. hypotension)
- Increasing CPB flow rate
- Increasing CPP
- Minimizing cerebral venous pressure to increase CPP, i.e. obstructed venous bypass cannula

$CMRO_2$, cerebral metabolic rate for oxygen; CPB, cardiopulmonary bypass; CPP, cerebral perfusion pressure; rSO_2, regional brain oxygen saturation.

consumption will generally increase rSO_2, and any factor that increases oxygen delivery to the brain will also generally increase rSO_2. Box 19.2 lists some of the common alterable clinical factors that can be used to change rSO_2. Since cerebral rSO_2 is influenced by arterial oxygenation, improving this parameter will often increase rSO_2, even if $SjvO_2$ is little altered.

For pediatric patients undergoing congenital heart surgery, baseline rSO_2 varies with cardiac lesion [184]. The baseline cerebral saturation is about 70% in acyanotic patients without large left-to-right intracardiac shunts breathing room air. On room air, rSO_2 for cyanotic patients, or acyanotic patients with large left-to-right intracardiac shunts, is usually 40–60%; hypoplastic left heart syndrome (HLHS) patients receiving <21% FiO_2 preoperatively have lower rSO_2, averaging 53%, versus those receiving FiO_2 0.21 and 3% inspired CO_2, where rSO_2 averages 68% [194].

Taking into account pediatric cardiac surgery outcome data, some practitioners would consider a relative decline from a baseline of 20% or more (e.g. from a baseline of 60% to a nadir of 48%) cause for intervention. The software on most oximeters will continuously calculate this relative difference from baseline. Other practitioners would use an absolute value of rSO_2 of 50% as cause for intervention.

Cerebral oximetry reflects a balance between oxygen delivery and oxygen consumption by the brain ($CMrO_2$). The cerebral oxygen content will therefore be affected both by the arterial saturation of hemoglobin and the hemoglobin concentration. There then must exist a cerebral saturation value, or ischemic threshold, below which brain injury is likely due to oxygen deprivation as demand outstrips supply. In a neonatal piglet study using frequency-domain NIRS [195], Kurth et al showed that cerebral lactate levels rose at rSO_2 values of 44% or lower; major EEG changes occurred when the cerebral saturation declined to 37%, with reductions in cerebral ATP levels when oximetry readings were 33% or lower. This concept was confirmed in another neonatal piglet model using hypoxic gas mixtures for 30 min at normothermia, demonstrating that rSO_2 >40% did not change EEG or brain pathology obtained 72 h later; rSO_2 30–40% produced no EEG changes, but at 72 h there were ischemic neuronal changes in the hippocampus, and mitochondrial injury occurred. At rSO_2 <30%, there was circulatory failure, EEG amplitude decreased, and there was vacuolization of neurons and severe mitochondrial injury [196]. Finally, in a similar piglet model, the hypoxic-ischemic cerebral saturation-time threshold for brain injury found rSO_2 of 35% for 2 h or more produced brain injury [197]. In general, most pediatric clinical studies use either 20% below established baseline or an oximetry reading of 45–50% for the threshold for treatment based on evidence of new MRI lesions or clinical examination that brain injury is more likely to develop under these circumstances [198,199].

In the absence of absolute criteria for intervention to prevent neurological injury (see section "Outcome studies of near-infrared spectroscopy"), each anesthesiologist must take into account the unique pathophysiology of each patient and the monitoring system used, and decide on criteria for intervention, much like all of the other physiological variables measured for surgery and critical care.

Clinical data in pediatric cardiac surgery

Changes in cerebral oxygenation have been characterized during cardiopulmonary bypass in children with or without deep hypothermic circulatory arrest [200]. rSO_2 predictably decreases during deep hypothermic circulatory arrest (DHCA) to a nadir approximately 60–70% below baseline values obtained pre bypass [200]; the nadir is reached at about 40 min, after which there is no further decrease. At this point it appears that the brain does not continue the uptake of oxygen, and interestingly this time period appears to correlate with clinical and experimental studies suggesting that 40–45 min is the limit for safe duration for circulatory arrest [201,202]. DHCA initiation at a higher temperature results in a faster fall in rSO_2, reaching the nadir sooner [203]. Reperfusion immediately results in an increase in rSO_2 to levels seen at full bypass flow before DHCA.

The question often arises whether bilateral cerebral hemisphere NIRS monitoring is necessary. In a study of 20 patients undergoing a special cardiopulmonary bypass (CPB) technique, antegrade cerebral perfusion, via the right innominate artery, half of the patients had a left–right difference of >10%. [204]. In 60 neonates undergoing surgery with conventional bypass, only 10% had a greater than 10% difference between left and right sides at baseline, and this difference persistent in only one patient [205]. Based on these data, bilateral monitoring is probably necessary only when special CPB techniques are used for aortic arch reconstruction, or when anatomical variants, i.e. bilateral superior vena cavae or abnormalities of the brachiocephalic vessels, are present.

Treatment of low rSO_2

Whether during adult or pediatric cardiac surgery with CPB, the general approach to treating low rSO_2 is similar and involves increasing oxygen delivery to the brain or decreasing oxygen consumption. One approach to treatment is displayed in Box 19.3.

In critical care medicine, cerebral NIRS has been used to monitor adequacy of cerebral oxygen delivery and as a surrogate for adequacy of global oxygen delivery in patients after cardiac surgery and patients on extracorporeal membrane oxygenation (ECMO) or ventricular assist devices [187,206]. Changes in rSO_2 have a close correlation with changes in mixed venous saturation (SvO_2) in both single- and two-ventricle patients after congenital cardiac surgery [207,208].

Clinical uses of somatic near-infrared spectroscopy in pediatric surgery and critical care

NIRS can be used to measure tissue oxygenation in surgery and critical illness and because of its non-invasive, continuous nature has intuitive appeal in conditions where low cardiac output and other causes of shock would benefit from such continuous monitoring.

Somatic NIRS using a probe placed on the flank at T10–L2 has been studied in a series of neonates after and during single-ventricle surgical palliation by Hoffman et al [192]. In nine neonates undergoing CPB with regional cerebral perfusion (RCP), mean cerebral rSO_2 pre bypass was 65% and somatic rSO_2 59%, and during RCP cerebral rSO_2 was 81% versus 41% somatic rSO_2, signifying relative tissue hypoxia due to lack of perfusion to subdiaphragmatic organs during this technique. After CPB, cerebral rSO_2 decreased to 53%, but somatic rSO_2 increased to 76% [192]. In 79 postoperative neonates undergoing Norwood stage I palliation for hypoplastic left heart syndrome, a cerebral–somatic rSO_2 difference of <10% significantly increased the risk for biochemical shock, mortality, or other complications [209] (Fig. 19.24). Mean somatic rSO_2 <70% was associated with a significantly increased risk of prolonged ICU stay, shock, and other complications.

Somatic NIRS has also been used to measure mesenteric rSO_{2in} neonates and infants after cardiac surgery, with a probe placed on the abdomen between the umbilicus and symphysis pubis. In a study of 20 patients, Kaufman et al [210] compared mesenteric NIRS and flank NIRS at T10–L2 to gastric pH measured by tonometry and lactate values. In 122 simultaneous measurements made in the first 48 h after surgery, mesenteric rSO_2 correlated significantly with gastric pH (r = 0.79), serum lactate (r = 0.77), and SvO_2 (r = 0.89). These correlations were all better than those using flank NIRS. The authors concluded that mesenteric NIRS is a sensitive monitor of splanchnic tissue oxygenation and may have utility in managing these patients and improving outcomes. In a recently published study of 214 neonates undergoing Stage I palliation for HLHS, low somatic and cerebral NIRS values in the first six postoperative hours predicted early postoperative mortality and need for ECMO [211].

These studies lend credence to the idea that NIRS-directed targeted interventions could be utilized to improve oxygen delivery to tissues and organs, and potentially improve

Box 19.3: Treatment algorithm for low cerebral oxygen saturation (rSO_2)

1. Establish baseline rSO_2 on FiO_2 0.21, $PaCO_2$ 40 mmHg, stable baseline hemodynamics, awake before induction of anesthesia, or pre bypass if possible
2. Treat decreased rSO_2 of >20% relative value below baseline, or <50% absolute value
3. Pre/post bypass (in order of ease/rapidity to institute):
   a. Increase FiO_2
   b. Increase $PaCO_2$
   c. Increase cardiac output/O_2 delivery with volume infusions, inotropic support, vasodilators, etc.
   d. Increase depth of anesthesia
   e. Decrease temperature
   f. Increase hemoglobin
4. During CPB:
   a. Increase CPB flow and/or mean arterial pressure
   b. Increase $PaCO_2$
   c. Increase FiO_2
   d. Decrease temperature
   e. Increase hemoglobin
   f. Check aortic and venous cannula positioning
   g. Check for aortic dissection

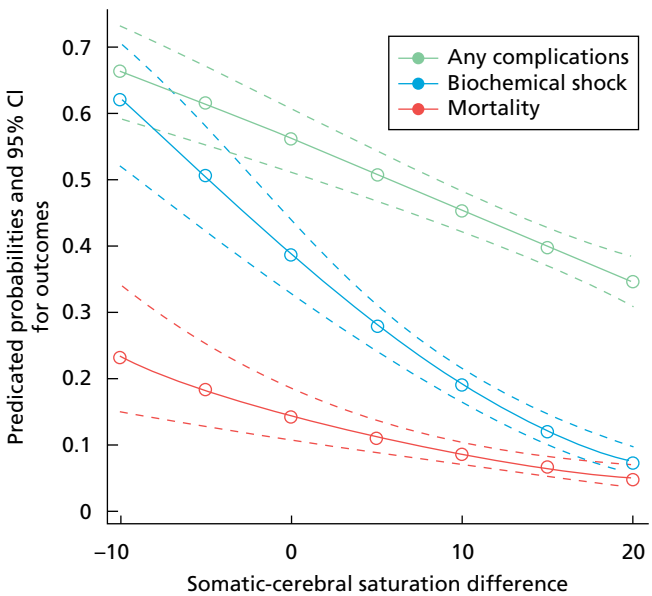

Figure 19.24 Relationship between somatic rSO_2–cerebral rSO_2 difference, and the incidence of complications in 79 patients in the 48 h after Norwood stage I palliation for hypoplastic left heart syndrome. *Source:* Reproduced from Hoffman et al [209] with permission of Elsevier.

outcomes from surgery, anesthesia, and critical illness. To date, there is a lack of such published studies, but the non-invasive continuous nature of NIRS monitoring should make such studies more likely to be performed.

Outcome studies of near-infrared spectroscopy

There is increasing evidence from pediatric cardiac surgery studies that prolonged low NIRS values are associated with adverse short-term neurological outcomes. Dent et al [198] studied 15 neonates undergoing the Norwood operation who underwent preoperative, intraoperative, and postoperative rSO_2 monitoring. A prolonged low rSO_2 (>180 min with rSO_2 <45%) was associated with a higher risk of new ischemic lesions on postoperative MRI when compared to the presurgical study, with a sensitivity of 82%, specificity of 755, positive predictive value of 90%, and negative predictive value of 60%. Therefore both the extent of decreased cerebral saturation (ischemic threshold) and the time spent below this ischemic threshold are important in predicting the development of new postoperative brain injury by MRI.

There is additional clinical evidence suggesting that low cerebral saturations correlate with adverse neurological outcome. In a study of 26 infants and children undergoing surgery utilizing DHCA [200], three patients had acute neurological changes – seizures in one, and prolonged coma in two – all of whom manifested low rSO_2. In these three patients, the increase in rSO_2 was much less after the onset of CPB, and the duration of cooling before DHCA shorter. In a retrospective study of multimodality neurological monitoring in 250 infants and children undergoing cardiac surgery with bypass [199], relative cerebral oxygen desaturation of more than 20% below prebypass baseline resulted in abnormal events in 58%. If left untreated, 26% of these patients had adverse postoperative neurological events.

In a study of 16 patients undergoing neonatal cardiac surgery with NIRS monitoring and pre- and postoperative brain MRI, six of 16 patients developed a new postoperative brain injury; these patients had a lower rSO_2 during the aortic cross-clamp period versus those without new brain injury (48% versus 57%, p = 0.008) [212]. In a study of 44 neonates undergoing the Norwood operation, who were tested at age 4–5 using a visual–motor integration (VMI) test, the first 34 patients did not have NIRS monitoring, and the last 10 did have NIRS monitoring with a strict treatment protocol for low rSO_2 values <50%. No patient with NIRS monitoring had a VMI score <85 (normal is 100), versus 6% without NIRS monitoring. Mean rSO_{2in} the perioperative period was associated with VMI score, with no patient with mean rSO_2 ≥55 having VMI less than 96 [213].

Toet et al [214] studied 20 neonates undergoing the arterial switch operation and monitored rSO_2 for 4–12 h preoperatively, intraoperatively, and 36 h postoperatively, without intervention. Seven patients had a mean preoperative rSO_2 ≤35%, and two of these patients had significantly abnormal Bayley Scales of Infant Development Scores at 30–36 months, of 1–2 standard deviations below the normal population mean.

Kussman et al [215] studied 104 infants aged 9 months or less undergoing complete two-ventricle repair of transposition of the great arteries, tetralogy of Fallot, or ventricular septal defect. Bilateral NIRS was monitored during the intraoperative period, and for 18 h postoperatively, but no intervention was made on the basis of rSO_2 values. The aim of the study was to evaluate changes in rSO_2 and to determine association between low rSO_2 and early postoperative outcomes, including death, stroke, seizures, or choreoathetosis. An rSO_2 threshold of 45% was chosen as the cut-off for analysis. pH stat blood gas management and hematocrit of 25–35%, along with brief DHCA and some low-flow bypass, was utilized. Eighty-one of 104 patients had no desaturation below 45%, 12 had brief desaturation below 45% for 1–39 min, and 11 had more prolonged desaturation of 60–383 min. Because no patient in the study died or suffered any neurological complication, the relationship between low rSO_2 and early neurological outcome could not be determined. There was also not a relationship between low rSO_2 and postoperative cardiac index, lactate, severity of illness, or days ventilated, in the ICU or hospital. Thirty-nine of these patients had a period of DHCA, and important data about the rate of decline of rSO_2 under optimal CPB conditions were reported (Fig. 19.25). (The important finding is that brief periods of DHCA <30 min did not result in nadir values of rSO_2, suggesting that this technique does not deplete the brain of oxygen stores and lending more credence to the idea that this practice is safe. The lack of an association between rSO_2 and early gross neurological outcomes is not unexpected, given that these were all two-ventricle patients, completely repaired, with normal arterial oxygen saturations postoperatively. The low incidence and severity of cerebral desaturation in this population have been previously described [216] (Fig. 19.26).

Another potential benefit of routine NIRS monitoring is to avert the rare but very real and devastating potential

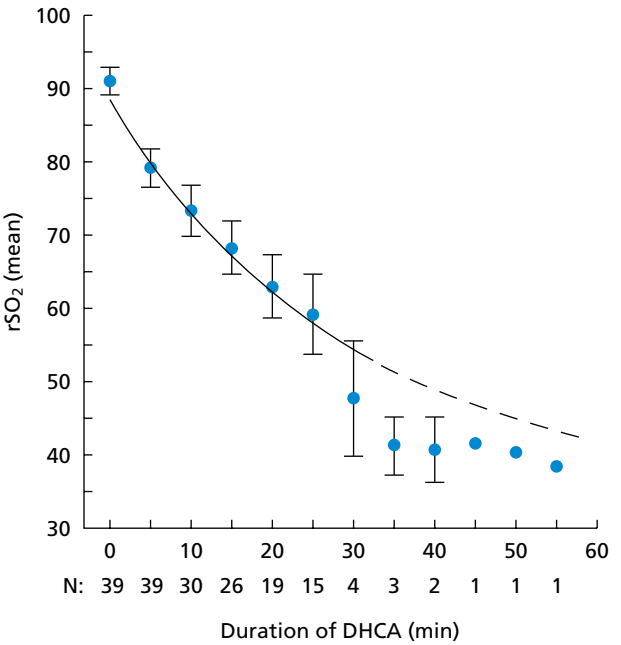

Figure 19.25 Pattern of cerebral rSO_2 during deep hypothermic circulatory arrest (DHCA) in 39 infants with D-transposition of the great arteries who underwent ≥5 min of DHCA. Data are presented as mean ± 1.96 SEM. The number of subjects (N) available for analysis at 5 min intervals of DHCA is shown. The fitted non-linear exponential decay curve (solid line) is base on data from 0 to 30 min with higher weight given to mean rSO_2 values calculated with more subjects. The fit is extrapolated beyond 30 min (dashed line). *Source:* Reproduced from Kussman et al [215] with permission of Wolters Kluwer.

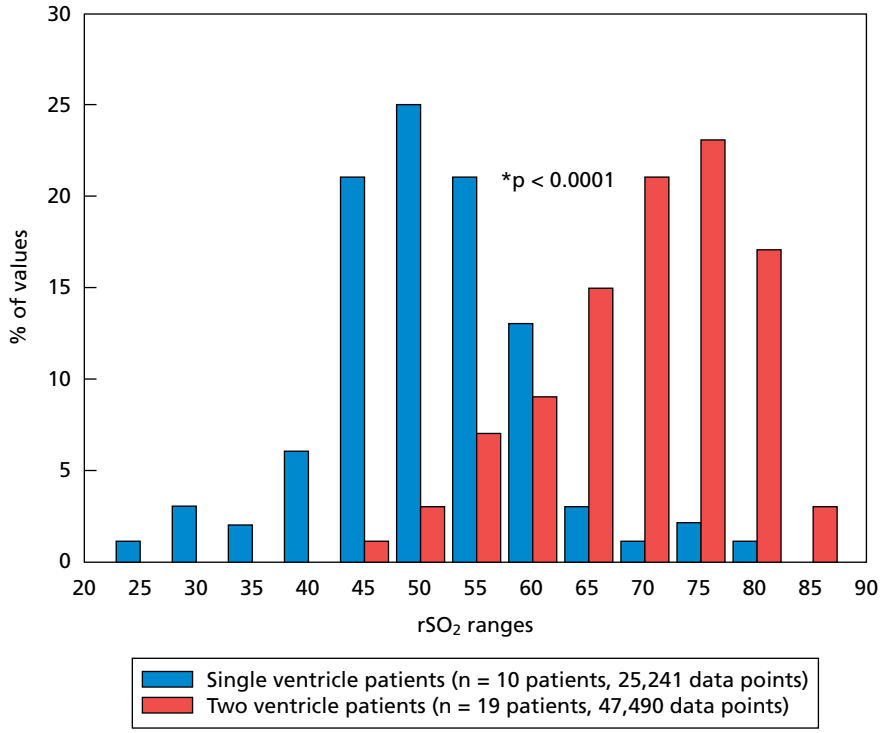

Figure 19.26 Frequency of rSO_2 values recorded at 1 min intervals in the first 48 h postoperatively in neonates undergoing repair of hypoplastic left heart syndrome (single-ventricle patients) or D-transposition of the great arteries (two-ventricle patients). *Source:* Reproduced from Andropoulos et al [216] with permission of Wolters Kluwer (CCC).

neurological disaster from cannulation problems, where rSO_2 declines dramatically from cannula malposition and cerebral arterial or venous obstruction, yet all other bypass parameters are normal [217,218]. In neonates and infants it is clear that mixed venous saturation in the bypass circuit bears very poor association with cerebral saturation, emphasizing the point that intracerebral desaturation may go unnoticed [219].

In a systematic review of 56 publications describing 1300 patients in whom NIRS monitoring was used for CHD in the operating room, ICU, and cardiac catheterization laboratory, Hirsch et al [220] concluded that the technology did serve as a reliable, continuous, non-invasive monitor of cerebral oxygenation. Additional recent patient cohorts document an association between low cerebral oxygen saturation in the perioperative period for congenital heart surgery and lower neurodevelopmental outcome scores at 1–5 years of age [221–223]. However, to date there have not been any published prospective, randomized, controlled studies of NIRS monitoring versus no NIRS monitoring, with short- or long-term follow-up in pediatric patients. Many centers where NIRS is now in routine clinical use will not have sufficient equipoise to conduct such a study.

A recent prospective study of 453 infants under 6 months of age undergoing non-cardiac and non-neurological surgery revealed only a 2% incidence of significant cerebral oxygen desaturation (<50% absolute value, or >30% below baseline value). These periods of cerebral desaturation were very brief, representing only 0.1% of anesthetic time [224].

Transcranial Doppler ultrasound

Transcranial Doppler ultrasound (TCD) is a sensitive, real-time monitor of cerebral blood flow velocity and emboli during congenital heart surgery. Currently available instruments utilize pulsed-wave ultrasound at 2 MHz frequency, which is range-gated, emits a power of 100 mW, and has a sample volume length of up to 15 mm. A display of the frequency spectrum of Doppler signals is easily interpreted, and peak systolic and mean flow velocities, in cm/s, are displayed, as well as a pulsatility index which is equal to the peak velocity minus the end-diastolic velocity, divided by the mean velocity.

The most consistent and reproducible technique for clinical use in patients of all ages is to monitor the middle cerebral artery (MCA) through the temporal window, which can usually be found just above the zygoma and just anterior to the tragus of the ear [225]. Several transducer probes are available, ranging from very small disk probes suitable for infants and children, to larger, heavier probes for adolescents and adults. The depth of the sample volume and angle of insonation are adjusted until the bifurcation of the MCA and the anterior cerebral artery (ACA) is detected. This is heralded by a maximal antegrade signal (positive deflection, toward the transducer) from the MCA, accompanied by retrograde flow (negative deflection, away from the transducer) of the same or very similar velocity and waveform, as the MCA flow. The same location should be monitored for an individual patient. Insonation at the MCA–ACA bifurcation also offers the advantage of minimizing interpatient variability. In addition, the MCA supplies the largest volume of tissue of any of the basal cerebral arteries [226]. In infants, an alternative site for monitoring is through the anterior fontanelle, using a hand-held pencil-type probe, placing the probe over the lateral edge of the fontanelle and aiming caudally, at a greater depth than for the temporal window.

TCD has been used extensively in pediatric cardiac surgical research to examine cerebral physiology in response to CPB, hypothermia, low-flow bypass, regional low-flow perfusion

to the brain, and circulatory arrest. Hillier et al [227] used TCD to study cerebrovascular hemodynamics during hypothermic bypass with DHCA in 10 infants, finding that cerebral blood flow velocity did not return to baseline levels after DHCA. Calculated cerebral vascular resistance (mean arterial pressure – central venous pressure/CBFV) was increased immediately after DHCA and remained so until the end of bypass. The observed decrease in cerebral blood flow velocity during cooling was thought to be due to decreased metabolic demand by the brain and thus less blood flow, although α-stat strategy was used. This could be explained by relative cerebral vasoconstriction during cooling in smaller arterioles downstream to the MCA and ACA, since these large arteries do not change their caliber in response to changes in $PaCO_2$ [228]. TCD of the MCA through the temporal window was used to describe the cerebral pressure–flow velocity relationship during hypothermic bypass in 25 infants less than 9 months old. Cerebral blood flow velocity was examined over a wide range of cerebral perfusion pressures (varying from 6 to 90 mmHg), and at three temperatures: normothermia (36–37°C), moderate hypothermia (23–25°C), and profound hypothermia (14–20°C). Cerebral pressure flow autoregulation was preserved at normothermia, partially affected at moderate hypothermia, and totally lost at profound hypothermia, results that agree with previous research done using xenon to quantitate cerebral blood flow [229].

TCD has also been utilized to determine the threshold of detectable cerebral perfusion during low-flow cardiopulmonary bypass. Zimmerman et al [230] studied 28 neonates undergoing the arterial switch operation with α-stat pH management. At 14–15°C the pump flow was sequentially reduced to 0 mL/kg/min. All patients had detectable cerebral blood flow down to 20 mL/kg/min, while one had no perfusion at 20 mL/kg/min, and eight had none at 10 mL/kg/min, leading the authors to conclude that 30 mL/kg/min was the minimum acceptable flow in this population. Finally, Andropoulos et al [231] used TCD of the MCA to determine the level of bypass flow necessary during regional low-flow perfusion for neonatal aortic arch reconstruction. They studied 34 neonates undergoing the Norwood operation or aortic arch advancement and established a baseline mean cerebral blood flow velocity (22 cm/s) under full-flow bypass (150 mL/kg/min) using pH stat management at 17–22°C. They then used TCD to determine how much bypass flow was necessary to match this value, finding that a mean of 63 mL/kg/min was necessary.

Cerebral emboli are a frequent threat during open-heart surgery in children. Emboli are easily detected by TCD, although this is subject to artifacts such as electrocautery and physical contact with the ultrasound transducer [232]. The number of emboli detected in the carotid artery during pediatric congenital heart surgery did not appear to correlate with acute postoperative neurological deficits [232]. However, acute drops in cerebral blood flow detected by TCD can allow for adjustment of aortic or superior vena cava cannulae, which may avert neurological disaster [233].

Although TCD is a useful research tool, and in some centers a monitor that is utilized for special CPB techniques such as regional cerebral perfusion, the complexity of the equipment and attainment of a consistent signal, and the lack of convincing long-term outcome data render TCD a monitor that is not routinely used in pediatric cardiac surgery.

Electroencephalographic technologies

The standard electroencephalogram (EEG) employing between two and 16 channels has been utilized in congenital heart surgery [199]. It is a rough guide of anesthetic depth, and can document electrocerebral silence before DHCA [234]. EEG is affected by several factors including anesthetic agents, temperature, and CPB. Impracticalities of the use of an intraoperative EEG include electrical signal interference and complexity of placement and interpretation. Newer devices using processed EEG technology are more user-friendly and have been extensively reviewed [235,236]. The value of perioperative EEG monitoring in congenital heart surgery is unclear. For example, HLHS neonates frequently have a normal perioperative EEG yet frequently demonstrate abnormalities on pre- and postoperative brain MRI suggestive of ischemia [187].

The Bispectral Index (BIS) monitor (Aspect Medical Systems, Nantick, MA, USA) is currently promoted to guide the depth of anesthesia. BIS sensor electrodes are applied to the forehead and temple producing a frontal-temporal montage, which connects to a processing unit. The device is easy to use, electrodes are easy to place, and the monitor requires no calibration or warm-up time. Via a proprietary algorithm of the Aspect Corporation, BIS uses Fourier transformation and bispectral analysis of a one-channel processed EEG pattern to compute a single number, the Bispectral (BIS) Index [237]. This index ranges from 0 (isoelectric EEG) to 100 (awake) with mean awake values in the 90–100 range in adults, infants, and children [238]. Depth of sedation is difficult to predict using BIS scores due to significant individual variability and anesthetic agent [239]. For BIS to be effective as a monitor of the depth of anesthesia, one would have to know exact BIS values for each anesthetic administered for an individual patient, thus reducing its value [240]. BIS can be used to recognize EEG burst suppression, or electrical silence, which could be useful during DHCA. The monitor displays a real-time EEG waveform but is subject to motion artifact, EMG activity, and radiofrequency interference from electrical equipment in the operating room. Few or no data exist in children on the use of other EEG devices such as the Physiometrix®, Narcotrend®, or Cerebral Function Monitor® [235]. During CPB, hemodilution and hypothermia alter pharmacokinetics and pharmacodynamics, which can lead to awareness under anesthesia. The overall incidence of awareness in adults undergoing cardiac surgery varies from 1.1% [240] to 23%, which is more than in general surgical procedures [241,242]. The incidence of awareness under general anesthesia is similar in children [243]. Although there are no documented reports of awareness under anesthesia in children undergoing heart surgery, BIS monitoring may still be useful to detect a level of awareness.

In a cohort of children undergoing open heart surgery with an anesthetic tailored for "fast-tracking," BIS scores increased during rewarming, a period considered at risk for awareness under anesthesia [244]. However, in this study, and in a similar study in infants less than 1 year of age [245], BIS did not correlate with stress hormone levels, a surrogate for light levels of anesthesia, nor with plasma fentanyl levels. At present there is little evidence to support the use of BIS in neonates and infants undergoing anesthesia and therefore the value of BIS to assess burst suppression during DHCA is in further doubt. This is due to the different sleep-arousal patterns in this subset.

Because of the similarities of the full EEG in children over age 12 to the adult EEG, processed EEG monitoring in older children above the age of 12 years will produce similar patterns to those of the adult; therefore it would appear more logical to use these devices in older patients, and especially under special anesthetic techniques, i.e. total intravenous anesthesia for spine surgery in the adolescent [246,247].

Recent publications of processed EEG methods in anesthetized children include assessments of amplitude-integrated EEG (aEEG), and spectral edge frequency at 90%, in children 24 days to 14 years of age [248]. These parameters can discriminate between anesthetized and awake states in older children, but in younger children the aEEG changes were less pronounced and the spectral edge changes either could not discriminate between states or responded paradoxically. Another study of a parameter termed permutation entropy in children aged 3–15 years determined that this parameter performed in similar fashion to the BIS Index; younger children were not tested [249].

Recent studies utilizing multilead EEG as a research tool have reported fascinating developmental changes and differences in different-aged pediatric patients at various stages and depths of anesthesia, including relative predominance of alpha waves and EEG coherence and discontinuity [250,251]. These studies emphasize the significant differences with age and development, and that any processed EEG algorithms must take these into account for valid application to all pediatric age groups. As of this writing there are no clinically available processed EEG monitors that accomplish this for young children.

KEY POINTS: CENTRAL NERVOUS SYSTEM AND SOMATIC MONITORING

- Near-infrared cerebral and somatic spectroscopy is an accurate indicator of oxygenation in cardiac and critically ill patients, can guide therapy, and correlates with early mortality and neurodevelopmental outcomes
- Transcranial Doppler ultrasound is a sensitive real-time indicator of cerebral blood flow velocity in major vessels and can be used for specialized bypass techniques such as regional cerebral perfusion
- Processed EEG technologies can be utilized to monitor depth of anesthesia in older children; existing devices are not accurate in infants and younger children due to developmental changes in the EEG

Point-of-care ultrasound

For more than a decade, high-resolution portable ultrasound devices have been available, first for central venous and arterial access, and then as an indispensable tool for regional anesthesia (see Chapter 20). In recent years, point-of-care ultrasound (POCUS) for other organ systems has been practiced in pediatric anesthesia after adaptation from adult medicine areas such as emergency medicine and surgery for rapid abdominal examination for trauma and other surgical conditions. The same portable ultrasound machines, with the proper probe and image parameter selection, can be used to image the heart, lungs, airway, gastric contents, abdomen, and bladder to assist in rapid diagnostic or procedural applications [252].

Transthoracic cardiac echocardiography affords excellent views, especially in infants and small children. The basic parasternal long and short axis, apical, and subxiphoid views are learned relatively easily. This modality can be extremely useful during unexpected hemodynamic deterioration to assess myocardial contractility, pericardial effusion, intracardiac air, or thrombus [253,254]. Response to therapies such as intravascular volume or resuscitation drugs can be assessed (Fig. 19.27).

Ultrasound of the airway has been utilized to confirm endotracheal intubation in children and neonates, and also to determine the position of the tip of the endotracheal tube in the mid trachea [255–258] (Fig. 19.28). In a recent meta-analysis of nine pediatric studies for a total of 460 ultrasounds for tracheal intubation, ultrasound had a sensitivity of 0.92–1.0 for confirming successful intubation, with a specificity of 1.0. Lung ultrasound to assess pleural sliding to confirm intubation had a sensitivity and specificity of 1.0. Tracheal tube depth assessment by visualizing the tip of the ETT had a sensitivity of 0.91–1.0, with specificity of 0.5–1.0 [258].

Ultrasound of the lung can be used to diagnose lung consolidation, pleural effusion, pneumothorax, and pulmonary edema (Fig. 19.29). A recent randomized controlled trial of 122 pediatric cardiac surgery patients utilized periodic lung ultrasound to guide recruitment maneuvers in intubated patients [259]. The incidence of postoperative desaturation was lower (27% versus 64%, $p < 0.001$), as was the duration of postoperative ventilation (26 versus 38 h, $p = 0.048$), in the intervention group.

Ultrasound of gastric contents can be utilized to assess the volume and composition of gastric contents (Fig. 19.30). In a study of 143 children undergoing non-elective surgery, 90% of

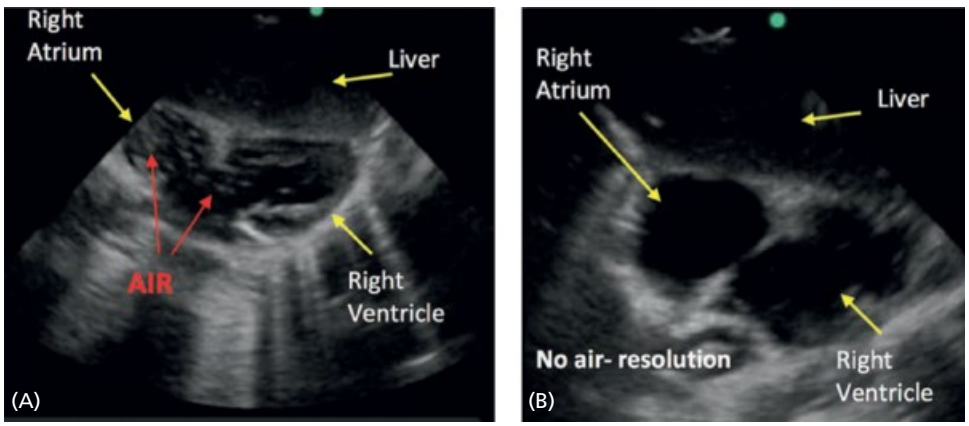

Figure 19.27 Intracardiac air embolus diagnosed by portable transthoracic echocardiography in a patient with hypoplastic left heart syndrome in the cardiac catheterization laboratory. (A) Subxiphoid view of systemic right ventricle and common atrium with intracardiac air (*red arrows*). (B) Resolution of intracardiac air. *Source:* Reproduced from Adler [253] with permission of Wolters Kluwer.

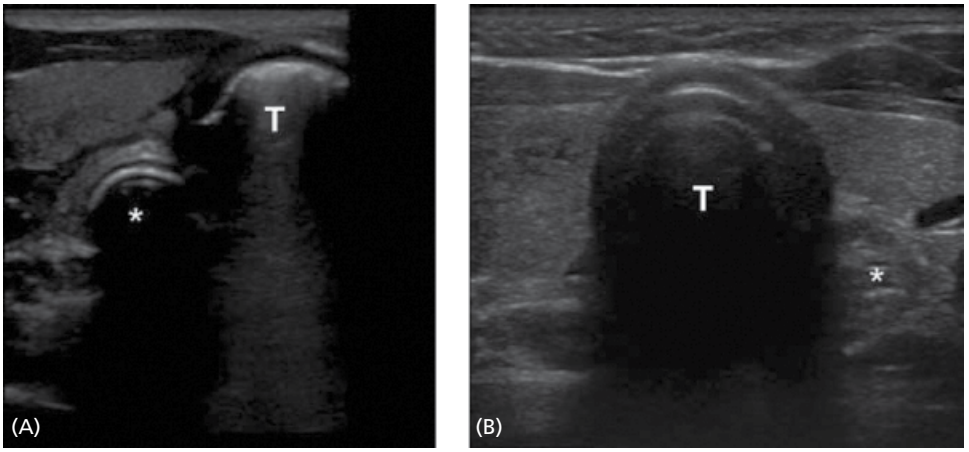

Figure 19.28 Ultrasound images of endotracheal tube placement. (A) Esophageal intubation. (B) Empty esophagus, tracheal intubation. T indicates trachea and * indicates esophagus. *Source:* Reproduced from Lin et al [258] with permission of Wolters Kluwer.

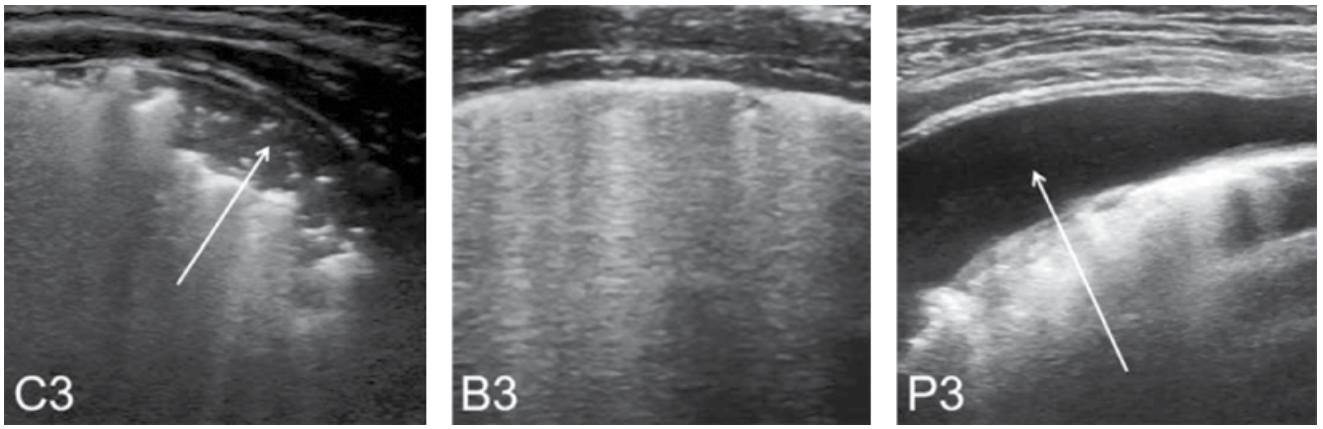

Figure 19.29 Lung ultrasound images in pediatric cardiac surgery patients. Chest wall is at the top of each image. (*Left (C3)*) Severe lung consolidation (*arrow*). (*Middle (B3)*) Severe pulmonary edema indicated by white lung appearance. (*Right (P3)*) Large pleural effusion indicated by echo-free black space (*arrow*). *Source:* Reproduced from Song et al [259] with permission of Wolters Kluwer.

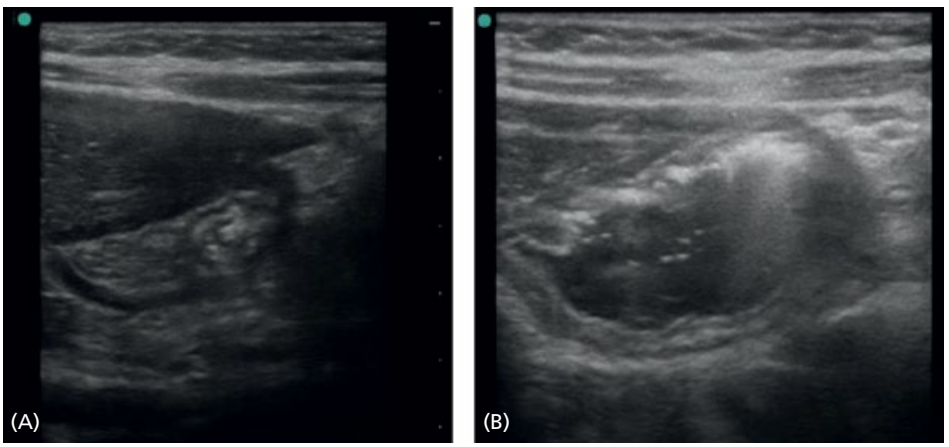

Figure 19.30 Gastric ultrasound to assess fluid presence and content. (A) Empty collapsed gastric antrum. (B) Full gastric antrum with mostly anechoic fluid content. *Source:* Reproduced from Gagey et al [260] with permission of Elsevier.

children had ultrasound images that were interpretable [260]. Using a 0 –2 grading scale for fluid or solids in the gastric antrum, 7% of children with grade 0 antrum (no contents), 65% with grade 1 (fluid in one view), and 95% with grade 2 (fluid in two views, or solid material) had gastric volumes above the 0.8 mL/kg threshold for increased aspiration risk. Gastric ultrasound led to a change in induction plan (i.e. rapid sequence or not) in 51% of patients.

CASE STUDY

A 3-year-old, 14.2 kg, 95 cm tall boy presented for major resection of stage IV Wilms tumor with inferior vena cava (IVC) extension [261]. He presented 3 months before the scheduled surgery with significant right-sided abdominal distension and pain. He did not have any other medical problems, and did not exhibit the phenotype of any genetic syndrome. Initial imaging with MRI revealed a unilateral large renal tumor with renal vein and IVC extension to just below the right atrium. Fine needle aspiration with computed tomography guidance revealed Wilms tumor with favorable histology. There were no intracardiac masses, but there were eight pulmonary nodules. Because of the IVC extension near the right atrium, preoperative chemotherapy with vincristine, actinomycin D, and doxorubicin was initiated. Long-term central venous access (Port-a-Cath®) was placed via the left subclavian vein 1 week after diagnosis. Echocardiography the day before surgery revealed normal cardiac anatomy and function, without intracardiac shunting, masses, or valvular disease. Tumor mass could be seen in the IVC just below the right atrium. Chest radiograph was clear. Vital signs were: blood pressure 120/85 mmHg, pulse 125 bpm, respiration 28/min, temperature 36.5°C, SpO_2 98% on room air. Preoperative laboratory studies included normal electrolytes, blood urea nitrogen (BUN) 16 mg/dL, creatinine 0.6 mg/dL, hemoglobin 10.5 g/dL, white blood cell count 7500/mm^3, platelet count 156,000/mm^3, and normal prothrombin and partial thromboplastin times, international normalized ratio (INR), and liver function tests.

A combined surgical procedure with cardiac and general surgeons was planned, via a right thoracoabdominal incision with CPB standby. Four units of irradiated, cytomegalovirus (CMV)-safe packed red blood cells (PRBC) were cross-matched. Because of the anticipated large blood loss and plan to leave the trachea intubated postoperatively, epidural analgesia was not used. After premedication with midazolam 2 mg IV, the patient was transported to the operating room where late generation pulse oximeter, ECG, and automated oscillometric blood pressure cuff were placed. After preoxygenation, anesthesia was induced with propofol 2 mg/kg, fentanyl 3 µg/kg, and vecuronium 0.3 mg/kg. After tracheal intubation with a 4.5 mm cuffed orotracheal tube, a 22 g right radial arterial catheter was placed. Because of the need to cross-clamp the IVC for tumor resection, a 20 g peripheral intravenous catheter (PIV) was placed in the right, and 18 g PIV in the left antecubital vein using ultrasound guidance. The patient's blood volume was estimated to be 75 mL/kg, or 1065 mL. It was decided that transfusion would be initiated at hematocrit of 25%, so allowable blood loss was calculated as 1065 mL × (32%-25%)/32% = 232 mL. Because of the anticipated large blood loss and fluid shifts, and variation in cardiac output, a continuous central venous oxygen saturation ($ScvO_2$) catheter was placed in the right internal jugular vein (IJV). Full sterile barrier precautions and ultrasound guidance were used, the IJV was entered first pass, and a 4.5 Fr double-lumen $ScvO_2$ catheter was secured at 8 cm after confirmation of guidewire placement in the vein. A pediatric transesophageal echocardiography (TEE) probe was placed to monitor for intracardiac tumor emboli, and cardiac filling and function. A 10 Fr urinary catheter and rectal temperature probe were placed, a full-body forced air warming blanket placed under the patient, and he was positioned in left lateral decubitus position. Anesthesia was maintained with isoflurane, 0.5–1.5% end-tidal concentration, and intermittent boluses of fentanyl, midazolam, and vecuronium.

The surgical plan was to perform the thoracoabdominal incision, expose the right kidney and tumor with retroperitoneal dissection, and then cross-clamp the IVC to debulk the tumor and prevent emboli. If it was not possible to cross-clamp above the tumor, a short period of CPB was planned to remove the IVC and right atrial tumor. The IVC was cross-clamped successfully with retraction of the right lung, after intravascular volume loading with 15 mL/kg 5% albumin resulting in an increase of central venous pressure (CVP) from 5 to 10 mmHg. A large decrease in venous return, accompanied by decrease of CVP to 3 mmHg, decreased blood pressure to 55/35 mmHg, and increase in heart rate to 135 bpm with a decrease in $ScvO_2$ from 74% baseline (calibrated with a measured oxygen saturation drawn from the CVP catheter) to 44% ensued. The end-tidal CO_2 also decreased from 37 to 23 mmHg, reflecting decreased cardiac output and pulmonary blood flow, but TEE revealed no evidence of pulmonary embolus. During the 30 min of IVC cross-clamp, necrotic but non-friable tumor mass was resected from the IVC down as far as possible toward the renal veins. Blood loss was 350 mL during this phase, and was replaced with 2 units PRBC, with an additional 6 units ordered at that time. Intermittent boluses of calcium chloride ($CaCl_2$), 10 mg/kg, and a low-dose epinephrine infusion of 0.03 µg/kg/min were used during this period to augment cardiac output and vascular tone, because of the intermittent hypotension and decrease in $ScvO_2$ to 40–50% range. After de-airing, and repair of the IVC incision, the cross-clamp was released and the patient suffered a period of bradycardia to a heart rate of 50 bpm, hypotension to 45/25 mmHg, arterial desaturation to 88%, and decreased $ScvO_2$ to 30%. This responded to two 10 µg/kg boluses of epinephrine, sodium bicarbonate 2 meq/kg, intravascular volume infusion with 5% albumin 10 mL/kg, additional $CaCl_2$, and hyperventilation. Using a point-of-care system in the operating room, arterial blood gases after cross-clamp removal and resuscitation revealed a pH of 7.25, $PaCO_2$ of 34 mmHg, PaO_2 of 250 mmHg, base deficit of -13, and lactate of 8.5 mmol/L, with hematocrit of 32%. End-tidal CO_2 had been as low as 18 mmHg, and returned to 32 mmHg after the period of cross-clamp. TEE revealed no tumor emboli during this period, but depressed biventricular function after removal of the cross-clamp. After additional sodium bicarbonate and increasing epinephrine to 0.05 µg/kg/min, biventricular function normalized.

The resection of kidney and tumor, retroperitoneal lymph node dissection, and removal of tumor from renal veins and the remainder of the IVC required 6 additional hours of surgery. Hourly values of vital signs, blood gas values, hematocrit, blood loss, and $ScvO_2$ are listed in Table 19.7. Urine output became bloody 2 h into the resection, and was maintained at 2 mL/kg/h with intravascular volume infusions without adding diuretics. Temperature was maintained at 35.5–36.5°C throughout the case with a forced air warming blanket set at 38°C, warmed intravenous fluids, colloids, and blood, with the fluid warmer set at 41°C, and room temperature warmed to 25°C, as well as the use of a condenser humidifier. A tissue factor-activated thromboelastogram (TEG) was sent 4 h into the case and with turnaround time of 20 min revealed a significant coagulopathy with prolonged r and K times, reduced α angle, and reduced maximum amplitude. This occurred after a total blood loss of 1000 mL, and resulted in infusion of half a pheresis unit of platelets (equivalent to three random single units), one unit of fresh frozen plasma (FFP), and two units of cryoprecipitate to treat the thrombocytopenia, hypofibrinogenemia, and depleted coagulation factors indicated by the severely abnormal TEG. Five hours into the resection the serum K+ level was 6.3 mmol/L, presumably secondary to transfusion of the 12 units of PRBC to that time. As serum glucose was 288 mg/dL at the time, the hyperkalemia was treated with regular insulin three units, 25% dextrose 0.5 mL/kg, $CaCl_2$, and sodium bicarbonate, and by the next hour K+ was 4.4 mmol/L. At the end of the case total blood loss was estimated to be 3250 mL, and the patient received 14 units PRBC, four units FFP, 8 units cryoprecipitate, and two full pheresis units of platelets. Additional fluids were 300 mL of 5% albumin and 100 mL Plasmalyte®. Urine output total was 250 mL. Total fentanyl dose was 150 μg/kg. TEE during the case revealed no evidence of air or tumor embolus, variable biventricular function and filling, but by the end of the case hemostasis had been achieved, cardiac function was normal, and epinephrine weaned to 0.02 μg/kg/min. The patient was transported with his trachea intubated to the pediatric intensive care unit after loading with 0.3 mg/kg of morphine, and additional midazolam. He was extubated 48 h later, and made an excellent recovery without significant end-organ dysfunction and with intact neurological status.

The case illustrates the use of continuous hemodynamic monitoring, including $ScvO_2$, to instantaneously guide treatment during a major tumor resection with wide hemodynamic swings due to massive blood loss, cross-clamping the IVC, and impendence of venous return during IVC compression. In addition, TEE was used to rule out tumor emboli. Hourly rapid point-of-care testing of arterial blood gases, electrolytes, hematocrit, glucose, lactate, and ionized calcium, as well as rapid TEG, was used to direct therapy to restore intravascular volume, cardiac output and oxygen delivery, and the coagulation system. End-organ injury was prevented by effective management guided by intensive monitoring.

Table 19.7 Hourly intraoperative values for Wilms tumor case study

Hour	1	2	3	4	5	6	7
BP (mmHg)	92/52	76/40	82/40	72/32	76/36	66/37	78/47
HR (bpm)	105	135	125	138	139	142	119
pH	7.36	7.25	7.32	7.30	7.28	7.26	7.34
$PaCO_2$ (mmHg)	36	34	35	38	36	37	38
PaO_2 (mmHg)	356	250	345	326	237	178	192
BE (calculated mmol/L)	–4	–13	–6	–6	–9	–11	–5
Hct%	32	32	26	28	30	31	34
$ScvO_2$%	74%	68%	57%	59%	60%	64%	69%
Ca^{2+} (mmol/L)	1.15	1.02	0.98	1.05	1.11	1.03	1.13
Glucose (mg/dL)	115	187	197	235	288	125	110
K+ (mmol/L)	4.2	4.6	4.9	5.2	6.3	4.4	4.5
Lactate (mmol/L)	1.8	8.5	8.6	9.0	8.8	8.4	7.6

BE, base excess; BP, blood pressure; Ca^{2+}, serum ionized calcium; Hct%, percentage hematocrit; HR, heart rate; K+, serum ionized potassium; $ScvO_2$, central venous oxygen saturation in superior vena cava.

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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Video clips

This chapter contains the following video clips:

Video clip 19.1 Ultrasound-guided internal jugular vein catheterization

Video clip 19.2 Doppler-assisted femoral vein catheterization.

Video clip 19.3 Radial artery catheterization.

They can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

CHAPTER 20
Pediatric Regional Anesthesia

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Introduction

Pediatric regional anesthesia has attained widespread use internationally because of its efficacy and safety; its use is supported by the existence of extensive data from the international literature underlining the safety and efficacy of this technique [1–4]. Recently the European Society of Regional Anaesthesia and Pain Therapy and the American Society of Regional Anesthesia and Pain Medicine have jointly published a practice advisory on controversial topics and on recommendations on dosage of local anesthetics and adjuvants in pediatric regional anesthesia [5,6]. Safer drugs and dedicated pediatric tools are the keys to success. This is so despite the fact that general anesthesia is necessary in most children for the regional block to be performed easily, safely, and effectively [5]. Indeed, the benefit to risk ratio is excellent, especially for peripheral blocks, even when beginners perform these blocks. Use of ultrasonography has improved the safety of pediatric regional anesthesia [7,8]. All the regional blocks require thorough knowledge of the sonoanatomy and anatomical landmarks, and specialists in pediatric anesthesiology should supervise trainees closely in order to prevent repeated errors [9]. Despite the well-known benefits of regional anesthetic techniques, clinical failures can occur during their application. Ultrasound guidance has been shown to improve block characteristics, resulting in shorter block performance time, higher success rates, shorter onset, longer block duration, reduction in volume of local anesthetic agents required, and better visibility of neuraxial structures and spread of local anesthetic.

Embryology and developmental physiology of the peripheral nervous system and age

The nervous system and the spinal cord are not fully developed at birth, and several morphological particularities must be considered. There are some differences in the anatomy of the spinal cord meninges between a neonate and an adult. During the embryonic period, the spinal cord fills the spinal canal, but from the fetal period onward, the growth of the spinal canal exceeds that of neural structures; consequently, the caudal end of the spinal cord and the dural sac occur at progressively higher levels. The tip of the spinal cord is at L3 at birth and L1–2 at 1 year. In the same way, the meninges are at S3 at birth and S4–5 at 1 year. In addition, infants and children weighing less than 15 kg have a relatively high

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

volume of cerebrospinal fluid (CSF), 4 mL/kg bodyweight, compared with adult values of 2 mL/kg bodyweight. The contents of the epidural space in infants differ from those in adults. Instead of having mature, densely packed fat lobules, divided by fibrous strands, infants have spongy, gelatinous lobules with distinct spaces permitting the wide longitudinal spread of injected solutions.

The spine undergoes significant morphological and structural change throughout childhood and adolescence. At birth, it displays a simple regular flexure throughout, so that any epidural needle with the same orientation can be inserted in any given intervertebral space. With the development of the cervical flexure in the sitting position, i.e. head position sustained upright, and subsequently that of the lumbar lordosis with the development of standing and walking, the orientation of the epidural needle must be modified accordingly. During infancy and early childhood, the vertebrae remain cartilaginous; ossification of the vertebrae is a progressive phenomenon. The ossification nucleus can be damaged by improper epidural block technique. Due to the late osseous fusion of the sacrum, intervertebral epidural approaches can be performed at all sacral levels throughout childhood.

Myelination begins in cervical neuromeres during the fetal period and continues downward and upward until the 12th year of life [10]. In an infant, the fiber diameter is smaller, the myelin sheath thinner, and the internodal distance smaller, so a lower concentration of local anesthetic is needed to achieve the nerve block and to avoid toxic effects. Furthermore, the relative resistance to epidural blockade of the L5–S1 nerve roots observed in adults does not occur in pediatric patients because of the smaller diameter of nerve fibers. The local distribution is excellent due also to the fact that nerve envelopes are loosely attached to underlying nerve structures, which favors the spread of local anesthetics along the nerves and the roots.

There are important differences between infants, small children, and adults in the physiological effects of central blocks. It is a constant finding that the incidence of clinically significant hypotension and bradycardia following spinal or epidural anesthesia is lower than in adult patients [11]. Blood pressure and cardiac index are not modified by the block despite the absence of prior intravenous volume loading and the high level of sympathetic blockade [12]. There is less vasodilatation in infants than in older children and adults, and infants respond to high thoracic sympathetic blockade by reflex withdrawal of vagal parasympathetic tone to the heart [13].

Local anesthetics and toxicity

Amide local anesthetics used for regional anesthesia in pediatric patients are potent sodium channel blockers, and thereby they block impulse conduction in axons. Local anesthetics (LAs) have other actions that may contribute both to local and systemic toxicities and to beneficial systemic actions on inflammatory responses [10] or chronic pain conditions. Amide local anesthetics are potent sodium channel blockers with marked stereospecificity, which consistently influences their action, especially their toxic action on the heart. At toxic concentrations, they induce severe arrhythmias with the potential for cardiac arrest.

The primary local anesthetic agents used in pediatric regional techniques are 2-chloroprocaine, lidocaine, bupivacaine, ropivacaine, mepivacaine, and tetracaine. The pharmacology of local anesthetics in children is similar to that in adults [14]. Nonetheless, volumes of distribution of local anesthetics in neonates and infants are larger compared to adults, thus preventing high serum drug concentrations from occurring after a single injection. The larger volume of distribution of local anesthetics in children reduces peak plasma concentrations after a single bolus dose. However, due to the longer elimination half-life, the risk of drug accumulation after a continuous infusion or several injections is increased. The volume of distribution of ropivacaine is smaller than that of bupivacaine in adults and probably in children. 2-Chloroprocaine 2% or 3% has a short time to onset of action and a short duration of action. Lidocaine 0.5–2% has a short time to onset and medium duration of action. It can be used for peripheral blocks or epidural anesthesia. Bupivacaine 0.1–0.5% has a longer onset time and duration of action than lidocaine or 2-chloroprocaine but has a greater potential for severe cardiotoxicity than other agents. It can be used for peripheral blocks, spinal anesthesia, and caudal or epidural anesthesia and analgesia. Tetracaine 1% is used for spinal anesthesia. Mepivacaine is approximately equally potent to lidocaine and can safely be used for peripheral nerve blocks. Mepivacaine can provide a rapid onset of block, with a shorter duration of motor block that may allow for rapid recovery in the postoperative period. Ropivacaine 0.2–1% and levobupivacaine 0.25 –0.5% may replace the racemic mixture of bupivacaine because of their decreased potential for central nervous system toxicity and cardiotoxicity. Ropivacaine differs from bupivacaine in various aspects: it is a pure S-enantiomer and its lipid solubility is markedly lower; these characteristics can significantly improve the safety profile of ropivacaine. Levobupivacaine, the S-enantiomer of racemic bupivacaine, is less cardiotoxic while showing similar local anesthetic properties and the potency of racemic bupivacaine. Indeed, several cases of central nervous system toxicity have been reported after inadvertent intravascular administration of ropivacaine or levobupivacaine in adults, but only some cases of cardiovascular toxicity have been reported to date [15,16]. The outcome of these inadvertent intravascular administrations was favorable, even in a neonate [17].

Pharmacokinetic factors

When injected into the body, the pure isomers do not undergo interconversion, meaning they do not transform into the usual racemic compounds.

LAs bind to blood components – erythrocytes and serum proteins such as α1-acid glycoprotein (AAG) and albumin [14]. These different buffer systems have different levels of importance; AAG is by far the most important because it is specific. The red blood cells play a lesser role in sequestration of LA, with only 15–22% of bupivacaine molecules bound in erythrocytes at varying total concentrations of the LA [18]. This buffer system may become important when the LA blood concentration is very high beyond toxic concentrations and with anemia (red blood cells bind less than 15% of molecules

of LA when the hematocrit is <30%). Binding of amide LA to serum proteins is more important. Like all weak bases, amides are mainly bound to AAG and serum albumin [14]. AAG concentration is 50–80 times lower in plasma than is albumin, particularly in infants. The determination of serum albumin LA binding is characterized by a low affinity but a high capacity, while the affinity of binding to AAG is high but the capacity is low.

AAG is the main serum protein involved in the binding of LA. Because AAG is a major acute-phase protein, its concentration rapidly increases when inflammatory processes develop, particularly during the first 6 h of the postoperative period [19]. In addition, the affinity of LA increases with the inflammatory processes; acidosis decreases this affinity. Neonates and infants have a lower AAG concentration in serum compared to adults [20], therefore their free fraction of LA is increased accordingly (Fig. 20.1). This has important clinical implications since, at least at a steady state, the toxic effects of LAs are directly related to the free (unbound) drug concentration. In summary, there are no differences in protein binding between R- and S-enantiomers of bupivacaine, at least when the concentrations, even toxic, are observed in clinical practice [21].

After passing through the bloodstream, the amide LAs are excreted by the liver. This phase involves the cytochrome P450. The clearance of bupivacaine, like that of ropivacaine and levobupivacaine, ranges from 3 to 6 mL/kg/min. The renal clearance is low, therefore the main metabolism of these agents is hepatic metabolism. Local anesthetics are metabolized by cytochrome P450 (CYP). The main CYP isoforms involved are CYP3A4 for lidocaine and bupivacaine [22] and CYP1A2 for ropivacaine [23]. CYP3A4 is not mature at birth but is partly replaced by CYP3A7 [24]. At 1 month of age, the intrinsic clearance of bupivacaine is only one-third of that in adults, and two-thirds at 6 months. CYP1A2 is not fully mature before the age of 3 years. Indeed, the clearance of ropivacaine does not reach its maximum before the age of 8 years [25]. However, at birth this clearance is not as low as expected [26], even with levobupivacaine [27], and ropivacaine and levobupivacaine may be used even in younger patients. Finally, the S- and R-enantiomers of LA kinetics are very similar, and the slight differences that have been described do not have any clinical consequences.

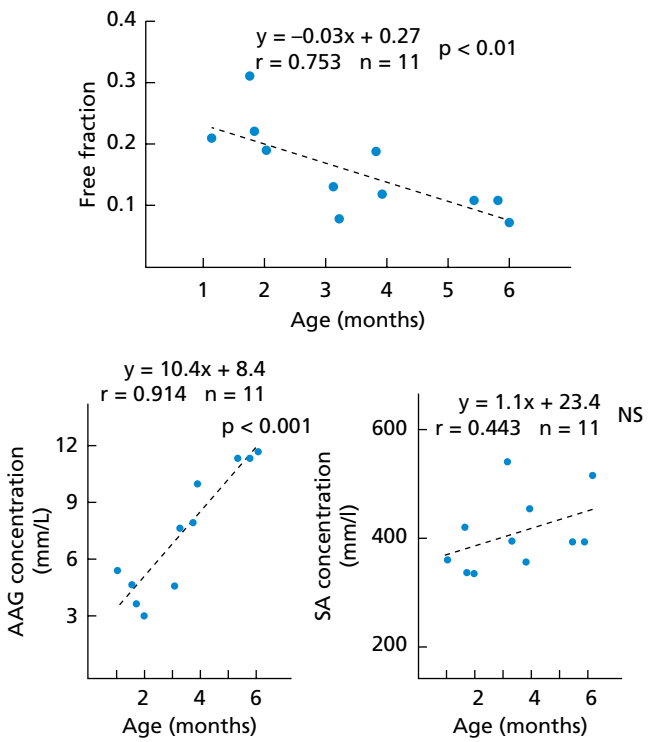


Figure 20.1 The major proteins involved in binding and the relationship between their concentrations and age (AAG, α1-acid glycoprotein; SA, serum albumin) (*bottom panel*), and the relationship between free fraction of bupivacaine in serum and age (*top panel*). The free fraction is increased until at least 6 months of life. *Source*: Reproduced from Mazoit et al [14] with permission of Wolters Kluwer.

Pharmacodynamic factors

The R- and S-enantiomers of a LA molecule have different pharmacodynamic effects on the myocardium and the nerve. The physiology of nerve activity is the summation of numerous complex events and interactions. A simple explanation is that in most cases modulation of impulse frequency and not modulation of amplitude is more important in blocking function of the nerve. Upon the basic background activity is imposed an added impulse, for example a painful stimulus. The effects of LAs can be improved when the signal they are trying to block increases in frequency. Thus, in addition to the basic block (tonic block), there is added a nerve blockade (phasic block) whose intensity will increase with the frequency of discharge of the nerve, or the heart rate in the case of myocardial toxicity. Purkinje fibers of the myocardium are more sensitive to the blockade of sodium channels by LA than other fibers or myocytes. While heart rate is rather slow (between 40 and 200 beats/min), the frequency of nerve impulses is much faster. Therefore, the nerves, when stimulated, are immediately blocked due to this high frequency of baseline activity, while the intensity of heart block increases with tachycardia. This is the physiological explanation for the preferential nerve block, well before any cardiac toxicity. The S-enantiomers are unique in that they cause phasic blocks smaller than the R-enantiomers (and therefore than the racemic mixtures). In the nerve, this difference is small because sodium channels involved at this level are minimally sensitive to the phasic block, because baseline frequency of nerve discharge is already rapid. In the heart the difference is more important [28,29]. When the heart rate increases, the S-enantiomers increase the block of the sodium channels they generate much more slowly than the racemic mixtures (the difference between ropivacaine and levobupivacaine remains the same, equal to the difference in power level of the nerve) [28] (Fig. 20.2). However, although there is no intrinsic difference between newborn and adult animals, phasic block (the one that increases with frequency) plays a very important role (Fig. 20.3) [30] and we can well imagine that an infant, whose heart beats at 150 beats/min, is significantly more sensitive than an adult, whose heart beats at 75 beats/min. In addition, elevated cardiac output in children tends to accelerate the vascular absorption of drugs from tissue, producing higher initial plasma concentrations and decreased duration of action.

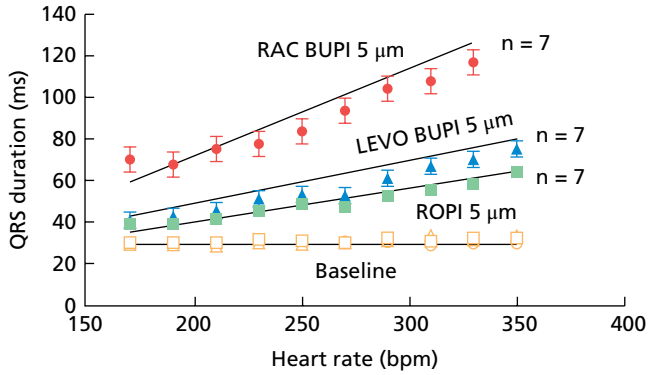


Figure 20.2 Rate dependence of QRS widening. QRS duration was measured at varying frequencies on isolated rabbit heart with racemic bupivacaine (RAC BUPI), levobupivacaine (LEVO BUPI), and ropivacaine (ROPI). The faster the heart rate, the more rapidly QRS widening occurred. *Source:* Reproduced from Mazoit et al [28] with permission of Wolters Kluwer.

The S-enantiomers levobupivacaine and ropivacaine cause moderate vasoconstriction, whatever the concentration range studied.

Adjuvants

The therapeutic index of LAs in infants may be so narrow that the maximum safe infusion rates of the amides are too low to provide sole analgesia for most major surgery in the thorax and the abdomen. This would indicate a need to combine LAs with either opioids or clonidine or, more recently, dexmedetomidine (or S+ ketamine, not available in some countries) to provide safe synergistic analgesic effects while maintaining safe LA dosing, administering acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) to provide an additional systemic analgesic effect, and permitting low-dose intravenous opioids as rescue analgesics [6] (Table 20.1).

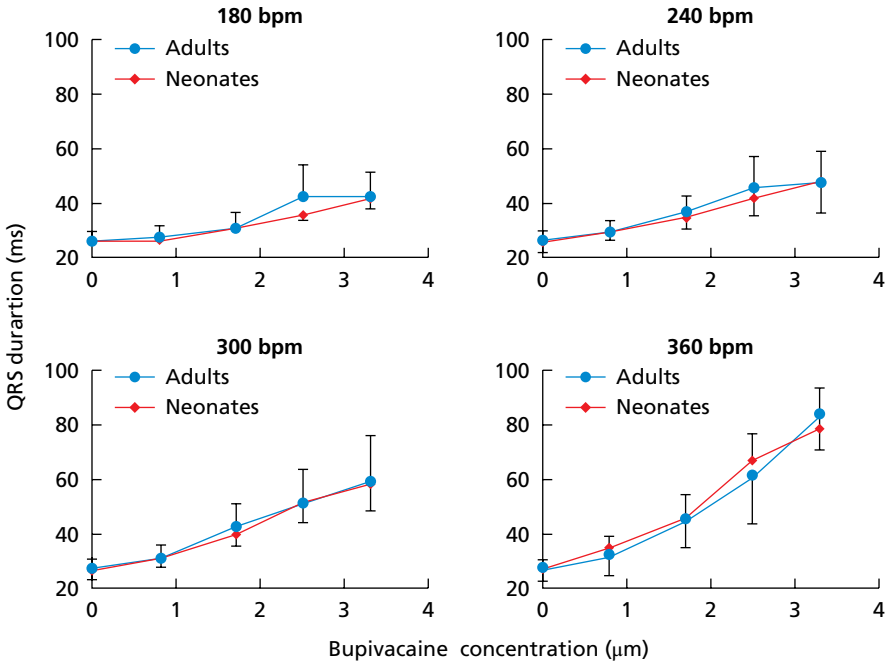


Figure 20.3 QRS widening as a function of bupivacaine concentration in the perfusate. The block is rate dependent, but no difference was found between adult and newborn rabbits. *Source:* Reproduced from Simon et al [30] with permission of Wolters Kluwer.

Table 20.1 Adjuvants to local anesthetics for regional anesthesia in children

Adjuvant	Route	Dose	Comments
Morphine	Epidural (C, L, T) single shot	30–50 µg/kg	
	Intrathecal	0.01–0.02 µg/kg	
Fentanyl	Epidural (L, T) single shot	1–2 µg/kg	
	Epidural continuous	0.2 µg/kg/h	
Sufentanil	Epidural (C, L, T) single shot	0.5–0.75 µg/kg	
	Epidural continuous	0.1 µg/kg/h	
Clonidine	Epidural (C, L, T) single shot	1–2 µg/kg	
	Epidural continuous	0.08–0.12 µg/kg/h	
	Intrathecal	1 µg/kg	
	Peripheral nerve blocks	1–2 µg/kg	
Dexmedetomidine	Epidural (C)	1–2 µg/kg	
	Peripheral nerve block	0.3 µg/kg	
Ketamine	Epidural (C, L, T) single shot	0.25–0.5 mg	S-ketamine is active isomer; do not administer intrathecally because of spinal cord apoptosis

C, caudal, L; lumbar; T, thoracic. See text for further details.

Intrathecal and epidural opioids were first administered to human subjects in 1979 [31], and since that time they have been proven to provide effective and prolonged analgesia. The presence of high concentrations of opioid receptors in the spinal cord makes it possible to achieve analgesia with small doses of morphine administered in either the intrathecal or epidural space. Intrathecal and epidural morphine produce more profound and prolonged analgesia than comparable morphine doses administered parenterally, and are capable of relieving both visceral and somatic pain. The use of morphine by the epidural route, either caudal [32] or lumbar [33], gives prolonged analgesia (more than 12 h with a single injection of morphine) following abdominal, thoracic, and cardiac surgery, and allows respiratory physiotherapy without pain. In addition, intrathecal morphine injection has been used to obtain postoperative analgesia following cardiac surgery or spinal fusion. A systematic review of post-thoracotomy analgesia concluded that a thoracic epidural infusion of LA with an opioid provided the most consistently effective analgesia [33]. The usual doses of epidural morphine range from 30 to 50 μg/kg. For single doses of epidural fentanyl, the dose range is 1–2 μg/kg, and for sufentanil 0.5–0.75 μg/kg. The dose for intrathecal morphine is 0.01–0.02 μg /kg. Continuous epidural infusion of LA can be combined with fentanyl 0.2 μg/kg/h or sufentanil 0.1 μg/kg/h. This improvement in analgesia has to be balanced against the high incidence of undesirable side-effects, which include respiratory depression (which may occur several hours after initial administration), nausea, vomiting, pruritus, and urinary retention [34]. Nalbuphine when administered for treatment of side-effects after epidural morphine is better than naloxone to treat pruritus and vomiting/nausea [35]. For peripheral nerve blocks, there was little evidence for any analgesic benefit of using opioid analgesics in brachial plexus block over systemic administration.

Clonidine acts at the dorsal horn level, reducing the release of substance P. It gives an antinociceptive potentiation, prolonging the analgesic effect of bupivacaine or mepivacaine. The sedation provided by epidural clonidine, due to an action at the locus coeruleus level, is dose dependent: sedation does not occur with a dose of 1 μg/kg or less, it is only apparent with a dose of 2 μg/kg or more. Usually, it is not considered a drawback for the pediatric patient (the child is both pain-free and quiet) and children are easily aroused. No side-effects have been described: no respiratory depression or hypotension (only with 5 μg/kg is there moderate hypotension). For continuous epidural infusion, clonidine doses lower than 0.08 μg/kg/h were not associated with any measurable effect, whereas doses of 0.08 μg/kg/h or greater produced both clinically and statistically significant improvements in postoperative analgesia [36]. Because a dose of 0.12 μg/kg/h was sufficient to provide excellent analgesia, higher doses may not be advisable as there is excessive sedation with no increase in analgesia. Dexmedetomidine has recently been shown to have positive effects as an adjuvant both for caudal and peripheral nerve blocks in children [37,38]. This drug does also seem to be associated with acceptable safety features and may, thus, be a new interesting alternative in this setting.

Ketamine is a potent anesthetic whose action occurs through the antagonism of N-methyl-D-aspartate receptors, present also at the spinal level and involved in pain modulation. Older studies were performed using the preservative-containing formula in adults and in children. Newer studies performed with preservative-free ketamine, both the racemic and the isomeric drug, show that a dose of S-ketamine ranging between 0.25 and 0.5 mg/kg is optimal for prolonging the pain relief provided by LA [39]. However, ketamine has been found to cause increased apoptosis when it is spinally administered [40].

Dexamethasone can be used in the context of postoperative analgesia. Indeed, the administration of systemic dexamethasone in the setting of a long-acting LA solution prolongs the analgesic duration of a single-injection caudal block compared with long-acting local anesthetic [41]. No safety data exist to add dexamethasone to perineural LAs.

The addition of bicarbonate reduces the pain on injection [42]. It alters the pKa of the solution, making the local anesthetic available in the active cationic form. See Chapter 37 for further discussion of pain management.

KEY POINTS: EVIDENCE-BASED CONCLUSIONS AND CLINICAL ADVICE FROM THE ESRA–ASRA JOINT COMMITTEE PRACTICE ADVISORY ON RECOMMENDATIONS ON LOCAL ANESTHETICS AND ADJUVANTS DOSAGE IN PEDIATRIC REGIONAL ANESTHESIA [6]

- Clonidine or morphine can be used to prolong the duration of spinal blockade
- Racemic ketamine and S-ketamine have been used as a neuraxial adjunct. Nevertheless, ketamine is not recommended for intrathecal use due to possible apoptosis in the spinal cord
- Dexmedetomidine prolongs postoperative analgesia when used as an adjunct to caudal blocks
- Synthetic opioids do not produce any relevant effect when used as adjuvants to caudal blocks in children. Fentanyl does not potentiate the effect of either bupivacaine or ropivacaine in caudal blockade
- Dexamethasone is not recommended as a neuraxial adjuvant in children
- α_2-adrenoceptor agonists can prolong the duration of peripheral nerve blocks in children

Systemic toxicity

Reports in humans suggest that lipid emulsion (Intralipid®) is an effective therapy for cardiac toxicity from high systemic concentrations of ropivacaine and bupivacaine, even in patients for whom conventional resuscitation is ineffective [43]. The solubility of long-acting LAs in lipid emulsions and the high capacity of binding of these emulsions most probably explain their clinical efficacy in case of toxicity. The long-chain triglyceride emulsion Intralipid appears to be about 2.5 times more efficacious than the 50/50 medium-chain/long-chain Medialipide® emulsion [44]. No data exist

in pediatrics except for a recent case in which a 20% lipid infusion was used to successfully treat a ventricular arrhythmia after a ropivacaine and lidocaine injection in a psoas compartment block in a healthy 13-year-old child was administered [45]. Indeed, a bolus of 1.5 mL/kg and then an infusion of 0.5–1 mL/kg/min of Intralipid in combination with usual resuscitation should be useful to treat LA cardiac toxicity in children.

Lipid rescue is preferably administered via a central venous catheter, but in its absence peripheral veins can also be used. A 20% lipid emulsion bolus over 1 min is recommended with an initial dose of 1.5 mL/kg, immediately followed by 10–20 μmcg/kg atropine and small boluses of 10 μg/kg epinephrine in order to limit the increase in heart rate which is deleterious as discussed previously [28]. Chest compressions should not be interrupted. The intralipid bolus can be repeated, with a maximum of 4 mL/kg/min. The lipid infusion is to be maintained at a rate of 0.5 mL/kg/min until hemodynamic recovery.

Lipid infusions act as an antidote to LA intoxication and should be readily available for emergencies, much in the way that type O-negative blood and dantrolene are now available universally. Intralipid has a low cost and a shelf-life of up to 1 year. The guidelines for the management of severe LA toxicity provide essential information and should be available in all hospitals, particularly in units where local anesthetics are administered. See Chapter 45 for further details of management of LA toxicity.

Local tissue toxicity

Skeletal muscle toxicity is a rare and uncommon side-effect of LAs, although experimental data show that intramuscular injections of these agents regularly result in calcified myonecrosis [46]. All LAs that have been examined are myotoxic: the extent of muscle damage is dose dependent and worsens with serial or continuous administration. Pathophysiologically, increased intracellular Ca^{2+} levels appear to be the most important element in myocyte injury [47]. Lipophilicity also determines the extent of Ca^{2+} release by local anesthetics, as effects of racemic bupivacaine and levobupivacaine were significantly more pronounced than those of ropivacaine isomers [48]. Consequently, a rank order of myotoxic potency (ropivacaine < bupivacaine < levobupivacaine) is suggested. The clinical impact of LA-induced myotoxicity is still controversial. Only a few case reports of myotoxic complications in adults after LA administration have been published. In particular, the occurrence of clinically relevant myopathy and myonecrosis has been described after continuous peripheral blocks; some experimental data have shown more toxicity in young animals [49], therefore particular attention must be paid with prolonged continuous infusion in infants.

Several studies have revealed that LAs might irreversibly damage chondrocytes in articular cartilage, which may contribute to cartilage degeneration [50]. Bupivacaine especially showed profound chondrotoxic effects in experimental models, and although these results cannot be directly extrapolated to the clinical setting, caution should be exercised in the intra-articular use of this agent. Ropivacaine seems to be less chondrotoxic than bupivacaine [51], whereas the chondrotoxic potency of levobupivacaine has yet to be assessed.

Blocks for infants and children

Advantages of regional anesthesia

Regional anesthesia, in combination with light general anesthesia, provides several advantages for the pediatric patient [5]. The most significant advantage, as demonstrated by several authors, is intra- and postoperative pain relief.

Regional anesthesia is also useful when general anesthesia is technically difficult or is associated with increased morbidity and mortality, such as in the case of the ex-premature infant with the risk of postanesthetic apnea [52], the child with severe chronic respiratory disease [53], or the child with myopathy [54]. Regional anesthesia may offer an alternative to general anesthesia in children with a history of malignant hyperthermia.

Compared with general anaesthesia, a central neuraxial block may reduce the 0–30-day mortality for patients undergoing surgery with intermediate to high cardiac risk [55].

Disadvantages of regional anesthesia

Regional anesthesia requires extra time to perform the block and allow it to become effective. Therefore, the use of an induction room will smooth the operating room work. If general anesthesia is needed to perform the block, an assistant can be helpful in supporting the airway and monitoring the patient during performance of the block. Critics of this combined technique suggest that one may be exposing the child to the risks and complications inherent in both. This fear, however, is more a theoretical consideration than a practical one. Indeed, the recent Pediatric Regional Anesthesia Network (PRAN) study has shown a trend of fewer complications of regional anesthesia with the practice of placing blocks in anesthetized patients. The pediatric anesthesia community should consider regional anesthesia after induction of general anesthesia a safe technique, and this should remain the prevailing standard of care [56].

Therefore, pediatric anesthesiologists now view regional anesthesia as an adjunct to general anesthesia, in much the same way that a neuromuscular blocking agent or intravenous narcotic supplements general anesthesia with a volatile agent [57].

Choice of regional anesthesia in children

Although blocks that are commonly used in adults are not always suitable for children, some regional blocks are particularly useful in children. The last Association of French Speaking Paediatric Anesthesiologists (ADARPEF) study has clearly shown a transition in practice from predominantly central blocks to an increased number of peripheral nerve blocks, including catheter techniques (Tables 20.2 and 20.3) [3]. The most common extremity blocks were axillary, both lateral and popliteal sciatic, femoral and iliofascial block. Face and trunk blocks represented the largest proportion of peripheral blocks. Trunk blocks were used significantly more often (41%). They are characterized by the emergence of techniques that were not clearly accounted for by the first ADARPEF study, i.e. (in order of decreasing frequency) ilioinguinal, paraumbilical, pudendal, and thoracic and lumbar

Table 20.2 Different regional block procedures according to patient's age: results from the first published ADARPEF study, local procedures excluded (*n* = 19,103)

Technique		0–30 days premature *n* = 149	0–30 days full term *n* = 398	1–6 mo premature *n* = 641	1–6 mo full term *n* = 2067	6 mo–3 yr *n* = 6164	3–12 yr *n* = 8114	>12 yr *n* = 1570	Total blocks	%
Neuraxial	Caudals	108	300	407	1536	4610	4978	172	12,111	63
	Other epidurals	5	38	30	176	413	1122	612	2396	13
	Spinals	30	25	188	137	50	18	58	506	3
Peripheral	Upper limbs	1	0	0	10	92	478	416	997	5
	Lower limbs	0	0	3	7	30	181	175	396	2
	Trunk, abdomen	5	35	13	201	969	1337	137	2697	14

Source: Giaufré et al [1].

Table 20.3 Different regional block procedures according to patient's age: results from the second published ADARPEF study (*n* = 31,132)

Technique		0–30 days premature *n* = 121	0–30 days full term *n* = 475	1–6 mo premature *n* = 822	1–6 mo full term *n* = 2442	6 mo–3 yr *n* = 10,499	3–12 yr *n* = 12,974	>12 yr *n* = 3799	Total blocks	%
Neuraxial	Caudals	76	189	403	955	4153	2734	41	8551	27.4
	Other epidurals	6	38	25	127	342	577	432	1547	5
	Spinals	9	9	38	40	43	60	188	387	1.3
	Other central	0	0	0	4	1	23	43	71	0.3
Peripheral	Upper limbs	1	2	5	36	454	1099	484	2081	6.7
	Lower limbs	2	12	14	62	529	1540	1665	3824	12.4
	Trunk, abdomen	22	154	288	1063	4506	6185	612	12,830	41.0
	Face, head	5	71	49	155	471	756	334	1841	5.9

Source: Ecoffey et al [3].

paravertebral blocks [1]. Facial blocks were now widely used for facial and reconstructive surgery, particularly in cleft palate repair.

This is the reverse of the PRAN study [4] (Table 20.4), which recorded more caudals than trunk blocks. Indeed, single-injection caudal blocks were the most frequently performed (44% versus 32% in the last ADARPEF study), compared to trunk blocks (19% versus 41% in the last ADARPEF study). In Europe the same trend is observed if we compare France with other countries: caudals constituted 12% in France versus 33% in Europe (22,224 general anesthetics, 19.6% with combined general/ regional anesthesia; unpublished data from APRICOT study from the European Society of Anesthesiology).

In addition, the last ADARPEF study recorded a significant number of catheter placements [3]. They were inserted for central as well as peripheral regional anesthesia, most of them being neuraxial. Indeed, neuraxial continuous epidural analgesia is one of the preferred techniques for obtaining pain relief in children (particularly postoperative pain relief in younger children). Perineural catheters have become a common practice, primarily in hip and foot surgery. Several prospective studies demonstrated the benefits of continuous peripheral nerve blockade after orthopedic procedures in children. Placement of a brachial plexus catheter for pain control is less common in children than in adults. The emergence of peripheral nerve catheter techniques allows provision of postoperative pain relief for the majority of orthopedic surgeries using regional anesthesia techniques [58,59] and to treat complex regional pain syndrome in adolescents [60]. The last ADARPEF study confirmed this emergence of peripheral catheters, mainly axillary and sciatic popliteal, and recorded slightly fewer neuraxial catheters than the United Kingdom audit, which reported 10,633 epidural catheters (about 2000 per year) [2]. These results confirmed a retrospective report from a single institution (10,929 regional anesthetics performed during a 17-year period) revealing a decrease in central neuraxial blocks [61]; continuous postoperative analgesia via perineural catheters emerged as routine practice in children in the late 1990s following both peer recommendations and evolution of devices. More recently the PRAN study also reported more neuraxial (thoracic and lumbar) catheters and lower

Table 20.4 Different regional block procedures according to patient's age: results from the PRAN study (n = 86,328)

Technique		Neonate	1–5 months	6–11 months	1–2 years	3–9 years	≥10 years	Total
Neuraxial	Caudals	520	5630	10,918	12,989	7515	544	38,316
	Other epidurals	5	37	41	69	243	459	838
	Spinals	19	201	18	41	185	1570	2034
Peripheral	Upper limbs	23	81	110	543	1675	3265	5697
	Lower limbs	4	38	89	527	3723	16,256	20,637
	Trunk, abdomen	129	1064	1109	2122	6679	4912	16,887
	Face, head	5	331	301	427	907	825	3501

Source: Walker et al [4].

extremity catheters (femoral, sciatic, and lumbar plexus) [4]. The practice of continuous pediatric peripheral regional anesthesia is different from adults due to the lack of surgery for total knee prosthesis.

Regional blockade with or without general anesthesia

Without general anesthesia

Most children do not like needles or injections. Small, frightened children are unlikely to keep still unless well sedated. Thus LA techniques alone are not usually used in children under about 8–10 years of age. After that age, a cooperative child who has had the procedure explained may tolerate a block for such procedures as suturing lacerations, reduction of a fracture, or minor procedures on the extremity. Adequate sedation and/or the presence of a reassuring parent facilitate the procedure. New methods of giving sedatives, opioids, and LAs transdermally will be of great benefit to peripheral LA techniques in the conscious child. The use of ultrasonography is helpful to perform peripheral blocks in an awake child, due to the lack of the painful elicited motor responses with the nerve stimulator technique previously used.

In addition there are concerns that anesthetic agents may have a direct toxic effect on the developing brain of preterm infants, even after reaching postmature age [62]. It is proposed that spinal anesthesia may avoid the risk of anesthetic-related neurotoxicity and possibly improve neurodevelopmental outcomes in preterm infants requiring surgery for inguinal hernia at a postmature age. However, the recent GAS study did not find a difference in neurodevelopmental outcome at age 2 years in a 722-subject multicenter randomized controlled trial of spinal versus general anesthesia [63]. Chapter 46 has an extensive discussion of anesthetic neurotoxicity.

With general anesthesia

In children, regional anesthesia is often combined with light general anesthesia, but there must be justifiable advantages to the child. Such potential advantages were summarized earlier. In addition, general anesthesia decreases central nervous system (CNS) toxicity and dysrhythmias caused by LAs [64,65]. The decision to intubate the trachea or to use a laryngeal mask airway should be based on the usual criteria, such as a full stomach, upper abdominal surgery, or the need to maintain adequate ventilation. If indicated, the trachea should be intubated before the block is begun.

Techniques for performing regional anesthesia

Patient monitoring

Monitors should be applied and functions tested before the block is performed. In particular, the electrocardiogram should be adjusted so that the P wave, QRS complex, and upright T wave can be seen clearly. Baseline systolic blood pressure and heart rates should be noted.

Skin preparation

Bacterial colonization of epidural and caudal catheters in children occurs at a rate of 6–35%. Gram-positive organisms are most common, although gram-negative colonization may also occur, particularly with caudal catheters. Children under 3 years of age are also most likely to have colonization of caudal catheters. Despite high rates of colonization, serious epidural infections are exceedingly rare. Chlorhexidine may be better than povidone–iodine for reducing the risk of catheter colonization in children [66].

Test dose

While placement of regional blocks under general anesthesia is considered standard practice in children, the search for the ideal "test dose" to reduce the risk of inadvertent intravascular injection continues. The original "test dose" described an increase in heart rate and blood pressure following intravenous (IV) administration of epinephrine 0.5 μg/kg, which is equivalent to 0.1 mL/kg IV injection of LA with epinephrine 1:200,000. In children these hemodynamic changes vary with the anesthetic agent used (halothane, sevoflurane, or isoflurane) and whether prior atropine has been administered. However, an increase in heart rate of 10 beats per minute above baseline occurring within 1 min of injection of 0.1 mL/kg of local anesthetic with 1:200,000 epinephrine is a reasonable predictor of intravascular injection for children anesthetized with sevoflurane. Monitoring the ECG changes, i.e. >25% change in T wave or ST segment changes irrespective of the lead chosen, is considered by some to be more specific and more reliable [67].

These changes have been questioned as it seems that similar changes in heart rate, blood pressure, and T wave may be seen following a painful stimulus (surgical incision). The temporal relationship is important, and a secondary drop in pulse rate detected after IV epinephrine distinguishes this from the

response seen after a painful stimulus [68]. Nonetheless, LA solution should be administered slowly over a period of at least 60–120 s, irrespective of the type of block, with repeated aspirations.

KEY POINTS: EVIDENCE-BASED CONCLUSIONS AND CLINICAL ADVICE FROM THE ESRA–ASRA JOINT COMMITTEE PRACTICE ADVISORY ON TEST DOSE [5]

- Because of the difficulty interpreting a negative test dose, test dosing should remain discretionary
- Injection of a LA solution should be performed slowly, in small aliquots, and with intermittent aspiration and observation of the ECG
- Any modification of the T wave or of the heart rate within 30–90 s after the injection of a test dose should be interpreted as an accidental IV injection until disproven
- Ultrasound may help to avoid or visualize accidental intravascular needle placement in peripheral blocks, but data are lacking in pediatric regional anesthesia to determine the value of these techniques

Sympathetic blockade

A clinically significant decrease in blood pressure related to sympathectomy from neuraxial blocks is rare in children younger than 8 years of age [11]. Volume loading before such blocks, commonly practiced in adults, is unnecessary in this age group. In older patients, the sympathetic block results in a slight (20–25%) but consistent decrease in blood pressure. Even in adolescents, however, fluids or vasopressors are rarely required to treat the hemodynamic effects of central neuraxial blocks.

More recently, the GAS study showed that spinal anesthesia reduces the incidence of hypotension and the need for intervention to treat if compared with sevoflurane anesthesia in young infants undergoing inguinal hernia repair [69].

Contraindications

Contraindications to central neuraxial blocks are few and similar to those in adults. These include coagulopathy, infection at the insertion site, true LA allergy, and abnormal superficial landmarks or lumbosacral myelomeningocele because of the risk of malposition of the cord or dural sac. Progressive neurological disease is a relative contraindication, primarily because of medico-legal concerns. The safety of central neuraxial techniques in the presence of a ventriculoperitoneal shunt has not been studied. Risks and benefits in these patients should be carefully considered on an individual basis.

Although it is rare to encounter opposition to the use of peripheral nerve blocks, certain conditions may call for a judicious avoidance of them. Relative contraindications include local infection, generalized sepsis, coagulopathy, predisposition to compartment syndrome, and parental or child dissent.

Ultrasound in regional anesthesia

A significant problem in regional anesthesia is that a large number of techniques still do not achieve a success rate of close to 100%. Indeed, the key to successful regional anesthesia has always depended on the accuracy of needle and LA placement in relation to the nerve structures to be blocked. In 1994, Kapral et al introduced ultrasound guidance into regional anesthesia [70]. About 10 years later, Marhofer et al introduced this technique into pediatric regional anesthesia practice [71]. Real-time ultrasound guidance allows the demonstration of the target, whether it is nerve, fascial plane, or anatomical space, and the monitoring of the distribution of the injected LA. Furthermore, ultrasound guidance with a high-frequency linear or hockeystick probe allows the anesthesiologist to reposition the needle in case of maldistribution of the LA. There is evidence to support ultrasound for various outcomes in pediatric regional anesthesia (Table 20.5) [72].

The possibility of visualizing the nerve structures as well as important nearby anatomical structures (e.g. vessels, pleura, and peritoneum) most likely reduces the incidence of inadvertent complications due to misplacement of the tip of the blocking needle. The reduced volume of LA needed to produce an adequate block should also reduce the risk for systemic toxicity due to rapid absorption of LAs from the injection site (Table 20.6). Indeed, using a conventional up–down technique and measuring the cross-sectional area of the ulnar nerve in the proximal part of the forearm [73] and of the sciatic nerve [74] in adults, a 95% median effective dose for an ulnar nerve block with 1% mepivacaine was estimated to be as low as 0.11 mL/mm^2 nerve, corresponding to a total volume of 0.7 mL to achieve an effective ulnar nerve block, and a 99% median effective dose to be 0.10 mL/mm^2 to achieve an effective ulnar nerve block. Thus, there is good evidence that effective peripheral nerve blocks can be achieved by using considerably smaller volumes of LAs when using ultrasound guidance.

More randomized controlled studies with significant outcomes are likely required to evaluate the potential for ultrasound compared to nerve stimulation technique to reduce complications of regional anesthesia in children. Because serious complications fortunately are very rare following peripheral nerve blockade in infants and children [1,3,4], it is unlikely that even large-scale studies will prove ultrasound guidance to be superior to other approaches with regard to the rate of complications. However, it does not seem reasonable to expect that the use of ultrasound should result in an increased rate of complications. To date, studies in adults have shown a lower incidence of IV LA injection and a trend to less nerve damage with ultrasonography compared to nerve stimulation [75,76]. Training in the use of ultrasound-guided techniques is now widespread [9], and ultrasound-guided techniques now predominate [77,78]. Indeed, the PRAN data have shown that peripheral nerve blocks are very often used for infants and children in the USA, and the use of ultrasound guidance may be driving that practice for many of these blocks [4].

Table 20.5 Statements of evidence and grades of recommendation for ultrasound guidance regional anesthesia outcomes

Evaluated outcomes	Statements of evidence	Grade of recommendation
Peripheral nerve blockade		
Reduces block performance time		
No evidence found	N/A	N/A
Hastens block onset		
Ultrasound guidance reduces onset of sensory block for upper extremity PNBs	Ib	B
Improves block success		
Ultrasound guidance does not improve block success rates in upper extremity PNBs when compared with nerve situation guidance	Ib	B
Ultrasound guidance improves the intraoperative block success for PNBs at the trunk	Ib	A
Improves block quality		
Ultrasound guidance prolongs analgesia for upper and lower extremity blocks	Ib	A
Ultrasound-guided blocks at the anterior trunk improve early postoperative pain relief for inguinal and umbilical procedures	Ib	B
Reduces local anesthetic dose		
Ultrasound guidance reduces the volume of local anesthetic required for successful perioperative analgesia in PNBs	Ib	A
Ultrasound guidance achieves sufficient intraoperative analgesia using minimal volumes (0.1 mL/kg) of local anesthetic for blocks of the nerves in the anterior trunk	Ib	B
Neuraxial anesthesia		
Clear visibility of landmarks		
Ultrasound enables sufficient visibility of the dura mater and ligamentum flavum in neonates, infants, and children	Ib	A
Good prediction of depth to LOR	III	B
Preprocedural ultrasound imaging offers a moderate prediction of the depth to LOR	III	B
Visibility of needle puncture of LOR		
Ultrasound offers visibility of a needle within the epidural space in neonates	III	B
Visibility of catheter (directly or indirectly)		
Ultrasound guidance can directly detect catheters during advancement in some young infants	III	B
Ultrasound guidance can confirm epidural catheter placement via surrogacy during injection of fluid	III	B
Reduces bone contact		
Bone contact can be reduced in most cases in infants and children using real-time ultrasound guidance	III	B

LOR, loss of resistance; N/A, not applicable; PNB, peripheral nerve block.
Source: Tsui and Pillay [72].

Table 20.6 Reduction of local anesthetic volume with ultrasound guidance

Technique	Ultrasound guidance dosages	Landmark dosages
Supraclavicular block [119]	0.3 mL/kg	0.5 mL/kg
Infraclavicular block [118]	0.2 mL/kg	0.5 mL/kg
Sciatic block [127]	0.2 mL/kg	0.3 mL/kg
Femoral block [127]	0.15 mL/kg	0.3 mL/kg
Rectus sheath block [154]	0.1 mL/kg each side	0.3 mL/kg
Ilioinguinal block [143]	0.1 mL/kg each side	0.4 mL/kg

Neuraxial blocks

Caudal block

This is the most useful pediatric central block, as it is widely applicable and technically simple. It can provide analgesia for surgery up to and including the umbilicus. This technique can be used successfully in neonatal rectal surgery [79].

Performance of a caudal block

The anesthetic agent is injected through the sacral hiatus, which is formed by failure of fusion of the fifth sacral vertebral arch. The hiatus is easily palpated in children as a triangular shaped depression bounded on either side by the sacral cornua (Figs 20.4, 20.5). Following induction of general anesthesia, the child is placed in the lateral position with the knees drawn up, the upper knee being flexed more than the lower. The best approach to the sacral hiatus is found at the apex of an equilateral triangle based on a line drawn between the two posterior superior iliac spines. A short beveled 22 ga needle is inserted at 45° to the skin. When the needle pierces the sacrococcygeal membrane and enters the sacral canal, a distinct "pop" is felt. Then the needle is advanced an additional 0.5–1 cm, depending on the child's age, on a plane parallel to the spinal axis. After aspiration to exclude bone marrow, dural puncture, or venipuncture, incremental doses of LA should be injected.

We do not recommend the use of caudal epidural catheters because of the risk of sepsis due to the proximity of the anus. Therefore, caudal block is a single-shot technique. The lumbar epidural route is preferred if reinjection is needed, or in children weighing more than 20–25 kg, to reduce the total amount of LA used. In this group of patients, we may use the lumbar epidural block as a single-shot technique. Moreover, if we want to prolong caudal block and to avoid a lumbar catheter, it is possible to use clonidine.

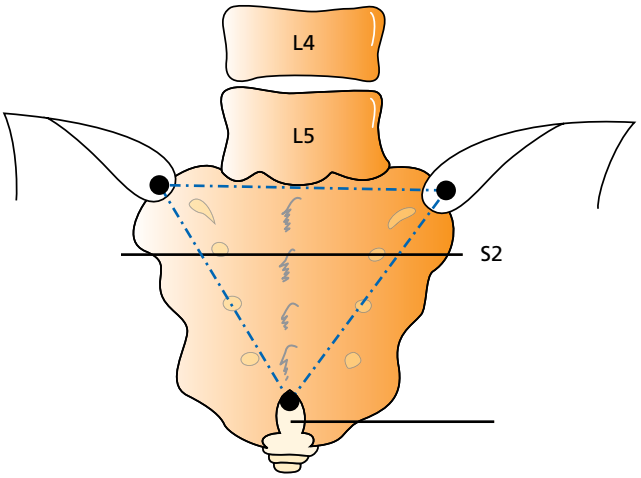


Figure 20.4 Bony landmarks for a caudal block. See text for further details.

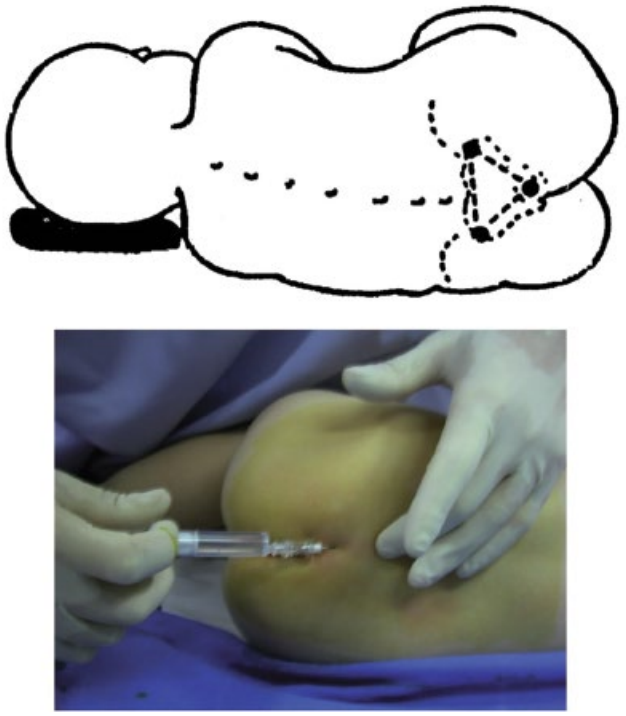


Figure 20.5 Cutaneous landmarks and needle injection for a caudal block. See text for further details.

Local anesthetic dosage

Several dosage regimens have been recommended, but the author prefers the bodyweight method. Thus, 0.25% bupivacaine 0.5 mL/kg for lumbosacral areas (i.e. orthopedic surgery of lower limb) and 1 mL/kg for the thoracolumbar area (i.e. herniorrhaphy and orchidopexy) is administered [80]. It has been shown that caudal analgesia with a larger volume of diluted ropivacaine (0.15%), i.e. 1.5 mL/kg, provides better quality and longer duration after discharge than a smaller volume of more concentrated ropivacaine [81]. However, caudal block with a high volume of LA can cause a greater increase in intracranial pressure than caudal block with a low volume of LA [82]. On the other hand, caudal block with 1 mL/kg of LA can also result in a significant increase in intracranial pressure.

Unfortunately, with ultrasound technique only a small correlation between injected volumes of LA and the cranial spread of caudally administered LAs was observed. The recent PRAN data reported a large variation in LA dose used in caudal blocks [83]. Indeed, the data suggest that approximately 25% of patients undergoing a caudal block receive a LA dose, i.e. >2 mg/kg, that has the potential to cause LA toxicity.

Use of ultrasound guidance

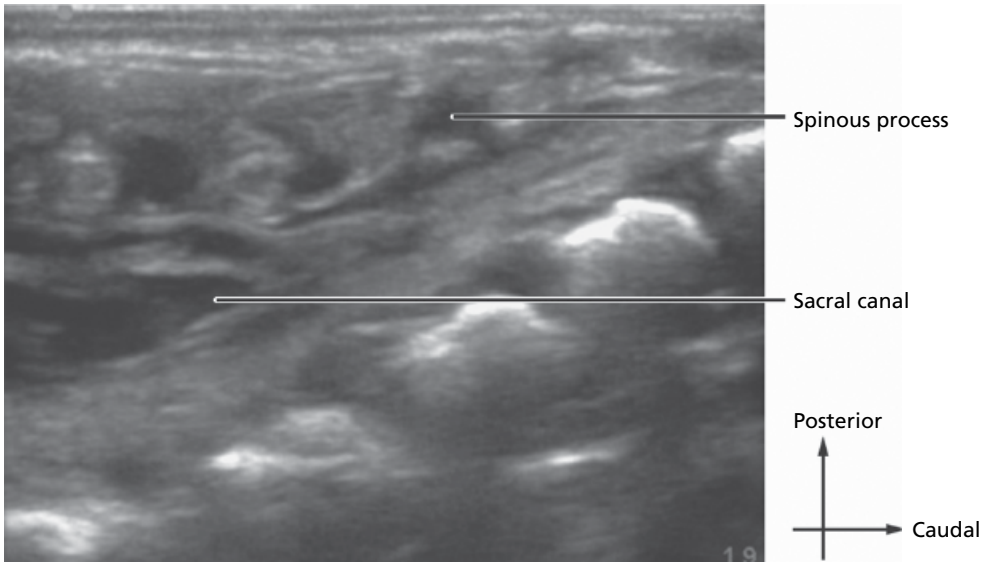
Ultrasound can be used to identify the sacral hiatus in obese children and can also be used to monitor whether the LA solution is injected in the correct anatomical location (Fig. 20.6). It is also feasible to monitor the cephalad spread of LAs within the caudal–epidural space [84]. In addition, the classic bony landmarks that comprise the vertex of an equiangular triangle formed by the inferior to posterior superior iliac spines as the location of the sacral hiatus are inaccurate in children younger than 6 years because in these patients the angle formed by the two lines connecting each posterior superior iliac spine and the real sacral hiatus is more than 60° [85]. Ultrasound may be a good alternative method of determining the location of the sacral hiatus in children with obscure anatomical structures and obesity (Fig. 20.6). However, so far there are no widely published data to support that ultrasound assistance does in fact provide any substantial benefits compared with a traditional landmark-based technique. Nonetheless, sacral hiatus injection with ultrasound-guided technique offers a reliable caudal block for pediatric inguinal hernia repair with the advantages of easier performance and fewer complications, i.e. bloody tap, compared with traditional sacral canal injection [86]. See Video clip 20.1.

Epidural block

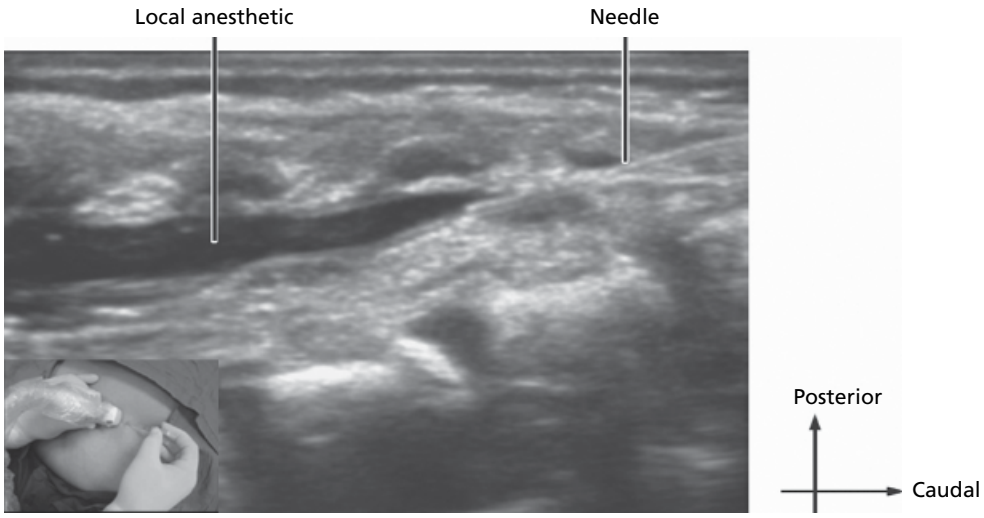
The greatest advantage of epidural block is the long-term analgesia it provides following major surgery of the chest and abdomen and some orthopedic procedures, with continuous LA injection combined with administration of opioids or clonidine [2,87,88].

Performance of an epidural block

As described previously with the caudal block, general anesthesia is first introduced. The technique of lumbar epidural anesthesia in children is similar to that in adults. The smaller the patient, the narrower the epidural space, and modifications of equipment are required if the epidural needle and catheter are to be safely placed and dural puncture avoided. The midline approach is preferred. However, the distance between the skin and epidural space depends on the age of the child. We use an 18 ga Tuohy needle (10 cm length) with a 20 ga epidural catheter in children older than 4 years and a 19 ga Tuohy needle (5 cm length) with a 21 ga epidural catheter in children younger than 4 years. The puncture is performed at the L3–4 or L4–5 interspace in order to decrease the potential risk of trauma to the spinal cord. Indeed, in infants the spinal cord may extend lower than the L2–3 interspace. The correct positioning of the Tuohy needle is ascertained by the loss-of-resistance (LOR) technique with an air-filled syringe instead of saline to avoid diluting the very small volumes of anesthetics used. Nonetheless, a patchy analgesia has been



(A)



(B)

Figure 20.6 Ultrasound imaging of the caudal region. (A) Before local anesthetic injection. (B) After local anesthetic injection. See text for further details.

reported with use of a large volume of air [89], and case reports of venous air embolism cause many pediatric anesthesiologists to prefer the saline LOR method [90].

KEY POINTS: EVIDENCE-BASED CONCLUSIONS AND CLINICAL ADVICE FROM THE ESRA–ASRA JOINT COMMITTEE PRACTICE ADVISORY ON LOSS-OF-RESISTANCE TECHNIQUE [6]

- Different experts support the use of either air LOR or saline LOR techniques
- The combination of air and saline may represent a better alternative, minimizing the risk of injecting air and reducing the volume of saline
- In neonates and infants, the volume of air should be limited to less than 1 mL and air injections should not be repeated if multiple attempts are made
- An air embolism with hemodynamic consequences is rare when air LOR is used, but air LOR should not be used in the presence of a right-to-left cardiac shunt

The catheter should be threaded with minimal resistance, and the tip should be placed as close as possible to the spinal nerves innervating the area of the surgical field, with no more than 2–4 cm of catheter inserted into the epidural space, as measured from the end of the needle. Luer lock adapters with bacteriostatic filters are connected to the free end of the catheter. Thoracic epidural analgesia may be provided for

upper abdominal and thoracic surgery, with the catheter tip placed at the level of the spinal dermatome innervating the area of the incision. After induction of general anesthesia and positioning the patient in the lateral decubitus position, the thoracic spine should be extended maximally by drawing knees to chest and flexing the cervical spine with chin to chest (paying attention to airway patency), with an assistant steadying the patient with a hand on the sternum to provide counterpressure during needle placement. Because of the more acute caudad angulation of the spinous processes of the thoracic vertebrae compared to the lumbar vertebrae, a more cephalad angulation of the epidural needle is required to pass between the spinous processes. A midline approach is used, and very careful attention paid to progress of needle excursion in the interspinous ligaments and ligamentum flavum. Because of lack of calcification of these ligaments, especially in younger children, the loss of resistance felt when passing through the ligamentum flavum is not as distinct. These features in younger children, coupled with the small distances involved and the presence of the spinal cord during thoracic epidural anesthesia, make ultrasound guidance potentially a very important technique to improve accuracy of placement [72,78].

Local anesthetic dosage

As for caudal anesthesia, ropivacaine 0.2% or levobupivacaine/bupivacaine 0.25% is used. A dose of 0.5 mL/kg is used for lumbar epidural initial loading (0.3 mL/kg thoracic epidural initial loading), and 0.25 mL/kg for subsequent "top-up" in order to obtain intraoperative analgesia. After injection into the epidural space, absorption into the bloodstream follows a biphasic process [91]. The buffering properties of the epidural space are important and prevent a rapid rise in concentration. Sometimes, in order to have better muscle relaxation, it is possible to use the LA in combination with intravenous muscle relaxants.

To obtain pain relief in the postoperative period a continuous infusion of 0.1–0.125% bupivacaine or levobupivacaine, or 0.1% ropivacaine, can be used. Epidural infusions of ropivacaine provided satisfactory pain relief in neonates and infants less than 1 year old [92]. As plasma concentrations of unbound ropivacaine are not influenced by the duration of the infusion, ropivacaine can be safely used for postoperative epidural infusion for 48–72 h. Levels of unbound ropivacaine were higher in the neonates than in the infants, but well below threshold concentrations for CNS toxicity in adults, i.e. ≥0.35 mg/L [93]. In the first weeks of life ropivacaine infusion should be used with more caution. Because of concerns about toxicity due to accumulation of amide LAs in infants and young children, chloroprocaine could be an alternative; indeed, continuous chloroprocaine epidural infusion appears to be an efficacious postoperative analgesia modality for neonates, infants, and children [94–96].

The disadvantages of continuous bupivacaine epidural infusion are a high risk of urinary retention and motor block of the legs. The latter can cause anxiety in children between 4 and 8 years old, who may not understand why they cannot move their legs. The use of ropivacaine or levobupivacaine could be useful in decreasing the risk of motor blockade [97].

KEY POINTS: EVIDENCE-BASED CONCLUSIONS AND CLINICAL ADVICE FROM THE ESRA–ASRA JOINT COMMITTEE PRACTICE ADVISORY ON RECOMMENDATIONS ON LOCAL ANESTHETICS AND ADJUVANTS DOSAGE IN PEDIATRIC REGIONAL ANESTHESIA FOR EPIDURAL ANESTHESIA [7]

- The local anesthetic dose for lumbar or thoracic epidural should not exceed 1.7 mg/kg of ropivacaine, bupivacaine, or levobupivacaine
- Continuous epidural anesthesia can be performed with a dose of 0.2 mg/kg/h for infants less than 3 months, 0.3 mg/kg/h for children 3 months to 1 year, and 0.4 mg/kg/h for children >1 year

Use of ultrasound guidance

Willschke and colleagues have investigated the potential usefulness of ultrasound assistance when performing epidural anesthesia in infants and children [98,99]. In addition, they compared epidural catheter placement using either the traditional landmark-based technique or ultrasound assistance and found a reduction in performance time by visualization of the distance between the skin and epidural space [100] (Fig. 20.7) and fewer episodes of bone contact when using ultrasound. The described technique does, however, require a very skilled assistant handling the ultrasound probe, and, apart from the need for a "skilled third arm," there is also interference between the operator and the ultrasound probe. Karmakar et al reported the use of ultrasound- assisted epidural blockade using a spring-loaded syringe in adults [101]. Such a modification of the technique makes it possible for a single operator to perform the block (holding the ultrasound probe in one hand and the Tuohy needle/spring-loaded syringe in the other). This may represent a modification of this approach that makes ultrasound assistance clinically valuable in the context of epidural blockade also. Finally, a simple preprocedural ultrasonography examination of the spine accurately delineates the underlying relevant anatomy, and permits assessment of the depth of the epidural space, which is relevant information in infants and children.

Spinal block

This block is a useful technique in the ex-premature infant scheduled for inguinal herniorrhaphy because it is the only form of pediatric regional anesthesia in which the block is routinely performed and the operation carried out on a conscious patient. It is well known that ex-premature infants are more prone to complications such as apnea, hypoxia, and bradycardia during the first postoperative hours following general anesthesia [52, 102], despite the fact that a recent trial and cohort studies suggest that an exposure of less than an hour does not increase the risk of poor outcome [103]. Moreover, premature infants with a history of bronchopulmonary dysplasia may be at even greater risk of developing postanesthetic complications because of the depressant effects

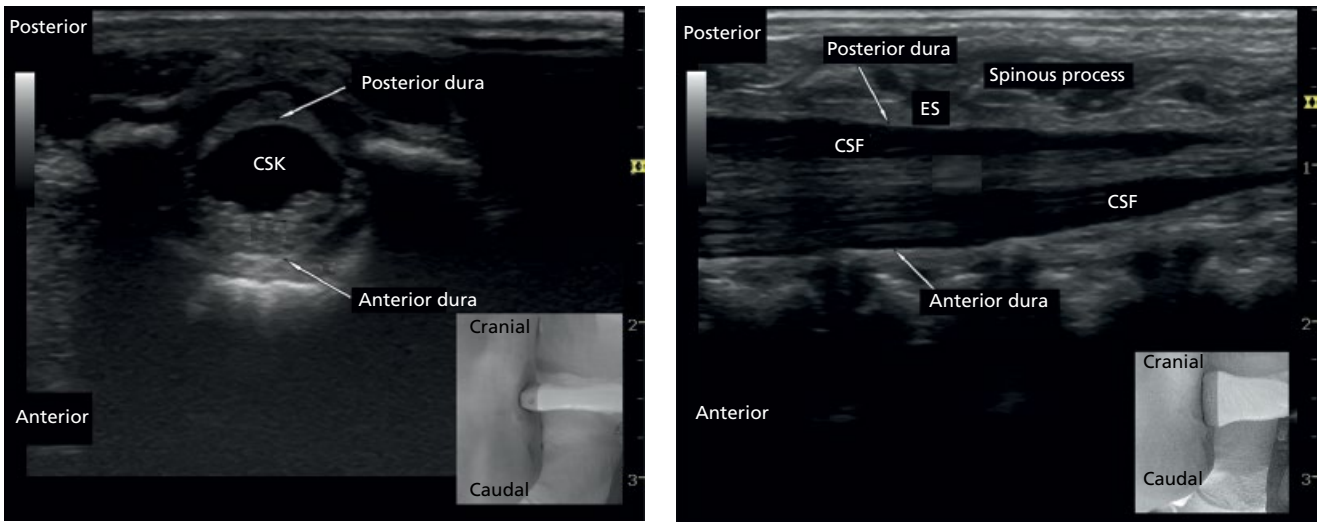


Figure 20.7 Ultrasound imaging of the epidural region. (A) Transverse view. (B) Paramedian longitudinal view. CSF, cerebrospinal fluid; ES, epidural space. See text for further details.

of halogenated agents on intercostal muscles, lung volumes, and chemo- and baroreceptor responses.

Avoiding general anesthesia is therefore very useful. Preclinical studies have consistently found that most general anesthetics produce accelerated apoptosis in the developing brain of animals. Spinal block in a conscious infant is a recognized technique that allows the avoidance of general anaesthesia and the potential risks associated with it.

Performance of a spinal block

As discussed with epidural block, the subarachnoid puncture should be made caudal to L3 to avoid possible damage to the spinal cord. The puncture is performed with the child turned in the lateral position with lower extremities flexed and the neck extended. It has been shown that hypoxemia occurs during lumbar puncture in the sick neonate when the infant's neck is flexed for the spinal tap [104]. A 22 ga, 3.5 cm styletted (or 25 ga 1.5 cm) lumbar puncture needle is inserted in a midline position. An unstyletted needle increases the risk of development of an epidermoid tumor. The needle is advanced slowly, and the stylet is frequently removed in order to watch for the free-flowing return of CSF.

Local anesthetic used

The most common local anesthetic used is 0.5% tetracaine with 5% dextrose: 0.13 mL/kg in infants weighing less than 4 kg, and 0.07 mL/kg in infants weighing more than 4 kg [102]. Tetracaine is no longer available in some countries. Hyperbaric bupivacaine or isobaric levobupivacaine or ropivacaine can also be used [105,106]. The duration of spinal block is shorter in infants than in adults, probably due to the larger volume of CSF. Indeed, a relationship between duration of motor blockade and age has been reported [11]. In addition, there is a proportionally greater blood flow to the spinal cord with a more rapid uptake of drugs from the subarachnoid space. These phenomena are most pronounced in preterm infants compared to full-term infants. The timing in relation to the baby's feeding requirements is important for two reasons. First of all, the crying of a hungry baby renders a hernia repair much more difficult. Therefore, a pacifier can usually keep the baby quiet, and the upper limb should be immobilized. Recently dexmedetomidine has been proposed as sedative agent [107]. Second, hypotension from sympathetic block following the spinal anesthesia can occur if fasting is prolonged [108].

In older children, there are few indications for spinal block, due to the short duration of postoperative analgesia. Nonetheless, the child with a full stomach scheduled for a testicular torsion should be a good candidate for a spinal block without sedation. The usual dosage of 1% tetracaine plus 10% glucose is 1 mg per year of age (below 3 years, 0.2 mg/kg). The other LAs can be also used in older children.

KEY POINTS: EVIDENCE-BASED CONCLUSIONS AND CLINICAL ADVICE FROM THE ESRA–ASRA JOINT COMMITTEE PRACTICE ADVISORY ON RECOMMENDATIONS ON LOCAL ANESTHETICS AND ADJUVANTS DOSAGE IN PEDIATRIC REGIONAL ANESTHESIA FOR SPINAL ANESTHESIA [6]

- Spinal anesthesia with tetracaine, bupivacaine, levobupivacaine, or ropivacaine can be performed with a dose of 1 mg/kg for newborn and/or infant and a dose of 0.5 mg/kg in older children (>1 year of age)

Use of ultrasound guidance

Caudal anesthesia has been shown to be technically less difficult than spinal anesthesia and to have a higher success rate. Its application as awake regional anesthesia technique in these patients seems more appropriate than spinal anesthesia [109]. However, theoretically, ultrasound could be used to help predict or determine (if used in real-time) the depth to

reach either the subarachnoid space or some depth within the spinal canal [110]. Nonetheless, the failure rate of spinal anesthesia was low; a bloody tap on the first attempt at lumbar puncture was the only risk factor significantly associated with block failure [111]. See Video clip 20.2.

Peripheral nerve blocks

Brachial plexus and branches

Fractures of the upper extremity, especially at the elbow and wrist, are common injuries during the summer months when children are outside playing on jungle gyms and skateboards. These patients often present in the late afternoon or early evening having eaten just prior to the traumatic event. Surgery focuses on reduction and realignment procedures with hardware insertion and casting. Use of sedation may complicate the anesthetic considerations of a full stomach. Brachial plexus blockade may be established with a variety of effective techniques. In addition, the use of ultrasound guidance is very useful [112,113].

Interscalene approach

There are few indications for interscalene brachial plexus blocks in the pediatric population, and few case reports have been published describing ultrasound-guided interscalene block in children [114]. With the patient positioned supine and head turned slightly to the contralateral side, in a transverse oblique plane at the level of the cricoid, the anechoic compressible internal jugular vein and pulsatile carotid artery are visualized medial to the anterior scalene muscle and deep to the triangular-shaped sternocleidomastoid muscle. The roots of the brachial plexus appear as distinct hypoechoic oval or round bodies arranged in a cephalocaudal orientation in between the bulky anterior and middle scalene muscles (Fig. 20.8). No serious adverse events were reported in prospectively collected data [115]. The upper limit of the confidence interval for these events is similar to that in awake or sedated adults receiving interscalene blocks. Based on these results, placement of interscalene blocks under general anesthesia in children is no less safe than placement in awake adults.

Periclavicular blocks

The *supraclavicular or infraclavicular approach* to the brachial plexus is recommended for elective or emergency surgery of the upper limb when lesions are located above the elbow or when the limb cannot be moved, either because of severe pain or because of the nature of the lesion itself [116]. Specific contraindications are acute or chronic respiratory insufficiency or whenever the surgery mandates bilateral supraclavicular block, due to the possibility of phrenic block. Some side-effects can occur: stellate ganglion block with a Horner syndrome, risk of damage to the vertebral artery or the large blood vessels of the neck, or pneumothorax. Because of the high risk of potentially serious side-effects, most anesthesiologists have avoided the supraclavicular and the infraclavicular approach in children, in whom the anatomical relations are even closer than in adults. With the introduction of ultrasound guidance, the supraclavicular or infraclavicular approach to the brachial plexus is once again becoming popular for children.

For the supraclavicular approach, the probe is first placed in a coronal oblique plane at the lateral end of and just above the upper border of the clavicle. It is then moved medially until an image of the subclavian artery appears in the middle of the screen (Fig. 20.9). At this location, the plexus is located superior and lateral to the artery, and the neurovascular structures are noted to be above the first rib. In the supraclavicular fossa, the divisions of the brachial plexus are visualized as a cluster of hypoechoic nodules immediately cephalad and lateral to the anechoic pulsatile subclavian artery and above the first rib. Using an in-plane technique, the needle is advanced into the plexus, and after aspiration, LA is injected until circumferential spread around the plexus trunks is seen (0.2 mL/kg may suffice depending on the age of the patient and accuracy of needle tip placement). Few published data are reported [117].

For the infraclavicular approach, the child is placed supine with the arm adducted, elbow flexed, and forearm placed on their abdomen. A linear probe is placed transversely below the clavicle to capture an image of the brachial plexus (presumably the cords surrounding the subclavian artery). The needle is inserted out of plane, 1 cm from the inferior aspect of the probe, and directed slightly cranially to direct it toward the lateral border of the plexus. The LA spread is viewed surrounding the plexus. However, the vertical infraclavicular brachial plexus block, which is very popular in adults, is dangerous in children because of its proximity to the cervical pleura [118]. In a prospective, randomized study, Marhofer et al compared ultrasound-guided and old nerve stimulator-guided infraclavicular brachial plexus blocks in children with upper extremity fractures [119]. The sensory and motor block characteristics were better in the ultrasound-guided group at 10 min after the completion of the block procedure.

De José María et al demonstrated that ultrasound-guided supraclavicular plexus block is as effective as ultrasound-guided infraclavicular plexus block in children aged 5–15 years [120]. However, the supraclavicular plexus block appeared to be associated with fewer failed blocks when compared with the infraclavicular approach. These data imply that, in experienced hands, a supraclavicular block is a safe and useful alternative for pediatric hand and arm surgery. See Video clip 20.3.

Axillary approach

The axillary approach to the brachial plexus was introduced into pediatric regional anesthesia in 1960 and is frequently used because of its low complication rate [121]. The indication for the axillary approach is elective or emergency surgery on the forearm and the hand. The specific contraindications are axillary lymphadenopathy or when the situation requires that the limb be immobile, such as with intense pain or an unstable fracture.

There is no original report of ultrasound-guided axillary block in children. The patient is positioned supine with the arm abducted to 90° and flexed at the elbow. With the probe placed perpendicular to the anterior axillary fold, a short-axis view of the neurovascular bundle can be obtained (Fig. 20.10). The nerves are pictured as distinct hypoechoic nodules with internal hyperechoic punctuations typically situated lateral (median nerve), medial (ulnar nerve), and posterior (radial nerve) to the anechoic pulsatile axillary artery. It is noteworthy that the

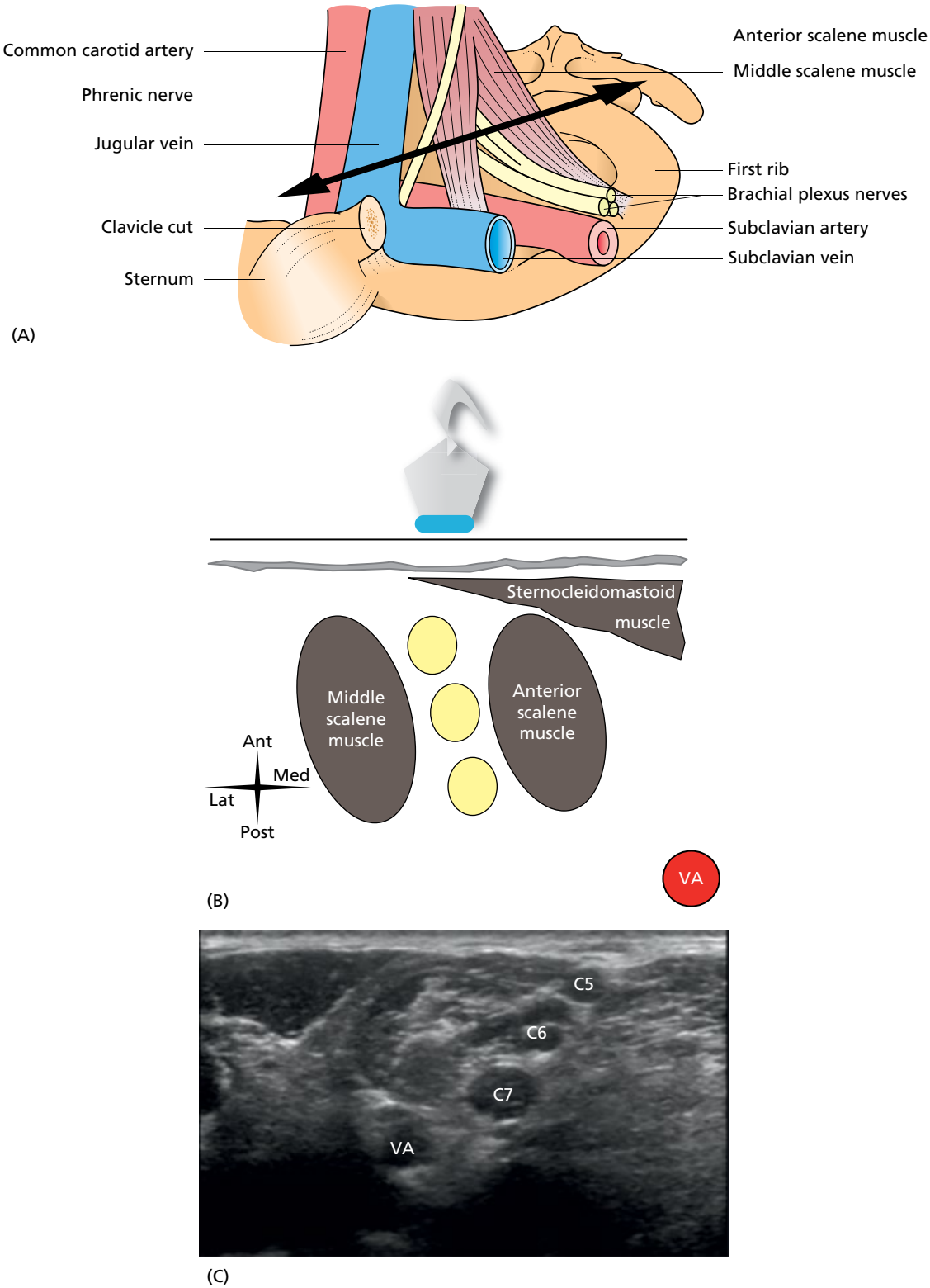


Figure 20.8 The interscalene region. (A) Anatomy. (B) Ultrasound imaging. The ultrasound probe is depicted at the top of the figure. The roots of the brachial plexus, depicted here in yellow, appear as distinct hypoechoic oval or round bodies arranged in a cephalocaudal orientation in between the bulky anterior and middle scalene muscles. (C) Ultrasound image. VA, vertebral artery. See text for further details.

location of these three nerves relative to the axillary artery can be highly variable. This block could be performed with similar techniques to those used in adults. A single needle insertion at this location facilitates the blockade of the radial, median, and ulnar nerves. It is important to note that the musculocutaneous nerve is situated outside of the axillary neurovascular sheath. Specifically, it lies between the biceps brachii and coracobrachialis muscles and is often blocked separately from the radial, median, and ulnar nerves [122]. In addition, topographic variations of the four main nerves at the axilla were found to be numerous [123,124]. A volume of 0.25–0.3 mL/kg is used (do not use more than 20 mL).

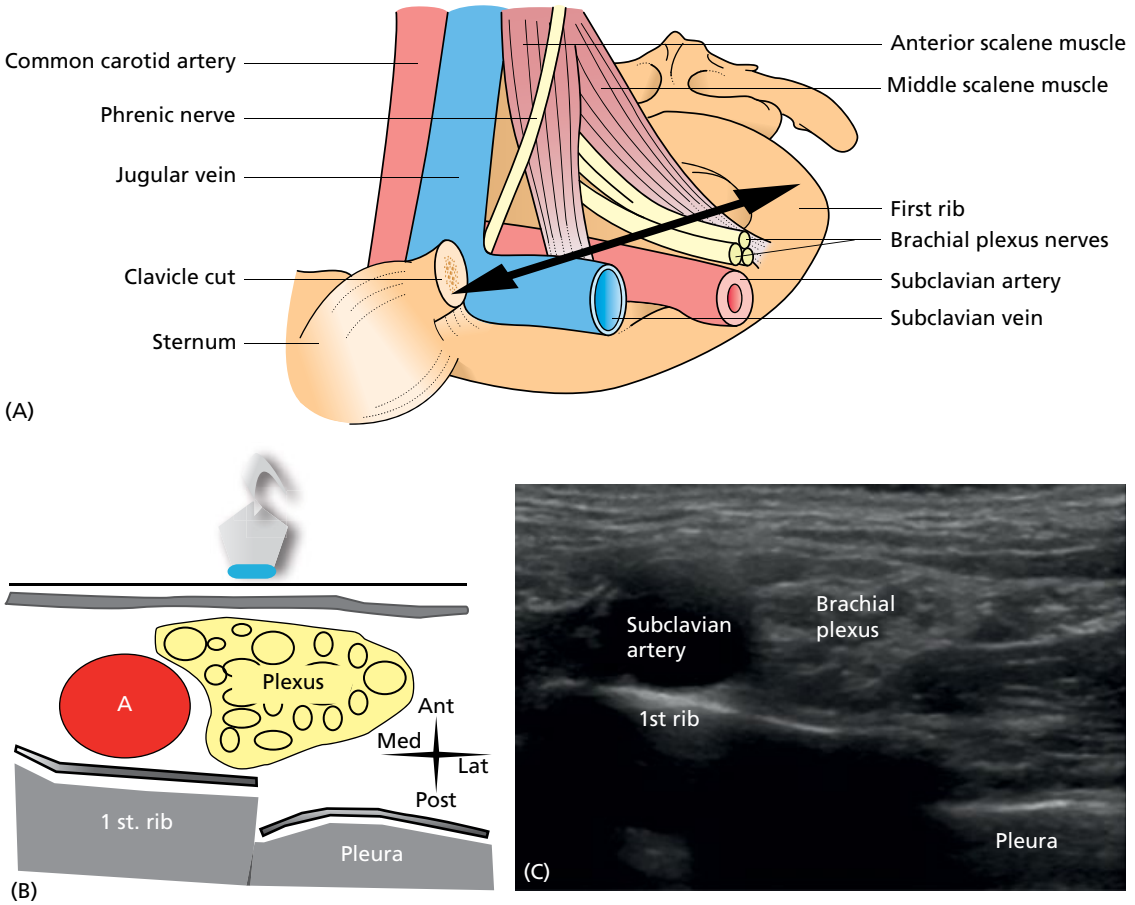


Figure 20.9 The supraclavicular region. (A) Anatomy. (B) Ultrasound imaging. The ultrasound probe is depicted at the top of the figure. The subclavian artery appears on the middle of the screen. (C) Ultrasound image. At this location, the plexus is located superior and lateral to the artery, and the neurovascular structures are noted to be above the first rib. A, subclavian artery. See text for further details.

Lumbar plexus and branches

The lumbar plexus originates from the nerve roots from T12 to L5. Its branches include the femoral, genitofemoral, lateral femoral cutaneous, and obturator nerves. The innervation of the skin, muscles, periosteum, and joints of the hip, thigh, and knee make blockade of the lumbar plexus particularly useful in pediatric patients. Analgesia for lower extremity procedures in children frequently involves areas innervated by branches of the lumbar plexus. Procedures involving joint or bone realignment, especially with insertion of hardware, are common, particularly in disabled children where the ability to sit upright in a wheelchair or to manage transfers from chair to bed and vice versa is vital to reducing their dependence on the family or nursing staff. In those with cerebral palsy, lengthening of muscle and tendons is equally important. Unfortunately these children may suffer from long periods of muscle spasm and pain following surgery. Due to their disabilities, communication regarding the efficacy of pain relief may be very difficult. Regional techniques, which effectively block the development of muscle spasm, eliminate the need for benzodiazepines and their supposed muscle relaxant effect. A clearer sensorium facilitates care delivery and assessment of pain relief. Congenital hip dislocation that does not respond to immobilization in plaster may require open reduction. In this setting, unilateral blockade of the lumbar plexus or bilateral blockade from a central approach makes life easier for all concerned.

Psoas compartment block

Posterior lumbar plexus block represents one of the most challenging techniques in terms of both ultrasound imaging and needle guidance. It should therefore only be performed or supervised by experienced clinicians. The clinical value of this technique has not yet been studied systematically. The well-recognized advantage of a posterior approach to the lumbar plexus is a reliable block of the femoral nerve, obturator nerve, and lateral cutaneous nerve of the thigh with a single injection.

Patients are placed in the lateral decubitus position, and the iliac crest and spinous processes are identified. The ultrasound probe is placed lateral to the midline, and the L4 or L5 transverse processes are located. Deep to the transverse process are the erector spinae and quadratus lumborum muscles. Beyond this, within the psoas major muscle, is the lumbar plexus. Because of this anatomical location, the plexus is often difficult to demarcate because it has similar echogenicity to the muscle [125].

In addition to the difficult performance of this posterior lumbar approach, one concern about this technique is that systemic LA toxicity might occur because of the rapid absorption of large volumes or because of inadvertent injection into one of the large paravertebral blood vessels [45]. Bilateral spread is also a known side-effect of posterior lumbar plexus block.

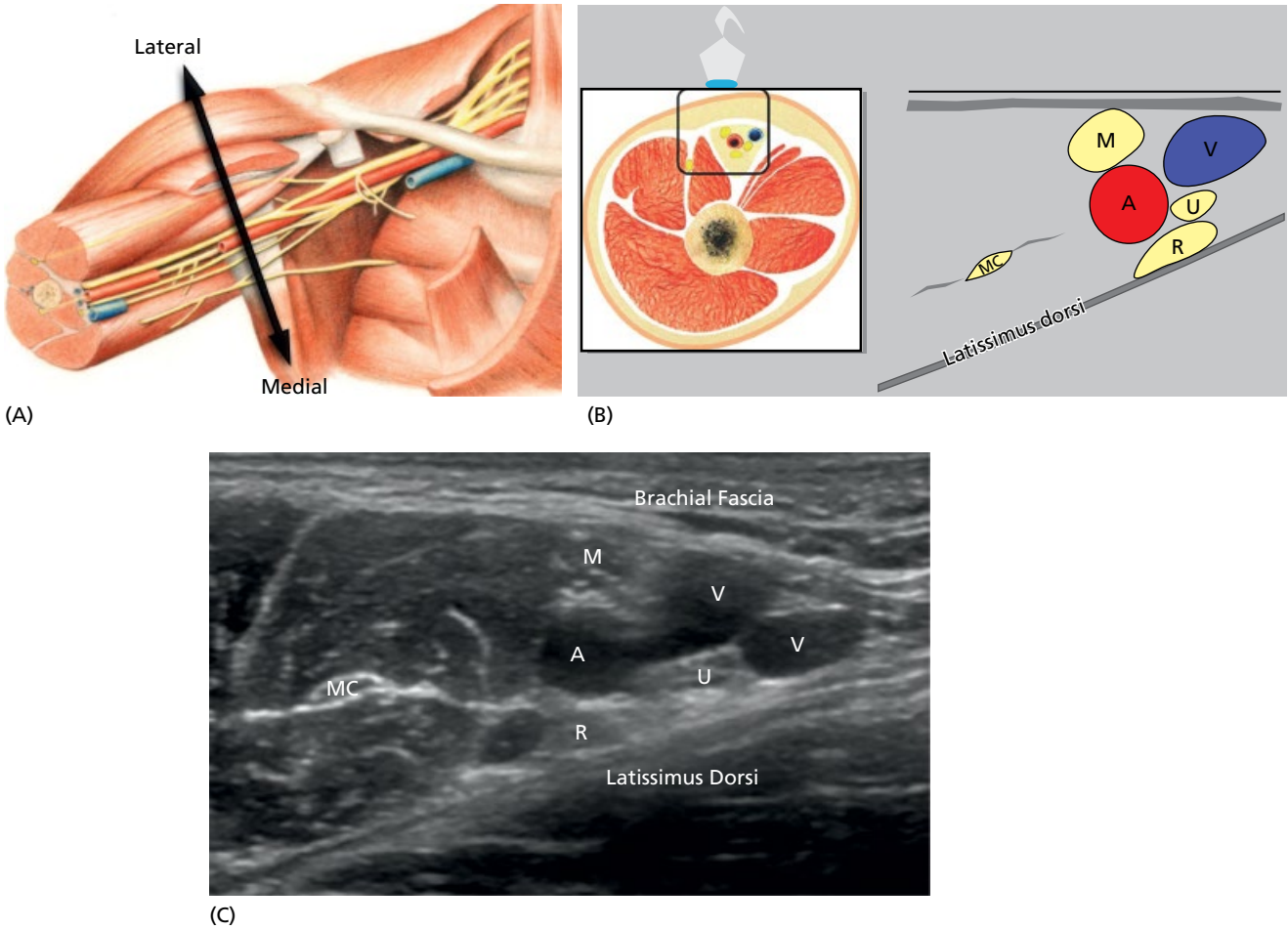


Figure 20.10 The axillary region. (A) Anatomy. (B) Ultrasound imaging. The ultrasound probe is depicted at the top of the left panel. The right panel is a magnified view. (C) Ultrasound image. The nerves are pictured as distinct hypoechoic nodules with internal hyperechoic punctuations typically situated lateral (median nerve), medial (ulnar nerve), and posterior (radial nerve) to the anechoic pulsatile axillary artery. A, axillary artery; V, axillary vein; MC, musculocutaneous nerve; M, median nerve; U, ulnar nerve; R, radial nerve. See text for further details.

Femoral block

The area anesthetized by a femoral block will be the quadriceps group of muscles, the periosteum of the shaft of the femur, the skin on the anterior aspect of the thigh, the medial part of the leg, and a small portion of the foot. It originates from the L2, L3, and L4 nerve roots. The indications are analgesia in patients with fracture of the femur [126] and surgery on the thigh, and analgesia for knee and leg surgery in combination with a sciatic block.

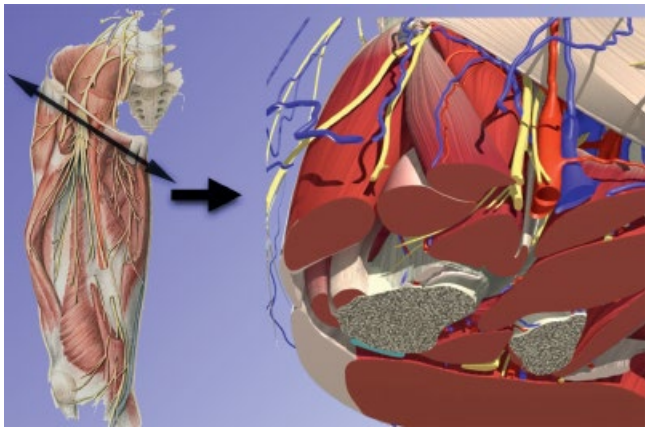
The femoral artery is the key landmark when using ultrasound guidance for femoral nerve blockade [127,128]. Indeed, the femoral nerve is anatomically lateral to the femoral artery and vein (Fig. 20.11). With the probe placed perpendicular to the nerve axis (i.e. coronal oblique) at the level of and parallel to the inguinal crease, the nerve appears lateral to the large, circular, pulsatile and anechoic femoral artery. An in-plane or out-of-plane approach can be used to guide the needle to the lateral portion of the femoral nerve and circumferentially surround it with local anesthetic. A volume of 0.25–0.3 mL/kg is used (do not use more than 20 mL). See Video clip 20.4.

Fascia iliaca compartment block

The fascia iliaca compartment block blocks the femoral nerve in all cases, and the lateral cutaneous nerve of the thigh and the obturator nerve is blocked in 75% of cases [129]. To perform the block, the child is placed in the supine position. The ultrasound probe is placed in the inguinal region and, following observation of femoral artery, the probe is moved a little lateral so that the iliopsoas muscle is identified as a hypoechoic area lateral to the artery and femoral nerve. Local anesthetic is injected between the fascia iliaca layer and iliopsoas muscle after passing the fascia iliaca layer.

Sciatic nerve

With contributions from the lumbar roots (L4, L5) and the sacral roots (S1, S2, S3), the sciatic nerve is the largest in the body. It provides innervation to the posterior thigh and the entire leg distal to the knee (excluding the medial component). The indications for sciatic nerve block include analgesia for trauma of the leg and foot. In elective surgery, a sciatic nerve block can be performed for surgery on the foot in combination with a femoral nerve block. Thus, any operation on the lower limb can be performed. In addition, pediatric orthopedic procedures on the lower extremity below the knee are performed primarily for congenital deformities such as talipes equinovarus and structural imbalances caused by cerebral palsy. Leg length discrepancy may also require prolonged treatment with an external fixator. In this setting, any leg



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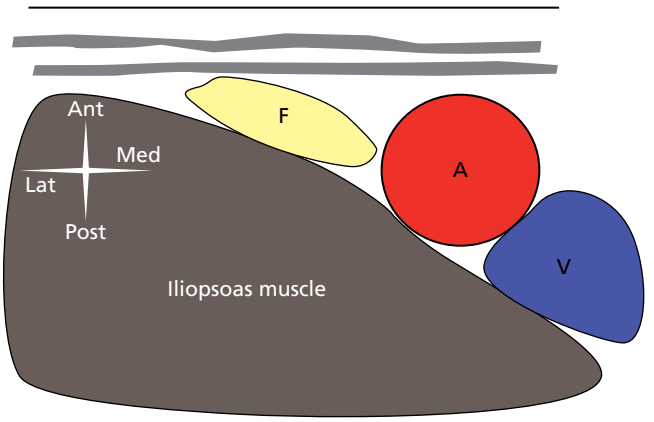

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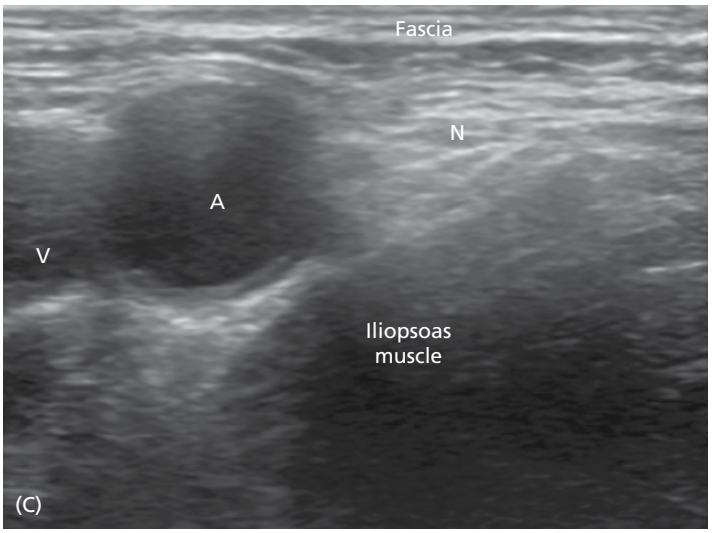


Figure 20.11 The femoral region. (A) Anatomy. (B) Ultrasound imaging. With the probe placed perpendicular to the nerve axis (i.e. coronal oblique) at the level of and parallel to the inguinal crease, the nerve appears lateral to the large, circular, and anechoic femoral artery. (C) Ultrasound image. F, femoral nerve; A, femoral artery; V, femoral vein. See text for further details.

length that can be obtained early with excellent analgesia from regional blockade will shorten hospital stay and reduce the associated expenses. The sciatic nerve can be blocked throughout its anatomical course using the subgluteal, anterior thigh, or popliteal approaches in children.

Gray et al published the first report on ultrasound-guided peripheral nerve block in children in 2003, in which they performed a sciatic nerve block in the subgluteal region of a 7-year-old [130]. More recently, studies of ultrasound-guided sciatic nerve blockade using a subgluteal approach have been published [128,131]. The subgluteal approach to the sciatic nerve requires the patient to lie in either the lateral decubitus position, with the hip and knee flexed, or in the prone position. In these positions, the ultrasound probe is placed between the greater trochanter and the ischial tuberosity (Fig. 20.12). The gluteus maximus muscle is identified, and deep to this is the sciatic nerve. An in-plane or out-of-plane technique can be used to advance the needle with ultrasound guidance to the nerve. The optimal needle insertion point is approximately halfway between the greater trochanter and the tip of the coccyx – a landmark readily palpable in neonates and infants [132]. The sciatic nerve appears predominantly hyperechoic and is often elliptical in a short-axis view.

The anterior approach to sciatic nerve blockade requires the patient to be in the supine position. This technique allows for the completion of the sciatic nerve block in non-anesthetized patients. With the patient's leg abducted and laterally rotated, the probe is placed inferior to the inguinal crease. The femur is identified, and the probe is moved medially to reveal the sciatic nerve in its location deep and medial to the femur.

A caudal-to-cephalad scan can effectively locate the sciatic nerve in the posterior popliteal fossa at a location where the tibial and common peroneal components have yet to separate. The child is placed prone or can remain in the supine position. At the popliteal crease, a transversely positioned linear probe captures the tibial and common peroneal nerves, the former located medially and lateral to the adjacent popliteal vessels (Fig. 20.13). The tibial nerve is often located in close proximity to the tibial artery and the tibial vein. The nerve appears round-to-oval and hyperechoic compared with the surrounding musculature. The hyperechoic border of the femur (condyles) may be apparent. The tibial nerve can be followed proximally to the junction with the common peroneal nerve, merging together to form the sciatic nerve. The sciatic nerve can be blocked here, or the tibial and common peroneal nerves can be specifically targeted at this location. See Video clip 20.5.

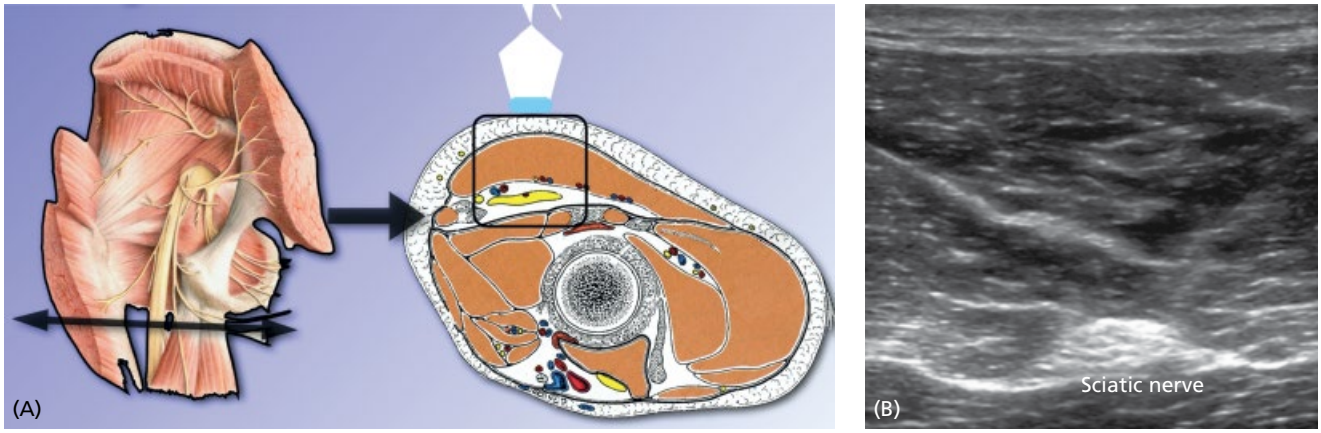
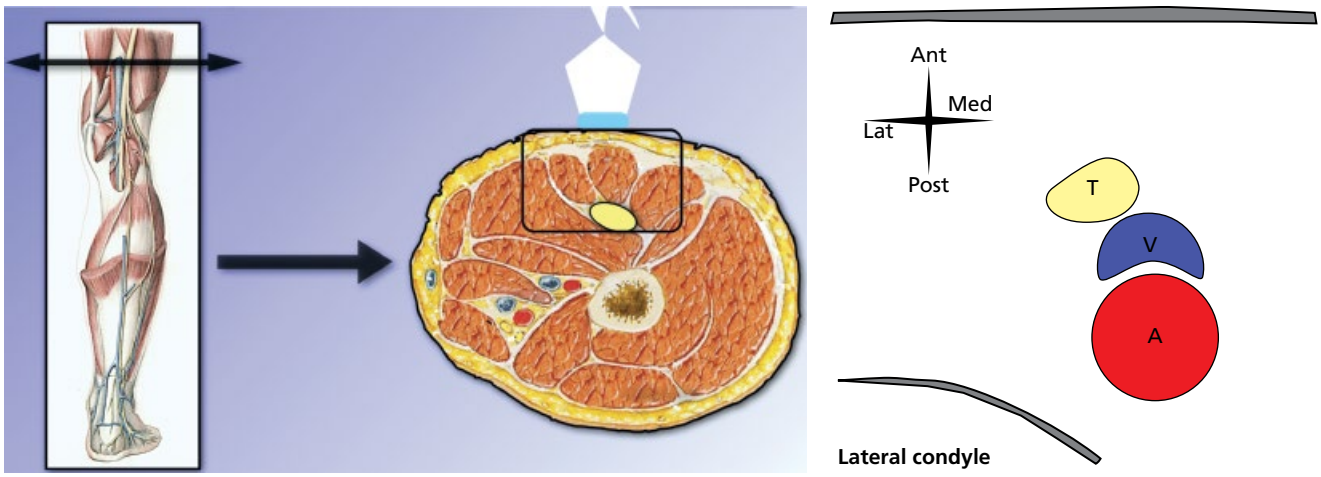


Figure 20.12 The gluteal sciatic region. (A) Anatomy. (B) Ultrasound image. The sciatic nerve is seen between the greater trochanter of the femur and the ischial tuberosity, just below the gluteus maximus muscle.



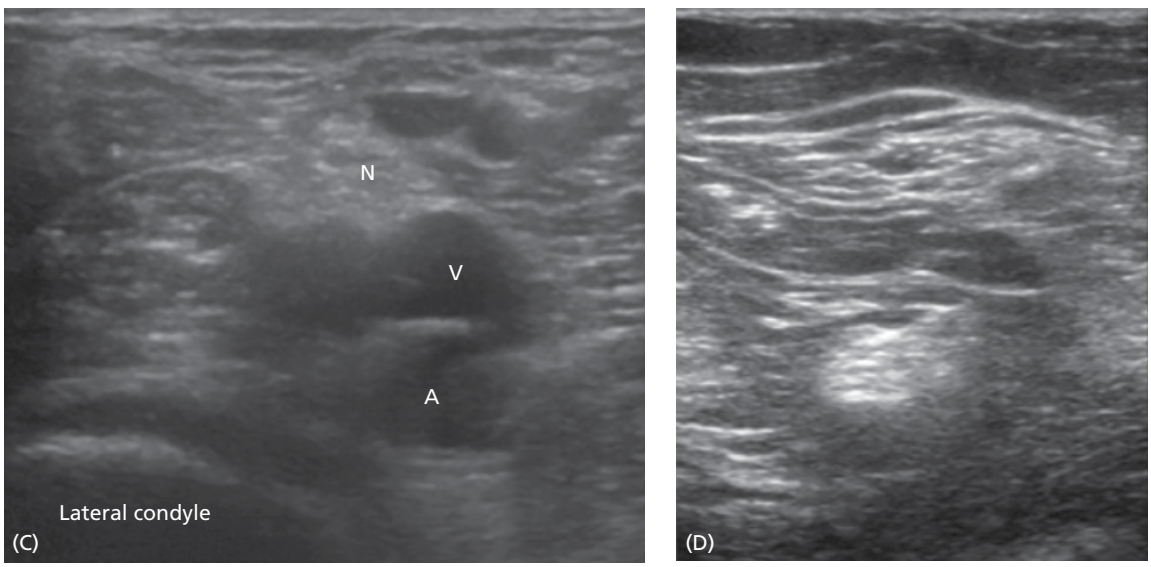


Figure 20.13 The popliteal sciatic region. (A) Anatomy. (B) Ultrasound image. At the popliteal crease, a transversely positioned linear probe captures the tibial and common peroneal nerves, the former located medially and lateral to the adjacent popliteal vessels. The tibial nerve is often located in close proximity to the tibial artery and the tibial vein. The nerves appear round-to-oval and hyperechoic compared with the surrounding musculature. The hyperechoic border of the femur (condyles) may be apparent. (C) Ultrasound image at the popliteal crease. (D) Ultrasound image where the sciatic nerve bifurcates. T, tibial nerve; A, tibial artery, V, tibial vein. See text for further details.

Continuous peripheral nerve blocks

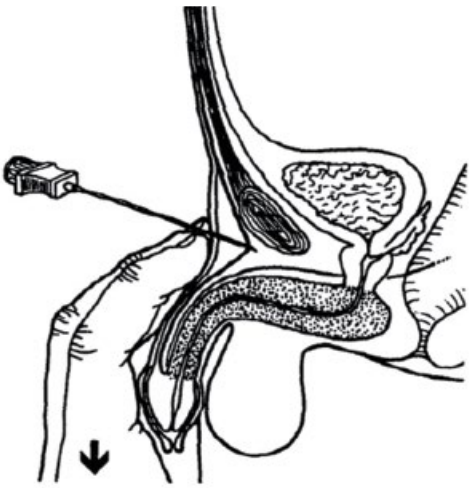
Single-shot peripheral blocks are now widely used in children but they can provide analgesia only for few hours. These blocks are even safer than central ones, but few studies have described continuous peripheral nerve block in children, except recently infraclavicular block [133] and sciatic block [58,134]. The indications for placing a catheter for continuous peripheral nerve blocks are severe pain, long intraoperative time requiring redosing, and the need for pain control for many days. Otherwise, painful rehabilitation and physiotherapy are probably the main indication, because good rehabilitation can only be performed if pain is under control. In adults, performance of such blocks has become daily clinical practice supported by a large quantity of data, providing effective analgesia, and allowing active physiotherapy that is essential for optimal functional recovery. Catheters can be maintained in position for several days and the patient is sometimes sent home with a catheter infusion [135]. One study has reported the efficacy of continuous peripheral nerve blocks with elastomeric disposable pumps associated with initial Bier blocks for the treatment of recurrent complex regional pain syndrome in children [136]. All the studies published so far underline the efficacy and safety of analgesia via a peripheral catheter, and no complications or side-effects linked to the long-term infusions have been described with only a few accidental removals and some drug leakage [136]. They are at least as efficient as epidural analgesia but produce fewer side-effects [135,137]. Sometimes a combination of peripheral blocks as a continuous sciatic block with a femoral single-shot block for tourniquet pain and light general anesthesia provides good intraoperative conditions for leg and foot surgery and adequate postoperative pain relief. Additional sedation to minimize the discomfort of a cast may be a consideration in the first 24 h [132]. As continuous regional analgesia is considered a safe and efficacious technique for postoperative pain relief in children after lower limb surgery, the feasibility of patient-controlled regional analgesia in a similar acute pain situation was evaluated. Both techniques are efficacious and satisfactory. However, patient-controlled regional analgesia with ropivacaine 0.2% can provide adequate postoperative analgesia for pediatric orthopedic procedures with smaller doses of ropivacaine and lower total plasma concentrations of ropivacaine than with continuous regional analgesia [138].

Other nerve blocks

Penile nerve block

The indication is surgery on the foreskin (phimosis, paraphimosis, circumcision). The anatomical landmark is the pubic symphysis (Fig. 20.14) [139]. The puncture is performed with a needle 22 ga in caliber and 30 mm in length. After gently pulling the penis downward, each pubic ramus is identified about 0.5 (infant) to 1.0 cm (older children) lateral to the symphysis pubis on either side, and immediately below the right and left inferior rami of the pubic bone. The needle is introduced at the puncture site, perpendicular to the skin. Penetration is halted in the subpubic space, after distinct elastic recoil is felt, corresponding to the crossing of the deep membranous layer of the superficial fascia. The depth of insertion correlates with age (8 mm for a newborn, 30 mm for a young adult). The same procedure is repeated on the opposite side. The volume should be 0.1 mL/kg for each side with 0.5% ropivacaine or levobupivacaine without epinephrine [140]. Epinephrine is absolutely contraindicated because it can lead to spasm of the dorsal arteries of the penis with subsequent ischemia and necrosis of the glans.

The use of ultrasound guidance is still debated. By placing a probe sagittally along the shaft of the penis, the subpubic space can be located as a triangle containing the deep penile fascia (inferiorly), the pubic symphysis (superiorly), and the membranous layer of the superficial (Scarpa's) fascia (Fig. 20.15). In a case report, Sandeman and Dilley describe placing a linear probe sagittally along the shaft of the penis to view the subpubic space [141]. Ultrasound-guided penile block improved the efficacy of the block compared with the landmark technique in terms of postoperative pain during the first postoperative hour and time to first requirement for postoperative analgesia [142].



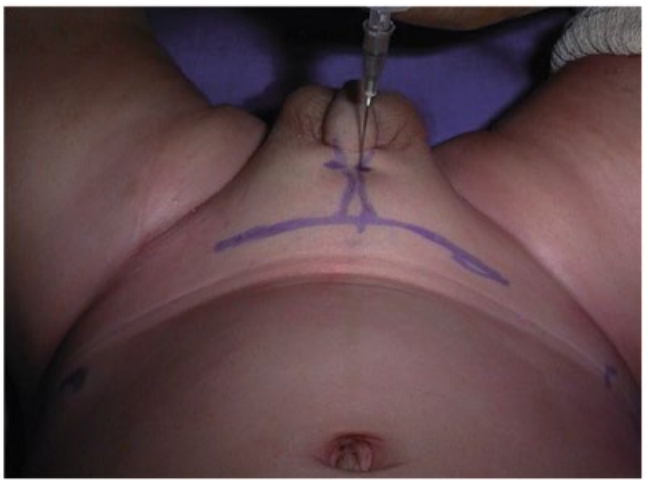


Figure 20.14 Anatomy and landmarks of a needle approach for a penile block. The anatomical landmark is the pubic symphysis. After gently pulling the penis downward, the two points are marked just below the pubic symphysis, each pubic ramus about 0.5–1.0 cm on either side of the pubic symphysis. The puncture is performed with a 22 ga needle, 30 mm in length. See text for further details.

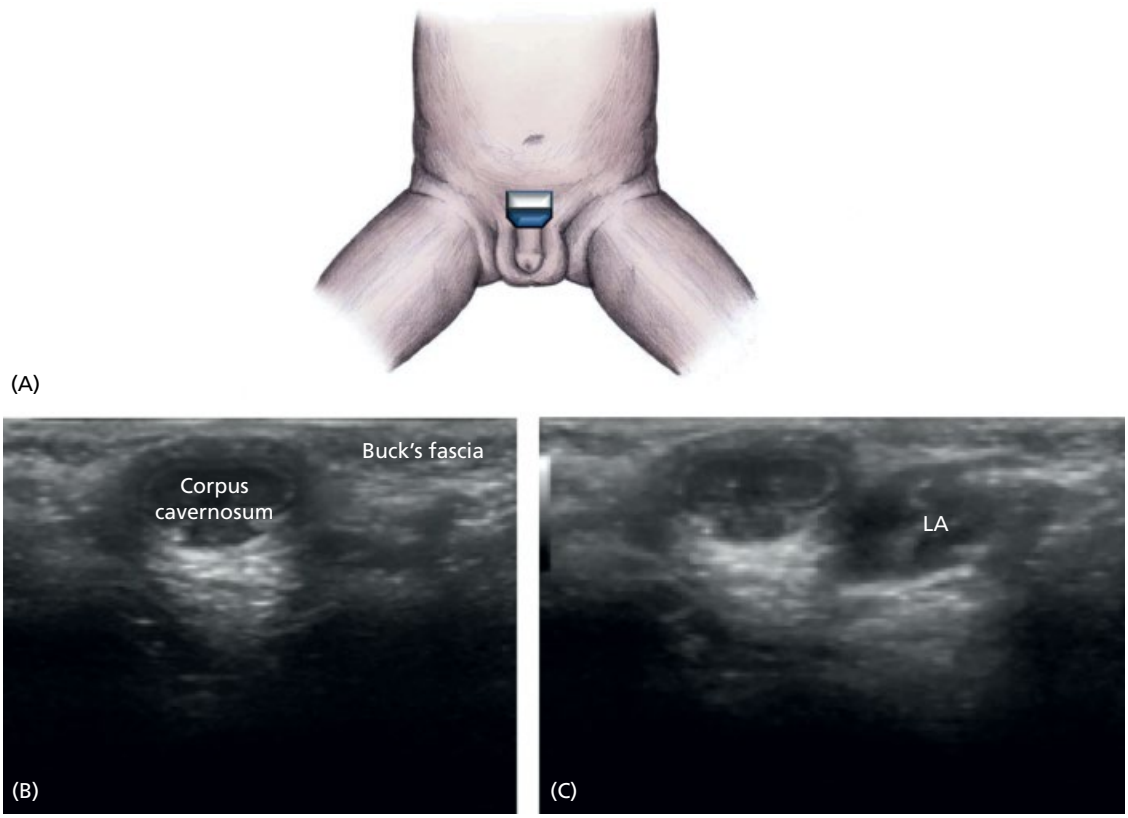


Figure 20.15 Ultrasound imaging of the penile block region. (A) Placement of linear or hockeystick ultrasound probe. (B) Puncture site without local anesthetic. (C) Subpubic space with local anesthetic (LA) in the correct place.

Ilioinguinal iliohypogastric block nerve block

The main indication is hernia repair. This peripheral nerve block is one of the best-studied with regard to the use of ultrasound guidance [143–147]. After placement of a linear or hockeystick probe along the anterior superior iliac spine (ASIS) with the probe oriented toward the umbilicus, the three layers of the abdominal wall muscles can be recognized. The ilioinguinal nerve and iliohypogastric nerves are seen as two hypoechoic structures between the internal oblique and transversus abdominis muscles (Fig. 20.16). A short-beveled needle (e.g. 22 ga, 40 mm with facette tip) is used. A reliable endpoint for the inexperienced practitioner of ultrasound-guided ilioinguinal/ iliohypogastric nerve block may be the transversus abdominis /internal oblique plane where the nerves are reported to be found in 100% of cases [146]. Using postinjection ultrasonographic control, Weintraud et al were able to show that the use of the classic landmark-based approach resulted in only 14% of the injections being made at the correct anatomical location [145]. Not surprisingly, the overall success rate of the ilioinguinal/ iliohypogastric nerve block was found to be only 61% in this study. In a prospective randomized study by Willschke et al, the use of an ultrasound-guided ilioinguinal/ iliohypogastric nerve block was compared with the landmark-based approach concerning efficacy of the two techniques [143]. It was clearly demonstrated that the use of the ultrasound-guided technique was associated with a significantly higher success rate, as evidenced by a reduced hemodynamic reaction to skin incision (4% versus 24%) and a considerable reduction in the number of patients needing supplemental analgesia in the recovery room (6% versus 40%). The same authors showed in a further study that a substantial reduction in the volume of LA (traditionally recommended volume 0.4–0.5 mL/kg) is possible when using ultrasound guidance. Using a modified up–down technique, they found that an effective ilioinguinal/ iliohypogastric nerve block can be achieved using a volume of LA as low as 0.075 mL/kg when using ultrasound guidance [144]. Weintraud and colleagues published a study in which plasma concentrations following either landmark-based or ultrasound-guided ilioinguinal/ iliohypogastric nerve block were analyzed following the administration of equal volumes and amounts of ropivacaine (0.25 mL/kg of 0.5%) [147]. Somewhat surprisingly, the maximum plasma concentration (C_{max}) was found to be higher and the time to maximum concentration (T_{max}) shorter when ultrasound guidance was used, indicating more rapid absorption when the LA was injected at the correct anatomical position. The most likely explanation for this unanticipated finding is that, when the LA is deposited between the fasciae of the internal oblique and the transversus abdominis muscle, the area of absorption will increase substantially compared with when the drug is mainly injected intramuscularly. Finally, a more recent study suggests that the needle should be placed much closer to the ASIS than the previously described anatomical landmark. In neonates, the LA needle should be inserted approximately 3 mm from the ASIS on a line drawn between the ASIS and the umbilicus [148].

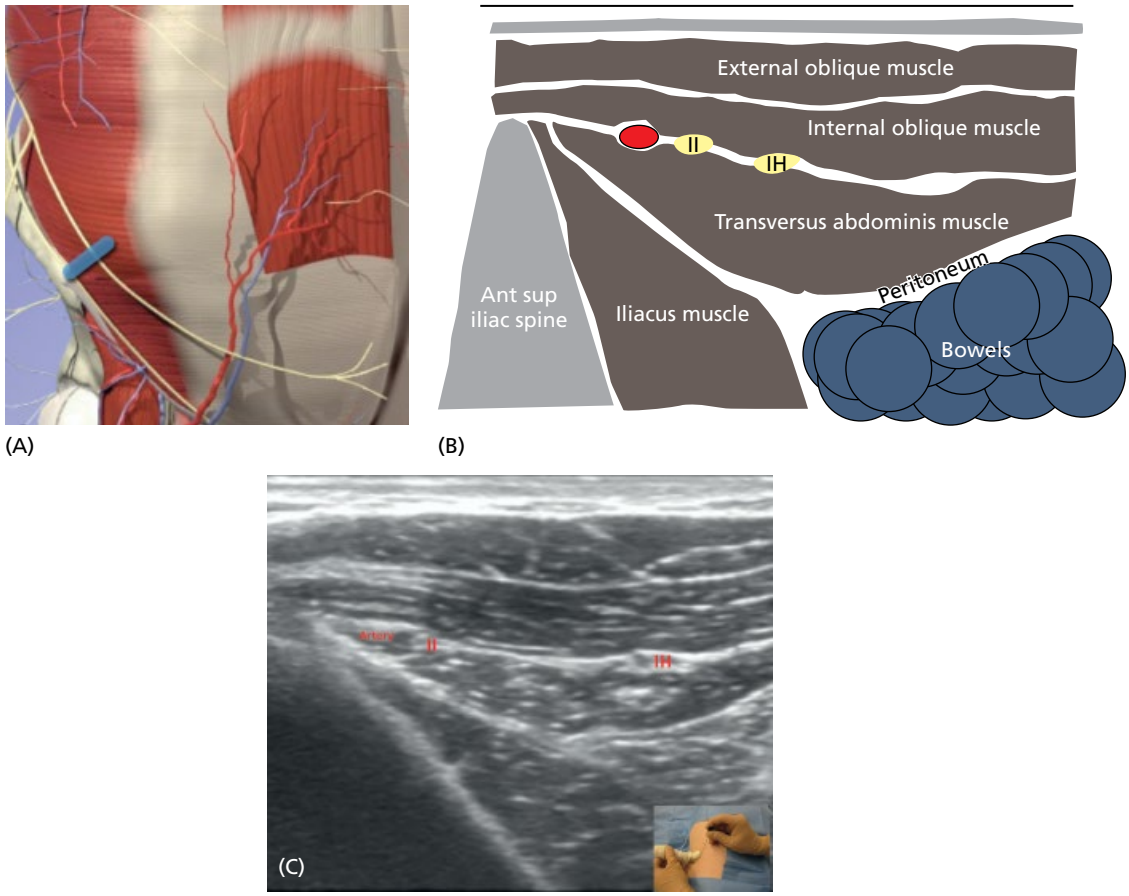


Figure 20.16 The abdominal region. (A) Anatomy. (B) Ultrasound imaging. After placement of a linear or hockeystick ultrasound probe along the anterior superior iliac spine with the probe oriented toward the umbilicus, the three layers of the abdominal wall muscles can be recognized. The ilioinguinal nerve and iliohypogastric nerves are seen as two hypoechoic structures between the internal oblique and transversus abdominis muscles. (C) Ultrasound image. II, ilioinguinal nerve; IH, iliohypogastric nerve. See text for further details.

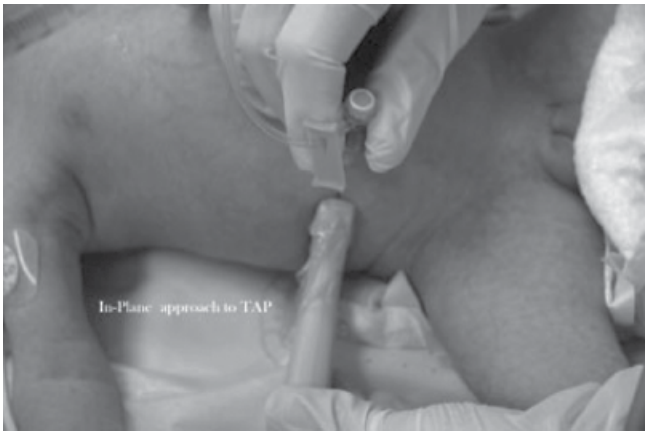
Transversus abdominis plane block

The transversus abdominis plane (TAP) block is increasingly being used to provide analgesia after surgery involving the abdominal wall. The block requires injection of LA into a plane between the transversus abdominis and the internal oblique muscle. A cadaver study demonstrated that with an ultrasound-guided single injection of 20 mL of aniline blue dye in the TAP, the ninth thoracic nerve (T9) was not surrounded by the injectate, whereas the segmental nerves T10, T11, T12, and L1 were surrounded by the injected dye in 50%, 100%, 100%, and 93% of the cases, respectively [149]. Ultrasound can help the practitioner readily visualize the muscle layers at the lateral abdominal wall, though it does not allow clear distinction between the individual muscles (Fig. 20.17). Linear and parallel hyperechoic striations are apparent, beneath which lies a hypoechoic-appearing region representing the peritoneum [150]. The external oblique abdominal muscle will lie superficial, overlying the internal oblique and transversus abdominis muscles. As for the rectus sheath and umbilical blocks, the nerves (in this block the lower thoracic and first lumbar spinal nerves) will not be viewed with clarity because they would appear with similar echogenicity as the muscle layers and travel tangentially to the ultrasound beam axis at this location. A short-beveled needle (e.g. 22 ga, 80–100 mm with facette tip) is used. A low risk of LA toxicity in neonates has been reported after a TAP block [151].

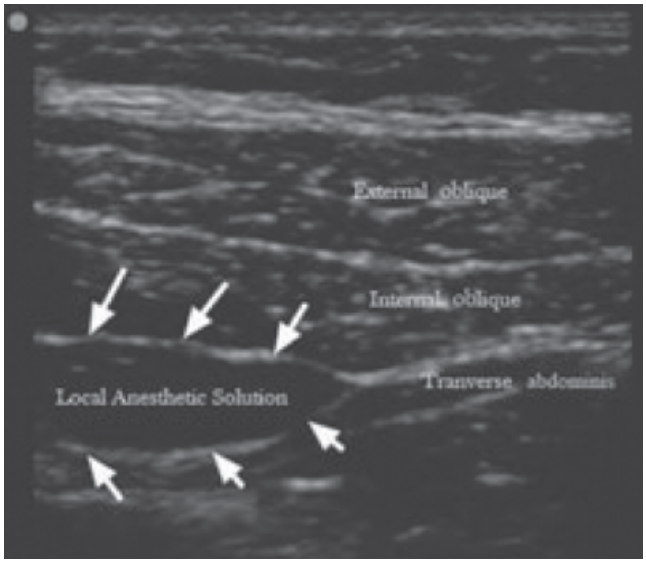
TAP block represents an interesting and effective regional anesthetic technique for pain relief after abdominal surgery due to a wide LA spread [152]. TAP block provides superior analgesia compared with wound infiltration in the setting of a multimodal analgesic regimen. The upper incidence of overall complications associated with the TAP block in children was 0.3% in a recent PRAN study [153]. Complications were very minor and did not require any additional interventions. Future studies should define the risks and benefits, and compare them with epidural techniques, which can be considered the "gold standard" for the provision of abdominal analgesia.

Quadratus lumborum block

The quadratus lumborum (QL) block was described in 2007 by Blanco and colleagues, and has been described for use in children for analgesia for abdominal and pelvic surgery, including pelvic and hip osteotomy [154]. Current literature describes four different approaches to this block, but the basic principle is to deposit LA anterior, posterior, lateral, or directly into the QL muscle [155]. From there, LA spreads between the posterior aspect of the QL muscle and the thoracolumbar fascia to block the intercostal nerves, and potentially into the thoracic paravertebral space to block the nerves exiting from the dorsal nerve roots (Fig. 20.18).



(A)



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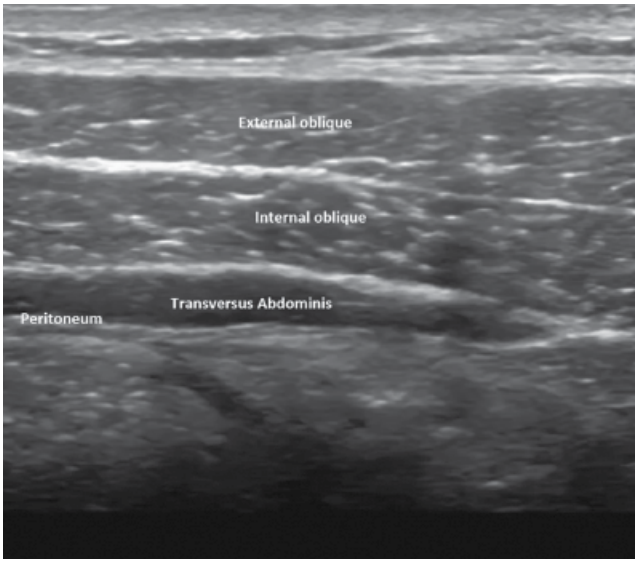


(C)

Figure 20.17 The transversus abdominis plane (TAP) region. (A) Anatomy. (B, C) Ultrasound imaging of the abdominal wall between the costal margin and the iliac crest reveals three muscle layers, separated by a hyperechoic fascia: the external oblique, the internal oblique, and the transversus abdominis muscles. The nerves of the abdominal wall are not visualized consistently. See text for further details. *Source:* Reproduced from Suresh and Chan [150] with permission of John Wiley and Sons.

LA can spread rostral–caudal as well, increasing the dermatomal coverage for a single-injection block. Despite this, a recent cadaver study documented spread of dye only to surround the intercostal nerves and not into the paravertebral space to affect the nerve roots [156]. The posterior QL block shares characteristics with the posterior TAP block [157].

To perform the anterior QL block, the patient is placed in the lateral decubitus position, with sterile preparation and draping from the subcostal area to iliac crest [155]. A low-frequency convex ultrasound probe is vertically oriented above the iliac crest (Fig. 20.19), and the needle is inserted in the triangle of Petit until placement anterior to the QL is confirmed (Fig. 20.20A). The needle tip is placed at the anterolateral border of the QL at the junction of QL with transversalis fascia, and the LA is injected. Using ultrasound, the LA is confirmed to be deep to the transversus abdominis aponeurosis (Fig. 20.20B).

A newly published randomized controlled trial of QL block versus TAP block in children undergoing lower abdominal surgery (inguinal hernia and orchidopexy) assessed outcomes of each block. In 53 patients 1–7 years of age, QL block was superior to TAP block at 1–24 h for FLACC score (faces, legs, activity, cry, consolability); p = 0.002–0.022. Additionally, time to first IV analgesia was 10 h in the TAP group versus 15 h in the QL group [158].

Rectus sheath block and umbilical block

To perform the rectus sheath block, the probe is placed just below the umbilicus (i.e. above the arcuate line). The anterior and posterior aspects of the rectus sheath and the enclosed rectus abdominis muscle are visualized. The sheath appears hyperechoic with multiple linear layers, lying on the anterior and posterior aspects of the rectus muscle. Willschke et al [159] and de Jose Maria et al [160] stated that their injection site was situated at the location where an optimal view of the posterior sheath was obtained. A short-beveled needle (e.g. 22 ga, 40 mm with facette tip) was inserted in an in-plane

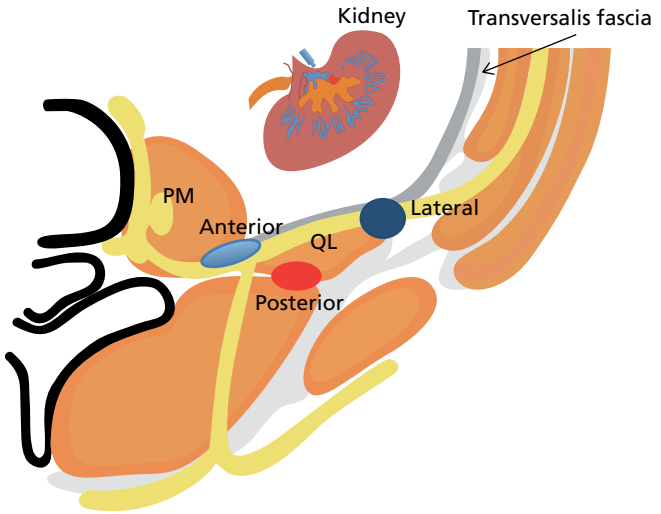


Figure 20.18 Anatomical view of quadratus lumborum (QL) block (anterior, lateral, and posterior). The lateral QL block injects the local anesthetic lateral to the QL muscle. The posterior QL block injects the local anesthetic posterior to the QL muscle. The anterior QL block injects the local anesthetic between the psoas major (PM) muscle and the QL muscle. Gray line, transversalis fascia. *Source:* Reproduced with permission from Ueshima et al [155]. https://www.hindawi.com/journals/bmri/2017/2752876/abs/. Licensed under CC BY.

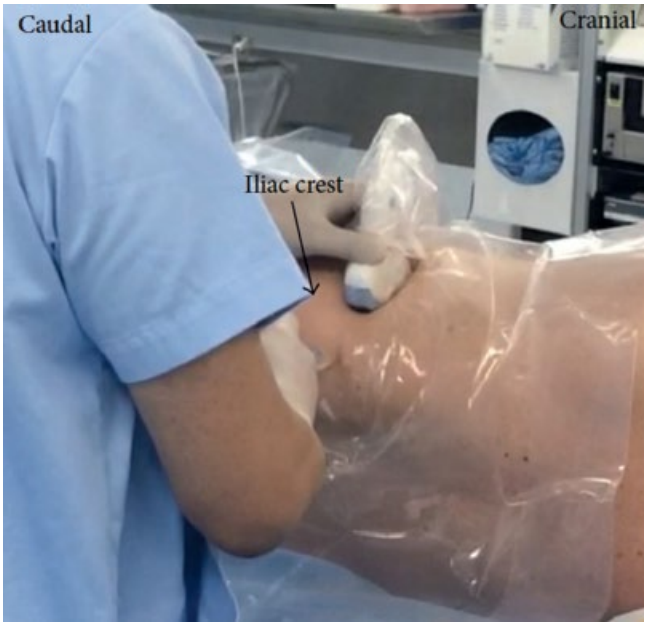
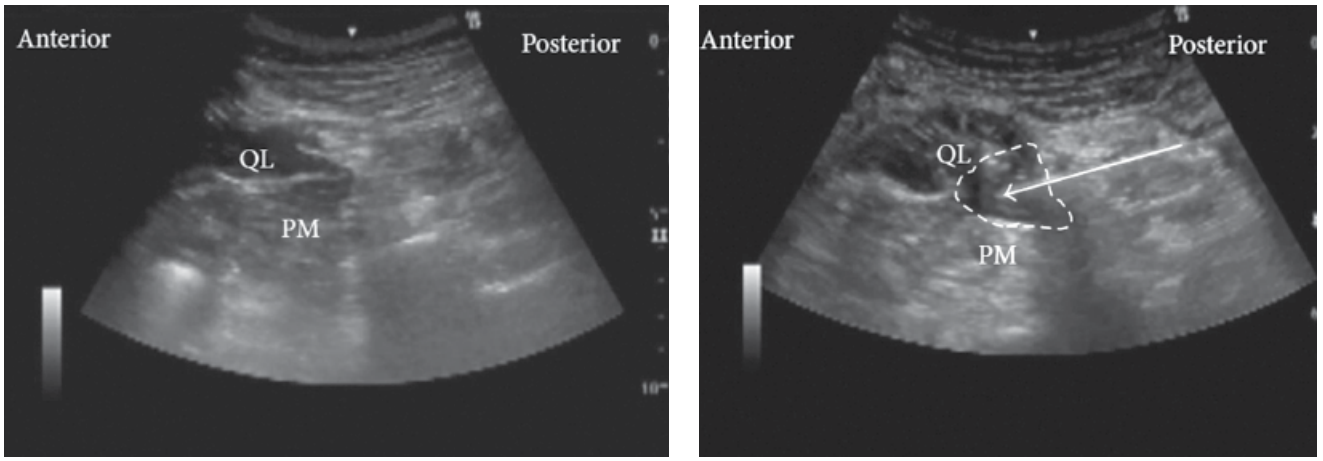


Figure 20.19 Probe position for anterior quadratus lumborum block. The convex probe is vertically oriented above the iliac crest. *Source:* Reproduced with permission from Ueshima et al [155]. https://www.hindawi.com/journals/bmri/2017/2752876/abs/. Licensed under CC BY.



(A) (B)

Figure 20.20 (A) Ultrasound image of anterior quadratus lumborum (QL) block before local anesthetic injection. (B) Ultrasound image of anterior QL block after local anesthetic injection. PM, psoas major. *Source:* Reproduced with permission from Ueshima et al [155]. https://www.hindawi.com/journals/bmri/2017/2752876/abs/. Licensed under CC BY.

approach at the inferior edge of a linear probe, using an angle most suitable for the depth of the sheath. The needle tip was placed just inside the rectus sheath near the posterior aspect of the rectus abdominis muscle.

Paravertebral block

A paravertebral block has been used to provide postoperative pain relief for adults and children in a variety of settings [161,162]. Satisfactory pain relief has been demonstrated for unilateral thoracotomies and urological surgery. Potential complications are pneumothorax and vascular puncture; hypotension is rare due to the lack of sympathectomy [163]. Indeed, the increased popularity of the paravertebral block can be attributed to its relative safety and comparable efficacy when compared with epidural analgesia [164].

Ultrasonographically, the transverse process of the thoracic vertebra and rib are identified at the appropriate thoracic level [165] (Fig. 20.21A, B). The transducer is moved cranially until an intercostal ultrasound view is obtained, indicated by visualization of the parietal pleura. An in-plane needle insertion approach from lateral to medial is

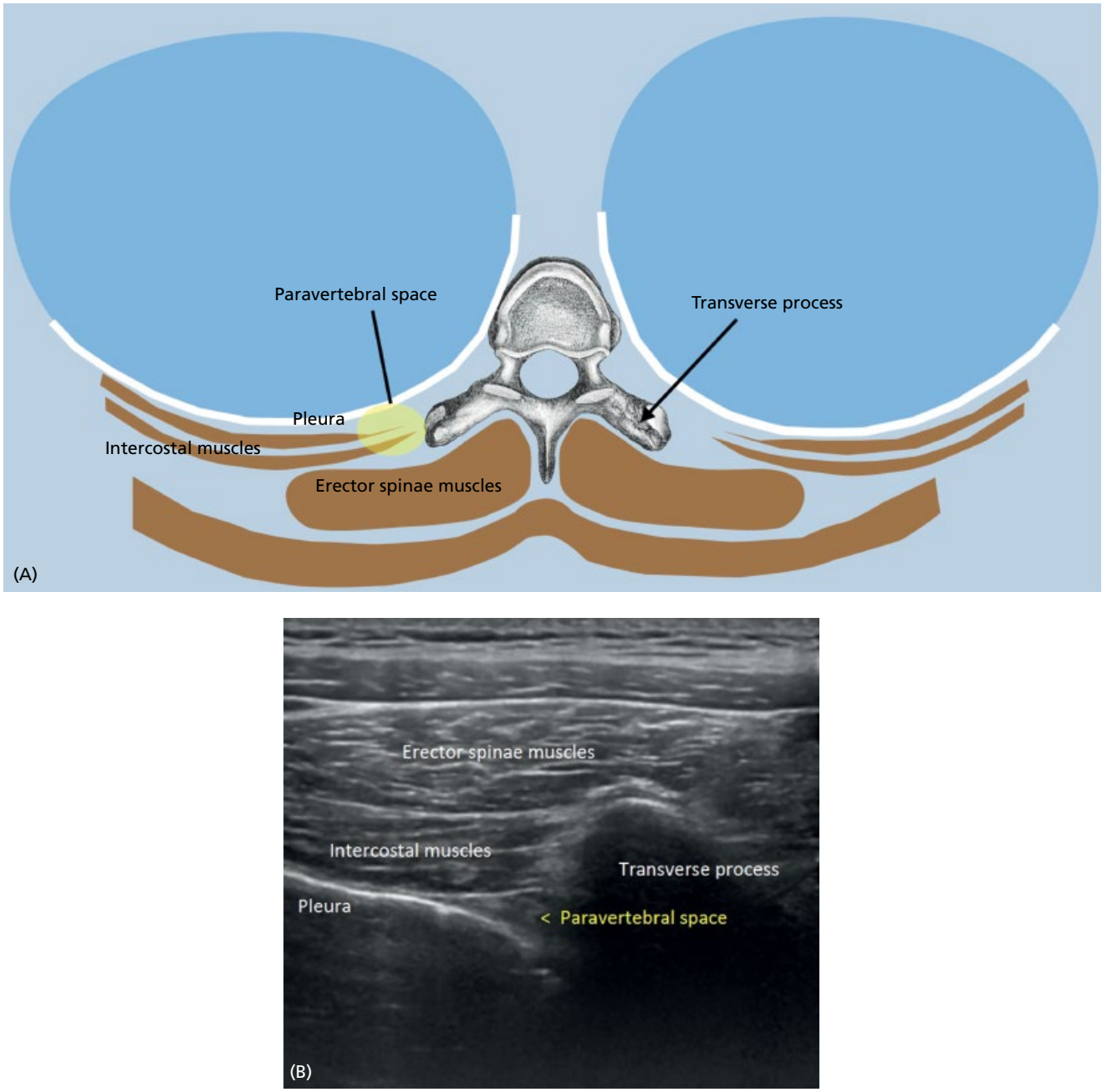


Figure 20.21 The paravertebral region. (A) Ultrasound anatomy. The paravertebral space is a wedge-shaped area positioned between the heads and necks of the ribs. The superior costotransverse ligament forms its posterior wall, the anterolateral wall is the parietal pleura with the endothoracic fascia, and the medial wall is the lateral surface of the vertebral body and intervertebral disk. (B) Ultrasound image. See text for further details. *Source:* Reproduced from O Riain et al [165] with permission of Wolters Kluwer.

used, and a total of 0.2–0.3 mL/kg of LA is injected through the needle and a subsequently threaded catheter, while the spread of LA is observed. An ultrasound-guided out-of-plane paravertebral block with the ultrasound probe positioned longitudinally to the paravertebral area has also been described.

Infraorbital nerve block

The infraorbital nerve is the terminal branch of the second division of the trigeminal nerve and is purely sensory. It leaves the skull through the foramen rotundum and enters the pterygopalatine fossa. There it exits the infraorbital foramen, dividing into four branches – the inferior palpebral, the external nasal, the internal nasal, and the superior labial. These branches innervate the lower lid, the lateral inferior portion of the nose and its vestibule, the upper lip, the mucosa along the upper lip, and the vermilion. This block can be used to provide postoperative analgesia and to favor early feeding resumption after cleft lip repair in infants [166,167]. It can also be used for nasal septal reconstruction or rhinoplasty, and in patients undergoing endoscopic sinus surgery.

Different approaches are used, including intraoral and extraoral; recently a suprazygomatic approach has been described [167]. For the intraoral approach, after palpation of the infraorbital foramen, the upper lip is folded back and a 27 ga needle is advanced to the infraorbital foramen parallel to the maxillary premolar [166]. By placing a finger at the level of the infraorbital foramen, the cephalad progression of the needle is checked. A volume of 0.5–1 mL of 0.25% levobupivacaine with 1:200,000 epinephrine is injected after careful aspiration. For the suprazygomatic approach, the needle puncture was located at the angle formed by the superior edge of the zygomatic arch below and the posterior orbital rim above. The ultrasound transducer allowed visualization of the pterygopalatine fossa, limited anteriorly by the maxilla and posteriorly by the greater wing of the sphenoid. The needle was advanced using the out-of-plane approach, and the needle tip was easily identified during movements.

Complications of blocks and their treatment

Performing a regional block may result in different complications, most of which can be avoided by learning the correct technique, using an appropriate device, and applying the basic safety rules. Despite the fact that most regional anesthetic techniques are performed under sedation or general anesthesia, large prospective and retrospective studies have demonstrated a low complication rate, particularly with peripheral nerve blocks, and fewer long-term sequelae when compared with adults having the same procedure.

Complications related to the device used

Block needles are used blindly and may thus damage a nerve trunk, especially when inserted without careful regard for nerve anatomy. Vascular lesions may lead to compressive hematoma and, at spinal levels, definitive paraplegia. If a spinal hematoma is suspected, a diagnosis must be established urgently by magnetic resonance imaging or computed tomography, and surgical treatment must follow immediately. Attempted peripheral nerve blocks can produce other injuries such as arterial wounds and pneumothorax, the presenting symptoms of which can be delayed by several hours. The technique of determining the nerve/space location may produce complications. These include nerve damage while seeking paresthesias, and complications related to the medium used for the LOR technique while locating the epidural space. The latter include dilution and increase in the injected volume of LA with saline headache, patchy anesthesia, lumbar compression, multiradicular syndrome, subcutaneous cervical emphysema, or venous air embolism. Headache is the most common complication of dural puncture in adults; its occurrence is less common in children. Treatment includes keeping the patient in a supine position, hydration with intravenous fluids, analgesia, and an autologous epidural blood patch (0.3 mL/kg) [168], which is not always free of complications. Failure to respond to the blood patch warrants further investigation. The use of caffeine or sumatriptan (a 5-HT_{1D} receptor agonist) has not been reported in children.

Complications of catheters

Insertion of an epidural catheter can lead to several complications: misplacement, kinking, knotting, rupture (especially if attempts are made to withdraw the catheter through the epidural needle). Secondary migrations into the subarachnoid space, a blood vessel, the subdural space, or the paravertebral space are sometimes reported. Leakage around the puncture point occurs in approximately 10% of cases, and inadvertent removal is not infrequent; several pediatric cases of catheter infection have also been reported. Some complications, such as cutting and knotting, become apparent only on removal of the catheter; in most cases, they are directly related to the length of catheter introduced into the epidural space, which usually should not exceed 2–4 cm. The frequency of catheter-related complications has been noted to be as high as 11% in a pediatric series [169]. The incidence of catheter malfunction (dislodgment/occlusion) is not higher in neonates [170]. Malfunctioning of infusion pumps is not uncommon.

Despite the overall excellent safety record of epidural catheter placement, as noted in the PRAN and ADARPEF studies, rarely, paraplegia has been observed as a complication of epidural catheter placement under general anesthesia. Commenting on a series of four cases of paraplegia, Berde and Greco offered recommendations to improve safety of epidural anesthesia in anesthetized children [171] (Box 20.1). Suspicion of neurological deficit should prompt immediate magnetic resonance imaging of the spine and neurosurgical consultation as appropriate; emergent laminectomy and decompression of the spinal cord in the case of acute epidural hematoma can restore function.

Box 20.1: Provisional recommendations for epidural analgesia safety in anesthetized children

1. Limit epinephrine dosing to the test dose (0.5 μg/kg in 0.1 mL/kg)
2. Prevent or promptly treat severe hypotension
3. Consider severe hypotension following test dosing or loading dosing of an epidural catheter under general anesthesia to be due to subarachnoid placement unless demonstrated otherwise
4. Consider severe hypertension following test dosing or loading dosing to possibly indicate a painful response to intraneural placement
5. Perform loss-of-resistance technique with saline, not air
6. Consider selective use of a Tsui nerve stimulation technique or fluoroscopy, as well as ultrasonography for infants, for cases of direct thoracic puncture under general anesthesia
7. Inject epidural loading doses slowly in anesthetized patients
8. Use dilute local anesthetic solutions for intraoperative epidural infusions
9. In the postanesthetic care unit, document the degree of sensory and motor blockade. If blockade appears dense, stop the infusion and observe for clear regression. If there is no regression at all over the next 3 h, consider emergent spine magnetic resonance imaging and neurosurgical consultation as appropriate. Note that wire-wrapped epidural catheters must be removed prior to magnetic resonance imaging
10. Consider patients receiving high-dose corticosteroids and/or morbid obesity to be at increased risk for epidural lipomatosis and reduced spinal canal compliance

Source: Reproduced with permission from Berde and Greco [171].

Complications related to faulty technique

Epidural abscess, meningitis, arachnoiditis, radiculopathies, diskitis, and vertebral osteitis have been reported following central blocks. Interposed bacterial filters are effective in preventing contamination. Inadvertent dural puncture with subsequent intrathecal injection of an epidural dose of LA results in total spinal anesthesia, the clinical expression of which is almost immediate respiratory arrest requiring rapid control of ventilation and, in adolescents, cardiovascular collapse. Subdural injection results in a delayed (20 min) and short-duration (60 min) block with an extensive distribution of analgesia (involving cranial nerves up to the fifth pair) but with no or minimal motor and sympathetic blockade. The injection of large volumes may result in excessive spread of the LA, which can reach distant nerves, or in too high levels of epidural/spinal anesthesia with subsequent respiratory failure due to intercostal muscle paralysis (above T4), or even in diaphragmatic paralysis (C4). Interscalene brachial plexus, lumbar plexus, and intercostal nerve blocks may lead to the same complications.

Complications due to the local anesthetic solution

The use of the wrong solutions or additives can lead to definitive neurological damage; a highly effective way to avoid syringe mismatch consists of using a specific cart for regional block procedures. Interruption of blood flow in the artery of Adamkiewicz, due either to the surgical procedure or, hypothetically, to vasoconstriction resulting from the administration of LAs with epinephrine, may result in anterior spinal artery syndrome, which combines definitive loss of lower limb motor function with, at least partially, intact sensory function. Epidural anesthesia has been implicated in the flaring of latent infections (herpes, neuroimmunological diseases such Guillain–Barré syndrome). Of greater concern is the risk of unmasking latent neurological diseases such as spinal cord compression, cerebral tumors, angiomas, or an epidural abscesses. Allergy to aminoamides is rare, and most adverse reactions are related to adrenaline.

Treatment of LA convulsions consists of supplementing the child with oxygen and providing respiratory assistance; if convulsions persist after oxygenation, it is recommended that small intravenous doses of benzodiazepines (diazepam 0.1 mg/kg, midazolam 0.05 mg/kg) or thiopental 4 mg/kg be administered. Persistent convulsions require muscle relaxation (succinylcholine injection 1.5–2 mg/kg), intubation, and assisted pulmonary ventilation to prevent acidosis.

Treatment of LA cardiac arrest: immediate treatment is required, including oxygen supplementation, ventilation, and, if appropriate, external cardiac massage, sodium bicarbonate, and inotropic support. Ventricular tachycardia or fibrillation requires electrical defibrillation. A 20% Intralipid bolus of 1.5 mL/kg and then an infusion of 0.5–1 mL/kg/min is also indicated. See Chapter 45 for more detailed discussion of treatment of LA toxicity including cardiac arrest.

Epidemiology of complications

Complications were rare and similar in both of the ADARPEF studies [1,3]. As reported by the literature, they were more frequent (by four times in the last ADARPEF study) in children aged <6 months than in children aged >6 months. Central regional anesthesia has the highest incidence of complications (seven times higher than peripheral). The incidence was low despite an increase in the use of central neuraxial blockade in the last 12 years. Significant complications are rare, as indicated by results from a UK audit (5 years, 10,633 epidurals performed) reporting permanent residual neurological deficit in a child aged 3 months (1-year follow-up), two epidural abscesses, one case of meningitis, one postdural puncture headache requiring active blood patching, and one drug error resulting in cauda equina syndrome. The UK audit also reported five cases of severe neuropathy/radiculopathy which resolved over a period of 4–10 months using pharmacological therapy in a pain clinic. Thus in this study the incidence of serious complications was 0.09% [2]. The last ADARPEF study [3] records a very low overall morbidity; almost six times lower that in central regional anesthesia. Despite two colonic punctures, that should encourage anesthesiologists to use peripheral rather than neuraxial (including caudal) blocks as often as possible when appropriate.

The use of catheters does not seem to increase the occurrence of complications, even if cardiac toxicity following a secondary injection through a catheter is due to an inadvertent displacement of the catheter. Some complications (at least drug error, wrong side block, lower limbs lifting resulting in extended spinal anesthesia) were avoidable. In the last ADARPEF study, LA toxicity resulted in one case of convulsions [3] while the UK audit only reported two respiratory arrests and one seizure following central regional anesthesia [2]. None of these complications required lipid rescue treatment. Some other complications (prolonged duration of spinal anesthesia in two premature infants, one drug error, and a case of cardiac toxicity without cardiac arrest) were probably also avoidable. It is thus possible to improve the safety of pediatric regional anesthesia if basic precautions are followed.

More recently, the PRAN results confirmed the safety of pediatric regional anesthesia [4]. Out of a total of 14,917 regional blocks, there were no deaths or complications with sequelae lasting more than 3 months. Single-injection blocks had fewer adverse events than continuous blocks, although the most frequent events (43% of all events) in the latter group were catheter malfunctions (kinking, disconnection, or inadvertent dislodgement). Peripheral nerve blocks were frequently used (35%), driven by the widespread use of ultrasound (83% of upper extremity and 69% of lower extremity blocks). This confirms the safety of ultrasound technique for peripheral blocks. However, the incidence of both postoperative neurological syndrome and LA systemic toxicity is similar in children and adults (Tables 20.7 and 20.8).

Table 20.7 Postoperative neurological syndrome (children versus adults).

Study	Incidence
ADARPEF Ecoffey et al (children) [3]	0.17/1000
PRAN Taenzer et al (children) [56]	1.31/1000
	>6 months 0.019/1000
Auroy et al (adults) [178]	0.19/1000
Sites et al (adults) [179]	1.8/1000
	>6 months 0.9/1000
Ecoffey et al (axillary block, adults) [76]	0.037/1000

Table 20.8 Local anesthetic systemic toxicity (children versus adults)

Study	Incidence
ADARPEF Ecoffey et al [3]	0.03/1000
PRAN Taenzer et al [56]	0.09/1000
Sites et al (adults, seizures) [179]	0.08/1000
Ecoffey et al (axillary block, adults) [76]	0.15/1000

Regional anesthesia and acute compartment syndrome

In children, the diagnosis of acute compartment syndrome is often more difficult (e.g. preverbal children), and the main warning sign is excruciating pain that is not directly related to the trauma itself. Regional anesthesia has often been considered by surgeons to be responsible for delaying the diagnosis by masking ischemic pain. However, Johnson et al [172] identified the following clinical signs of impending compartment syndrome in the lower limbs: increasing pain with increasing need for analgesics, pain remote from the site of surgery, paresthesia not attributable to analgesia technique, signs of reduced perfusion of the painful site, local swelling, and pain on passive mobilization of the painful site. They also stressed that the nurses and doctors caring for the child in the postoperative period should be aware that he/she is at increased risk for acute compartment syndrome.

KEY POINTS: EVIDENCE-BASED CONCLUSIONS AND CLINICAL ADVICE FROM THE ESRA–ASRA JOINT COMMITTEE PRACTICE ADVISORY ON ACUTE COMPARTMENT SYNDROME [6]

- There is no evidence that regional anesthetics increase the risk for acute compartment syndrome or delay its diagnosis
- A preoperative discussion with the patient's family and the surgical team should inform them of this rare but serious complication
- We suggest the following "best practice rules" to reduce or avoid the risk of compartment syndrome in children undergoing surgery with perioperative regional anesthesia:
  - Use 0.1–0.25% bupivacaine, levobupivacaine, or ropivacaine because they are less likely to mask ischemic pain and/or produce muscle weakness
  - For continuous infusions of bupivacaine, levobupivacaine, or ropivacaine limit concentrations to 0.1%
  - For tibial compartment surgery or other high-risk surgeries for compartment syndrome, restrict both the volume and concentration in sciatic catheters
  - LA additives should be used with caution because they can increase the duration and/or density of the block
  - High-risk patients should be followed up by acute pain services to allow early detection of potential signs and symptoms
  - If acute compartment syndrome is suspected, compartment pressure measurements should be urgently obtained

Caudal analgesia and hypospadias complications

Caudal anesthesia has been utilized frequently for a number of years for hypospadias repair, but in recent publications concerns have arisen about a possible increased rate of postoperative urethrocutaneous fistula development with caudal analgesia compared to penile block. The mechanism is postulated to be penile engorgement from increased blood flow, and tension on the suture lines, leading to suboptimal healing and fistula formation. A prospective, randomized study of penile block versus caudal analgesia in 54 patients revealed a 27% increase in penile volume with caudal analgesia versus 2.5% with penile nerve block ($p < 0.001$); analgesia was improved and longer lasting with the penile nerve block [173]. All five cases of urethral fistula were in caudal block patients. Four subsequent retrospective studies in over 3300 patients have yielded mixed results, with three indicating increased incidence of fistula with caudal analgesia [174,175] and two not finding a difference [176,177].

Conclusion

The goal of regional anesthesia in the pediatric population must always be the provision of effective, safe analgesia with low rates of morbidity and low risk of adverse side-effects. Indeed, safety concerns are prominent because most children coming for surgery and anesthesia are healthy and tolerate systemic opioids with a good safety margin.

Studies have demonstrated a diminished stress response, fewer episodes of hypoxia, greater cardiovascular stability, faster return of gastrointestinal function, a reduced need for postoperative ventilation, and a shorter stay in intensive care in children who have had surgery performed under regional anesthesia.

In this era of evidence-based medicine, purists would claim that further prospective studies with larger sample sizes are necessary to demonstrate that regional anesthesia has significant benefits and offers a better outcome than other forms of analgesia in children.

Finally, ultrasound guidance has been shown to improve the block characteristics and the safety of regional anesthesia in pediatrics.

CASE STUDY

A 7-year-old child was scheduled for primary, elective, unilateral metatarsal osteotomy which was expected to require lengthy administration of potent analgesics and hospitalization of 4–5 days. The anesthetic procedure was combined general anesthesia and regional anesthesia with continuous popliteal sciatic catheter on an ambulatory basis. The parents were therefore required to (1) live within a 1-h drive of the hospital, (2) be able to contact medical staff or nurses 24 h a day, (3) be able to return to the hospital quickly if required, (4) understand a visual analog scale, (5) provide rescue oral analgesics, (6) observe the analgesic device (catheter and elastomeric pump) and the skin under the dressing, and (7) screen for possible local anesthetic-related complications. A peripheral intravenous catheter was placed under general anesthesia just before surgery. After premedication with oral midazolam, anesthesia was induced and maintained using sevoflurane, oxygen, and nitrous oxide via a facemask. Intravenous saline solution, at a rate of 5–10 mL/kg/h, was infused throughout the procedure. The child received an antibiotic and antiemetic prophylaxis (0.2 mg/kg dexamethasone). With the child in the lateral position, ultrasound-guided placement of a peripheral nerve sciatic catheter was performed. We were able to view the catheter exiting the needle tip and during advancement while using long-axis views of the nerves [134]. After confirming the nerve identity using a long-axis plane, the probe was rotated 90°, and the needle and catheter were introduced in-plane at a tangential angle. Injection of local anesthetic confirmed the needle tip and catheter location. The catheter was introduced 15 mm beyond the introducer cannula, affixed securely to the skin by a "U" stitch, covered by a transparent dressing, and taped onto the thigh. After negative aspiration, 0.2 mL/kg of ropivacaine 5 mg/mL was injected in divided doses via the catheter, with gentle aspiration every 2 mL. During the surgical procedure, if intravenous opioid rescue was required, the blockade would be considered ineffective and the catheter removed. Since the surgery lasted more than 1 h, an additional injection of 0.1 mL/kg of the same local anesthetic solution was administered hourly. For the surgical procedure, a tourniquet was applied at the thigh and inflated according to the surgeon's discretion. In the postanesthetic care unit, the sensory and motor blockade of the foot was evaluated. As soon as the child's toe motor function recovered, the sciatic popliteal catheter was connected to a multirate, disposable infusion elastomeric pump (Infusor LV; Baxter, Deerfield, IL, USA), containing 200 mL of 0.2% ropivacaine, with 1.5 µg/mL clonidine (mainly for its sedative effect in children), giving a fixed infusion rate according to the child's weight (0.1 mL/kg, i.e. 2.5 mL/h; infusor-rate possibilities 0.5–5 mL/h). In the hospital, if pain control was considered insufficient, intravenous acetaminophen or opioids were given as rescue. The criteria for discharge from the hospital depended on the presence of a plaster splint (observation day 1 in hospital) and the absence of local postoperative complications. Totally efficient continuous sciatic nerve block, i.e. the ability to ambulate with crutches without assistance or dizziness, and urinary voiding were also required before home discharge. Before home discharge, nurses gave the parents the following training: extensive explanation about the use of the visual analog scale to diagnose pain, elastomeric device surveillance, and evaluation of sensory and motor blockade, spontaneous mobility, and short delay in capillary refill after pressure on the child's test toes. When the child fulfilled the criteria for discharge, the medical staff checked both the child's and parents' comprehension of the provided instructions. The parents agreed never to leave their child alone, and to record (four times daily, at breakfast, lunch, dinner, and bedtime) the following items: changes in behavior, sleep disturbance, quality of appetite, play activity, the occurrence of any adverse effects and technical problems possibly related to the analgesic technique, temperature, evaluation of the blockade and the integrity of the child's dressing, episodes of pain, and the use of an oral rescue analgesic (acetaminophen twice a day, or a combination of acetaminophen and codeine at bedtime). Instructions were provided regarding protection of the anesthetized limb, signs of local anesthetic toxicity, a direct return to the hospital if needed, and 24-h contact information. The elastomeric pump was filled before discharge. At the end of the procedure, the child returned to hospital and met with the medical staff. The parents shared their feelings and observations about the postoperative period at home, and their overall satisfaction. The catheter was then removed, and its distal portion was sent for bacteriological analysis.

A total of 47 children were treated with this protocol in a prospective feasibility study [135]. The main finding of this observational study is that analgesia at home by continuous sciatic nerve block with an infusion elastomeric pump is effective, with pain control rated excellent or good in 89% of patients. It is also feasible and associated with no major complications in this study, and enables children to experience ambulatory or shortened hospital stays [135]. Another interesting point is that parents trained by nurses readily understood the method of pain screening, and managed the analgesic device well.

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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Video clips

This chapter contains the following video clips:

Video clip 20.1 Caudal block.
Video clip 20.2 Spinal block.
Video clip 20.3 Supraclavicular nerve block – ultrasound guided.
Video clip 20.4 Femoral nerve block – ultrasound guided.
Video clip 20.5 Sciatic nerve block – ultrasound guided.
They can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

CHAPTER 21

Anesthesia for Fetal Intervention and Surgery

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Introduction

In 1963, Sir (Albert) William Liley, a New Zealand perinatologist, was the first to demonstrate that fetal diagnosis and treatment were possible when he administered a intraperitoneal blood transfusion to treat Rh disease-induced fetal hydrops (erythroblastosis fetalis) [1]. He had determined the severity of rhesus isoimmunization by analyzing the spectral absorption from a sample of amniotic fluid. Others attempted exchange transfusion by directly cannulating fetal vessels through a small uterine incision. Early results were not encouraging and further attempts at fetal intervention were initially abandoned [2]. A decade later, G.C. Liggins, another New Zealand perinatologist, demonstrated the beneficial effects of maternal glucocorticoid administration to augment fetal surfactant production in fetuses at risk for respiratory distress syndrome [2]. In 1981, after careful experimentation in sheep [3–5] and monkeys [6], the first successful human fetal surgery was performed at the University of California San Francisco by Michael Harrison to treat lower urinary tract obstruction-induced bilateral hydronephrosis by creating a vesicostomy [7].

Fetal surgery would not have been possible without the improvements in sonographic resolution that occurred in the early 1980s. Advances in prenatal diagnosis substantially improved the ability to recognize and more precisely delineate fetal anatomy and anomalies. In addition, ultrasound-guided percutaneous umbilical blood sampling (PUBS) was now possible. Associated with these advances in imaging were advances in amniotic fluid analysis for detection of many metabolic disorders and chromosomal abnormalities, assessment of fetal pulmonary maturity, and determination of severity of fetal anemia. Advances in fetoscopy allowed direct visualization of the fetus and diagnostic tissue sampling.

Serial sonographic examinations of fetuses facilitated delineation of the pathophysiology and natural history of congenital diaphragmatic hernia, hydrocephalus, nonimmune hydrops, and obstructive hydronephrosis. However, most anatomical malformations diagnosed *in utero* are unsuitable for antenatal fetal intervention. Thus, only a few fetal malformations are appropriate for intrauterine surgery.

Fetal surgery would also not be possible without the information sharing and collective conceptualization between physicians from a wide variety of disciplines interested in fetal diagnosis and therapy. This was greatly facilitated by Harrison et al's early (1981) organization of a symposium with worldwide experts [8]. A registry for fetal interventions was established and ethical guidelines adopted, leading to the creation of the International Fetal Medicine and Surgery Society and subsequently to the journal *Fetal Diagnosis & Therapy*. These founding guidelines remain relevant with minor modification (Box 21.1) [8,9]. The pioneering work from a few medical centers spawned the field of fetal medicine worldwide. Fetal treatment centers around the world now rely on the expertise of radiologists, geneticists, perinatologists, pediatric cardiologists, neonatologists, social workers, support staff, and many others, as well as fetal surgeons and anesthesiologists.

Before undertaking a specific fetal surgical procedure, its feasibility, safety, and efficacy must be assured. Fetal surgery requires that a fetus has a normal karyotype and an accurately diagnosed and isolated anomaly that has a high probability of death, severe disability, or irreversible harm before fetal lung maturity occurs, and for which removing the lesion might

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

Box 21.1: Guidelines for performing fetal procedures

1. Accurate diagnosis and staging of a condition is possible
2. Singleton fetus with other anomalies contraindicating fetal intervention excluded
3. Progression and severity of the condition is understood and prognosis established
4. Currently no effective postnatal therapy and if not treated before birth the anomaly would result in fetal death, irreversible organ damage, or other severe morbidity
5. *In utero* surgical procedure proven feasible in animal models, reversing deleterious effects of the condition and allowing development to proceed normally
6. Maternal risk is acceptably low
7. Interventions performed in specialized multidisciplinary fetal treatment centers within strict protocols and approval of the local ethics committee, with informed consent of the mother or parents
8. Access to high-level specialized medical care including a high-risk obstetric unit, bioethical counseling, and psychosocial care

Source: Adapted from Sudhakaran et al [9] and Harrison et al [8].

allow development to proceed relatively normally. Accurate and complete diagnosis is required to avoid intervention when the procedure would be futile or when the fetus is so mildly affected that postnatal treatment would be equally effective. There should be a good physiological rationale previously tested in animals and controlled human trials that established efficacy and safety of the procedure. Family counseling for risks and potential benefits must be comprehensive and include options for elective termination of pregnancy or continuation of pregnancy without therapy. Consent must also include a discussion that the surgery and potential benefits for the fetus might incur risks for the mother. Maternal risk should be small, and careful preoperative assessment is mandatory to ensure that the risk is acceptably low [10].

Fetal surgical interventions are broadly categorized into three different kinds of procedures. *"Open procedures"* involve maternal laparotomy and hysterotomy and uterine stapling to seal membranes to the endometrium and provide myometrium hemostasis. Most myelomeningocele repairs, resections of congenital pulmonary airway malformations (CPAMs), and sacrococcygeal teratoma debulking are performed "open." Open procedures are technically the most complicated of fetal procedures and entail the most risk, particularly for separation of membranes, preterm premature rupture of membranes (PPROM), preterm labor and delivery, infection, hemorrhage, pulmonary edema, and fetal complications that include heart failure, intracranial hemorrhage, and fetal demise. Chorioamniotic membrane separation can cause amniotic bands, umbilical cord strangulation, and fetal demise [11]. Preterm delivery causes significant morbidity and mortality for fetuses that otherwise might benefit from these interventions. Consequently, preoperative, intraoperative, and postoperative tocolysis is crucial.

Fortunately, overall maternal risks are minimal, but include blood loss, blood transfusion, infection, placental abruption, and pulmonary edema from tocolysis [10,12]. Location of the uterine incision mandates cesarean delivery for all subsequent pregnancies after open procedures secondary to increased risk of uterine dehiscence.

The second type of fetal surgery is *"minimally invasive or percutaneous"* and involves intrauterine access using needles or trocars that allow endoscopic or sonographic guided procedures. Minimally invasive procedures are less risky than open procedures, but PPROM is still a major problem. These techniques are employed for fetal blood sampling, treatment of fetal anemia by intrauterine transfusion, percutaneous fetal cardiac valvuloplasty, treatment of obstructive uropathy, thoracoamniotic shunting to mitigate CPAM, treatment of unbalanced blood flow between monochorionic twins, radiofrequency ablation (RFA) of umbilical blood flow of a nonviable twin, and tracheal occlusion by endoluminal balloon placement to treat congenital diaphragmatic hernia. The trend in fetal surgery is to develop minimally invasive techniques to avoid open procedures. An example of this trend is the advancement of myelomeningocele (MMC) repair from an open technique requiring hysterotomy to one where the repair is completed using endoscopic access to the uterus following laparotomy.

The third type of fetal surgical intervention, the *EXIT procedure* (*ex utero* intrapartum treatment) is a modification of cesarean section [13]. EXIT procedures preserve placental gas exchange during surgery and provide time to secure a difficult airway by tracheal intubation or tracheostomy for conditions that would make newborn tracheal intubation unfeasible or very difficult (e.g. cystic hygromas, cervical teratomas). The EXIT procedure is also used for thoracotomy to treat cystic adenomatoid malformation (CCAM, otherwise referred to as CPAM by some), transitioning from placental gas exchange to extracorporeal membrane oxygenation (ECMO) for anticipated pulmonary insufficiency, or complete resection of a giant cervical teratoma.

Fetal surgery: indications, procedures, and outcomes

The following sections summarize the rationale for fetal intervention, a description of both surgical and anesthetic considerations for each procedure, and a review of outcome data. Details of anesthetic techniques are presented in sections that follow.

Congenital diaphragmatic hernia

Approximately 1 in 2000–5000 neonates have a congenital diaphragmatic hernia (CDH). Incomplete fetal diaphragm formation allows the abdominal contents to enter the thoracic cavity and produce varying degrees of pulmonary parenchymal and vascular hypoplasia. Pathophysiological changes include decreased number of alveoli, thickened interstitial tissue and alveolar walls, decreased surface area for gas exchange, reduced lung compliance, and decreased pulmonary vasculature that has medial hyperplasia and adventitial thickening [14]. After birth, hypoxia, hypercarbia, and acidosis induce further pulmonary vasculature constriction and pulmonary hypertension. This increases right-to-left shunting of blood and causes further hypoxia and acidosis. The majority of CDH defects are left-sided, and more than half are associated with other birth defects [15]. Mortality is associated with the degree of pulmonary insufficiency and pulmonary hypertension present [16,17]. Survival has improved

significantly over the past two decades at many tertiary centers. The following elements have led to this improved survival of patients with CDH: (1) removing the herniated abdominal contents from the chest and closing the diaphragm defect postnatally; (2) ventilation techniques that cause less barotrauma (high-frequency oscillation); (3) administration of surfactant; and (4) ECMO. Postnatal CDH survival now typically occurs in more than 70% of patients, but varies widely among centers and is significantly affected by the presence of other defects [18–20].

It was postulated that correction of CDH *in utero* might improve fetal lung development and significantly reduce the degree of pulmonary hypoplasia found at birth. In controlled trials, fetal lamb models of CDH confirmed the benefit of *in utero* repair by decreasing the progression of pulmonary hypoplasia and pulmonary vascular changes and improving newborn survival [3]. Although removing the abdominal contents from the chest and repairing the defect is technically feasible, it is difficult in human fetuses, and this intervention had limited success in those with severe disease [21]. Lessons learned from these patients included that an abdominal patch needed to be placed to prevent increases in intra-abdominal pressure and the associated compromise of the ductus venosus blood flow, and that both a thoracic and an abdominal incision was required to facilitate removing the liver from the chest and placing a diaphragmatic patch. However, replacing the liver in the abdomen often caused acute and severe decreases in cardiac preload and was associated with increased intraoperative fetal mortality [21]. Problems with blood loss from the uterine incision and amniotic fluid leaks after closure were solved by use of a stapling device. However preterm labor remained a significant problem after surgery and caused neonatal morbidity and mortality. Results from a small prospective trial of open fetal surgical intervention comparing *in utero* repair with surgical repair after birth failed to demonstrate improvement with open fetal surgical intervention [17].

Given the difficulties encountered with primary repair of CDH *in utero*, another strategy was pursued. It was known that fetal lungs secrete about 100–125 mL/kg/day of fluid that normally passes through the fetal trachea and mouth into the amniotic fluid. Since fetuses with congenital high airway obstruction cannot expel the fluid, they develop hyperplastic lungs [22]. Reversibly obstructing the trachea causes lung fluid accumulation and allows the developing lungs to expand and grow and decrease the amount of pulmonary hypoplasia [23]. The concept, "plug the lungs until it grows" (PLUG), was tested in fetal lambs and shown to decrease pulmonary hypoplasia and herniation of abdominal contents and improve neonatal respiratory function [24]. Although *in utero* tracheal occlusion decreases much of the pulmonary hypoplasia and hypertension, there are fewer type II pneumocytes and less secreted surfactant. Removing the tracheal obstruction before delivery may reduce this unwanted effect [25,26].

The initial method of creating a reversible, controlled tracheal occlusion during open fetal surgery required both maternal laparotomy and hysterectomy, and involved either an internal tracheal plug or external tracheal clip [27]. Since the clip or plug had to be removed surgically, the EXIT procedure was developed (see section "*Ex utero* intrapartum treatment procedure").

Unfortunately, few patients survived these initial open procedures. Of the first 13 fetuses undergoing this treatment, only 15% survived compared to 38% of fetuses receiving standard postnatal treatment [28]. Preterm labor occurred at 30 weeks' gestation and was a major cause of mortality in the fetal treatment group; the postnatal treatment group was born at 37.5 weeks. A second series of 15 fetuses with CDH treated with external clips at the Children's Hospital of Philadelphia had a 30% survival rate [29], but tracheal occlusion did not consistently improve the lung hypoplasia or postnatal pulmonary function.

Improvements in endoscopic and ultrasound imaging techniques allowed video-assisted fetal endoscopic (FETENDO) techniques to replace open surgical procedures for tracheal occlusion. Application of external fetal tracheal clips by FETENDO improved survival to 75% in eight fetuses [28]. To reduce fetal laryngeal nerve and tracheal trauma, a small balloon was placed in the trachea by percutaneous endoscopic endotracheal intubation at University of California San Francisco (UCSF). The balloon, which is typically used for endovascular occlusion of intracranial aneurysms, is inflated to occlude the tracheal lumen, detached, and left in place until delivery via EXIT procedure (Figs 21.1, 21.2). The balloon is deflated and removed prior to birth by endoscopy.

A prospective randomized controlled trial (1999–2001) compared fetal tracheal occlusion (n = 11) for intrauterine treatment of severe CDH with repair after birth (n = 13) [30]. Eligibility included 22–28 weeks' gestation, a left-sided CDH, herniation of the liver into the left hemithorax, normal karyotype, and a lung to head ratio (LHR) <1.4. LHR is the ratio of cross-sectional area of the contralateral lung to the head circumference as determined by two-dimensional ultrasound. The LHR is a good indicator of the severity of pulmonary hypoplasia and the likelihood of survival [31]. The trial was stopped due to an unexpected high survival rate in the control arm (77% versus 73%). Secondary measures of neonatal morbidity were not different between groups, but PPROM and preterm delivery was more common in the fetal treatment group (30.8 weeks versus 37.0 weeks) [30]. A reason for the lack of difference in morbidity at 90 days may have been overly broad LHR inclusion criterion. Using an LHR of 1.4 likely allowed inclusion of many fetuses who would survive with standard care. Table 21.1 compares outcomes of expectant management and fetoscopic tracheal balloon occlusion in fetuses with left-sided CDH and liver herniation, showing improved outcomes for *in utero* treatment of fetuses with LHR ≤1.0.

Minimally invasive fetoscopy for tracheal occlusion and prenatal tracheal balloon removal before delivery may improve lung growth, minimize effects on type II alveolar cells [32], and avoid morbid EXIT procedures. Comparison of the EXIT procedure to predelivery balloon removal at 34 weeks' gestation in 24 fetuses with severe CDH (LHR ≤1.0 plus intrathoracic liver) that underwent fetal endoscopic tracheal occlusion (FETO) at 26–28 weeks' gestation demonstrated improved 28-day survival (p = .013) in the balloon reversal group (83%) compared to the EXIT group (33%) [33]. There were no instances of maternal hemorrhage, pulmonary edema, or infection. This "plug–unplug sequence" may be more ideal in that the cyclical occlusion

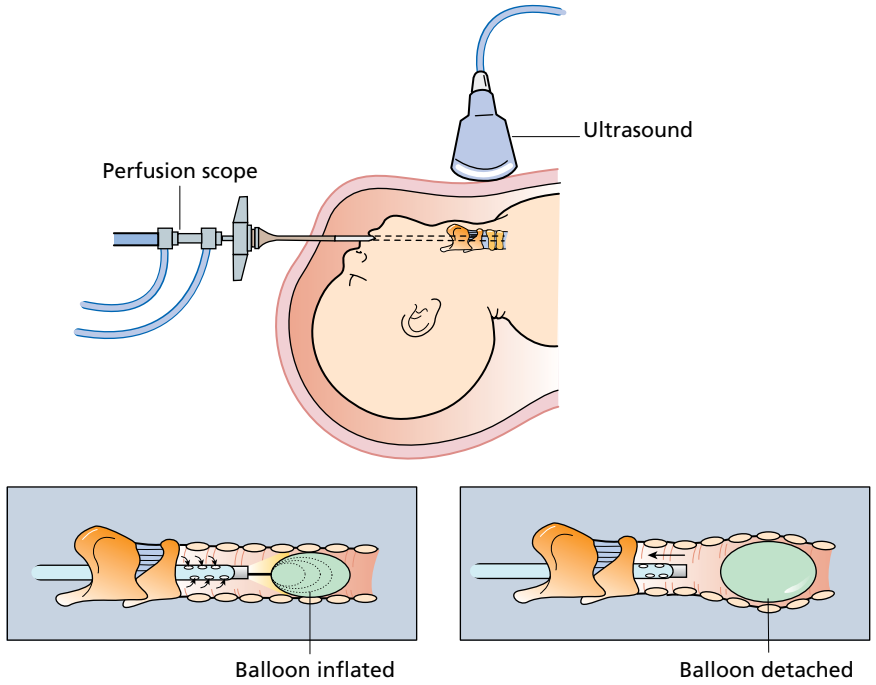


Figure 21.1 Schematic of video-assisted fetal endoscopic (FETENDO) fetal balloon placement. *Source*: Courtesy of UCSF Fetal Treatment Center.

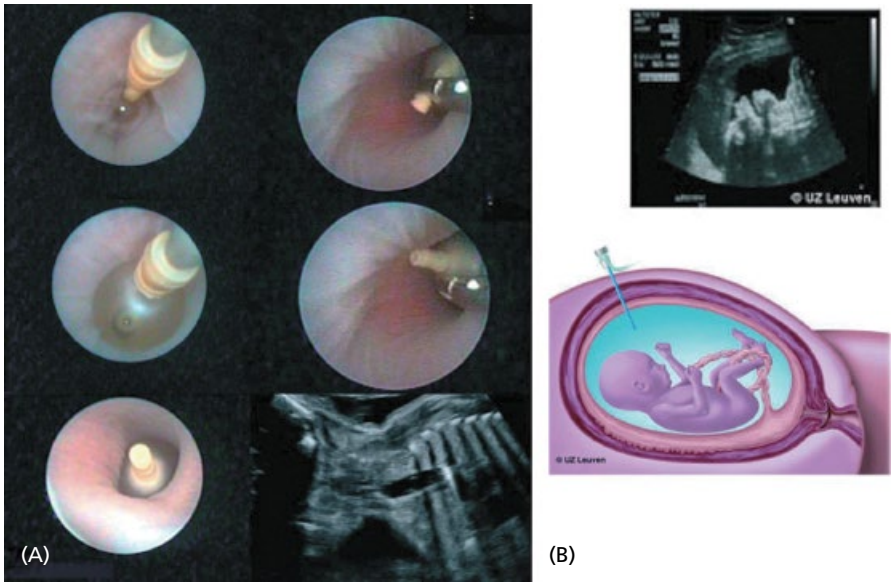


Figure 21.2 (A) Fetoscopic images of tracheal balloon insertion. (*Left column, top to bottom*) The catheter, loaded with the balloon, is inserted, the balloon is inflated between carina and vocal cords and then detached. (*Right column*) The upper two images show the balloon being retrieved by fetoscopic extraction, using a 1 mm forceps. The bottom panel is an ultrasound image of the balloon in place. (B) Schematic drawing of cannula insertion toward the fetal mouth. Above the schematic is the ultrasound image in the direction of the cannula. *Source*: Reproduced from Gucciardo et al [220] with permission of Elsevier.

and release may allow pulmonary structural maturation, pulmonary artery remodeling, and pneumocyte maturation [33]. A detachable tracheal balloon is endoscopically placed in the trachea and removed prenatally by a second fetal endoscopic tracheoscopy prior to labor. If premature labor occurs prior to endoscopic removal, an EXIT procedure is occasionally required. Postnatal therapy includes neonatal tracheal intubation, high-frequency ventilation, and nitric oxide or ECMO if needed in addition to surgical repair of the diaphragm.

A recent single-institution prospective observational cohort study compared treatment of severe CDH (LHR <1.0 and liver herniation) using FETO with historic controls [34]. Balloon placement occurred at a mean of 28 weeks' gestation with endoscopic removal at 34 weeks. The *in utero* treatment group showed an increased 2-year survival rate (67% versus 11%) and less need for ECMO. A recent meta-analysis of five trials of severe CDH noted that *in utero* FETO treatment favored survival with an odds ratio of 13 compared to historic controls [35]. Despite these compelling results it is important to

Table 21.1 Postnatal survival rate in fetuses with left-sided congenital diaphragmatic hernia and intrathoracic liver herniation based on fetal lung to head ratio at 23–29 weeks' gestation.

LHR (mm)	Expectant management		Fetoscopic tracheal occlusion	
	n	Survival	*n*	Survival
0.4–0.5	2	0	6	1 (16.7%)
0.6–0.7	6	0	13	8 (61.5%)
0.8–0.9	19	3 (15.8%)	9	7 (77.8%)
1.0–1.1	23	14 (60.8%)	–	–
1.2–1.3	19	13 (68.4%)	–	–
1.4–1.5	11	8 (72.7%)	–	–
≥1.6	6	5 (83.3%)	–	–
Total	86	43 (50%)	28	16 (57.1%)

LHR, lung to head ratio.
Source: Reproduced from Jani et al [39] with permission of Elsevier.

understand that these comparative results may contain significant selection bias or improvement in clinical techniques and care with time. Consequently, it is too early to recommend FETO for treatment of CDH as part of routine clinical care [36]. An ongoing multicenter randomized European study titled Tracheal Occlusion To Accelerate Lung (TOTAL) growth started in 2009 [37]. It has two treatment arms that compare standard postnatal management to both early FETO intervention (27–30 weeks' gestation) for severe lung hypoplasia and later FETO intervention (30–32 weeks' gestation) for moderate hypoplasia. Balloons are removed endoscopically at 34 weeks in both of these treatment arms. Because LHR changes during gestation, this trial also utilizes a ratio of observed to expected LHR as a more predictive measure of survival likelihood [38,39]. Trial results are expected to better determine the optimal gestational age for *in utero* intervention. Chapter 22 presents information about postnatal treatment of CDH.

KEY POINTS: CONGENITAL DIAPHRAGMATIC HERNIA

- A lung to head ratio (LHR) of ≤1.0 indicates severe CDH that may be amenable to fetal therapy
- Video-assisted fetal endoscopic techniques to insert a balloon to occlude the trachea, with removal by a second procedure before birth, have resulted in improved survival in recent series
- The TOTAL randomized trial comparing standard postnatal treatment to early or late tracheal occlusion will add important data to management options for CDH

Twin–twin transfusion syndrome

The majority of monochorionic twins have abnormal chorionic blood vessel connections in the placenta that can result in twin–twin transfusion syndrome (TTTS). Normally, the umbilical artery carries deoxygenated blood to the surface of the placenta where it branches, traverses the placental surface, and then descends into capillary divisions where gases and nutrients are exchanged with the maternal circulation. The returning "paired" system consists of a vein that lies directly next to an artery as it returns to the umbilical cord (Fig. 21.3A, B). This vascular configuration is associated with placental cotyledons and represents normal fetal placental vascular anatomy.

In TTTS, a branch from an umbilical artery travels along the surface of the placenta and descends into the cotyledon, where instead of connecting with a paired vein, it connects with an *unpaired* vein that now carries blood to the other twin [40] (Fig. 21.3C, D). With this abnormal arterial–venous (AV) connection, blood moves unidirectionally from one twin to the other. Whether the flow goes to or from either fetus depends on which one contributes the arterial vascular

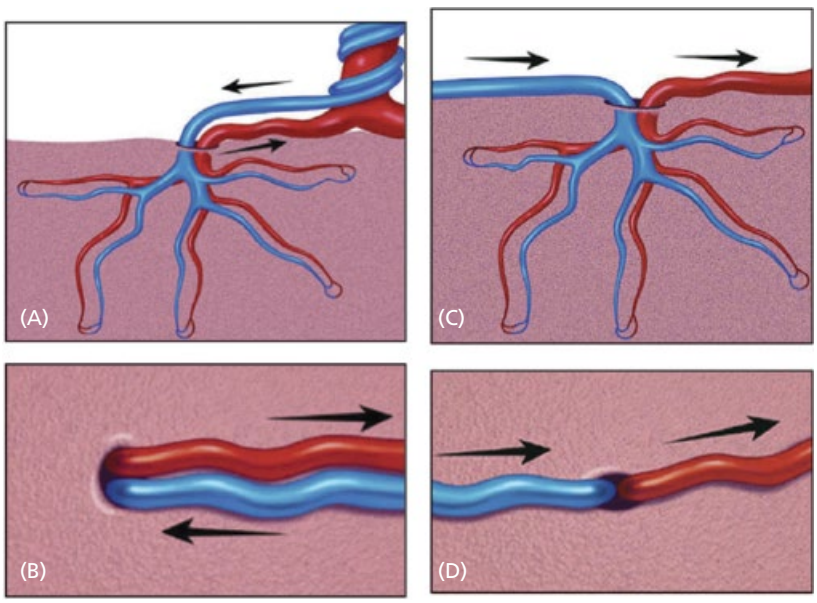


Figure 21.3 (A) Normal angioarchitecture (cotyledon). (B) Superficial view of bidirectional flow into and out of a cotyledon. (C) Abnormal inter-twin connection: arteriovenous anastomosis. (D) Superficial view of unidirectional flow into and out of the cotyledon as a result of the inter-twin arteriovenous anastomosis. *Source*: Reprinted with permission from Rand and Lee [221] with permission of Elsevier.

connection. These one-way AV connections are common in monochorionic placentas [41], yet only about 10–15% of monochorionic pregnancies have TTTS, which suggests that the abnormal AV connections and overall blood flow are relatively balanced between most fetuses.

The unequal chronic blood flow distribution between the twins causes the symptoms of TTTS [42,43]. Artery-to-artery (AA) and vein-to-vein (VV) end-to-end anastomoses also occur in monochorionic placentas. An AA connection protects against TTTS if it equalizes overall resistances and blood flow between the twins. AA anastomoses are associated with nine times less TTTS [41]. Placental sharing, vasoactive mediators, and abnormal cord insertion may also influence the development of TTTS [44]. This syndrome usually presents at 15–26 weeks' gestation in approximately 10% of monochorionic twin pregnancies [42,45].

The unbalanced flow of TTTS causes hypovolemia, oliguria, oligohydramnios, and intrauterine growth restriction in the donor twin (often referred to as a "stuck" or "pump" twin). This twin is at risk of developing neonatal renal failure, renal tubular dysgenesis and dysfunction, and high cardiac output-induced hydrops fetalis. Part of the mechanism of TTTS may be hypovolemia-induced upregulation of the renin synthesis system, increased angiotensin II, aldosterone, and antidiuretic hormone, which causes further fetal vasoconstriction and reduction of placental blood flow in the donor fetus [46]. The recipient twin has polycythemia, polyuria, polyhydramnios, and hypertrophic cardiomyopathy. The recipient is at risk for hydrops fetalis and fetal death.

A major threat to both twins is polyhydramnios-induced PPROM and preterm labor. Survivors of TTTS are also at risk for central nervous system white matter lesions and long-term disability. The increased risk of impaired neurodevelopment is associated with higher gestational age at intervention, increased severity stage of TTTS, and lower gestational age at birth [47]. Diagnosis of TTTS requires both the presence of a monochorionic diamniotic pregnancy and the presence of a maximal vertical pocket (MVP) <2 cm in one amniotic sac with a MVP >8 cm in the other sac [45]. Multiple staging systems have been developed that are based on progression of the disease and abnormal changes in the twins. These staging systems are helpful for prognosis of outcome, treatment options, and communication between physicians and centers [44]. The Quintero staging system is commonly used and detailed in Table 21.2. TTTS has an overall survival of 85% if it remains in stage I, but higher stages result in ≥80% mortality if untreated, with significant risk of morbidity in survivors [45,48].

A variety of treatment strategies for TTTS have been devised. Each is intended to decrease morbidity and improve survival of one or both twins. These include: (1) serial amnioreduction to control polyhydramnios and decrease preterm labor; (2) surgical microseptostomy of the inter-twin amnion membrane to equalize amniotic pressures; (3) selective fetoscopic laser photocoagulation (SFLP) of selected abnormal inter-twin vascular anastomoses to equalize the resistance and blood flow between the twins; and (4) fetoscopic cord coagulation to selectively terminate the severely affected recipient twin to improve survival of the donor.

Table 21.2 Staging of twin–twin transfusion syndrome severity

Stage	Parameter	Ultrasound criteria
I	Amniotic fluid	MVP <2 cm in donor twin amniotic sac and MVP >8 cm in recipient twin amniotic sac
II	Fetal bladder	Unable to image the fetal bladder in the donor twin during 60 min of observation
III	Flow velocity change in UA, UV, or DV	Absent or reversed UA diastolic flow waveform Pulsatile UV flow waveform Reversed DV a-wave flow waveform
IV	Fetal hydrops	Hydrops in either twin
V	Fetal demise	Absent fetal cardiac activity

DV, ductus venosus; MVP, maximal vertical pocket of amniotic fluid; UA, umbilical artery; UV, umbilical vein.
Source: Adapted from Quintero et al [53] and Society for Maternal-Fetal Medicine and Simpson [45].

Amnioreduction

Serial amnioreduction was the first treatment utilized for TTTS and was designed to decrease the morbidity from polyhydramnios in the recipient twin. Amnioreduction was shown to decrease preterm delivery and improve uteroplacental perfusion by reducing intrauterine pressure [49]. Mari et al used international registry data to examine the effects of amnioreduction on 223 sets of twins diagnosed with TTTS before 28 weeks' gestation [50]. They reported medians of two amnioreductions, 3550 mL of fluid removed, and a gestational age at delivery of 29 weeks. Intrauterine death occurred in 18% of recipients and 26% of donors, with an overall survival rate at birth of 78%. By 4 weeks of age, only 60% of infants were alive: 65% of recipients and 55% of donors survived [50]. Possible complications from amnioreduction included infection, placental abruption, PPROM, and preterm labor.

Microseptostomy

Microseptostomy using an ultrasound-guided needle was developed to improve uteroplacental blood flow by equalizing pressures between the two amniotic cavities. In a prospective randomized trial, 73 women with TTTS were treated with either serial amnioreduction or septostomy. No difference was found in either overall perinatal survival (64% versus 70%) or survival of at least one infant in pregnancy (78% versus 80%) [51]. Microseptostomy is seldom used today because it offers no survival benefit, and if a single amniotic cavity is created, there is a risk of umbilical cord entanglement.

Selective fetoscopic laser photocoagulation

In utero SFLP is a minimally invasive procedure that coagulates abnormal communicating vessels between the twins. A Nd:YAG or diode laser is introduced through a semiflexible endoscope. Typically, the fetoscope and laser are inserted percutaneously via a 3 mm cannula into the recipient twin's amniotic sac that has polyhydramnios (Fig. 21.4). Neuraxial blockade or infiltration of local anesthesia at the planned trocar insertion site in the myometrium is commonly employed for anesthesia. Fetoscope placement is determined by placental location and is guided by ultrasonography. Vascular

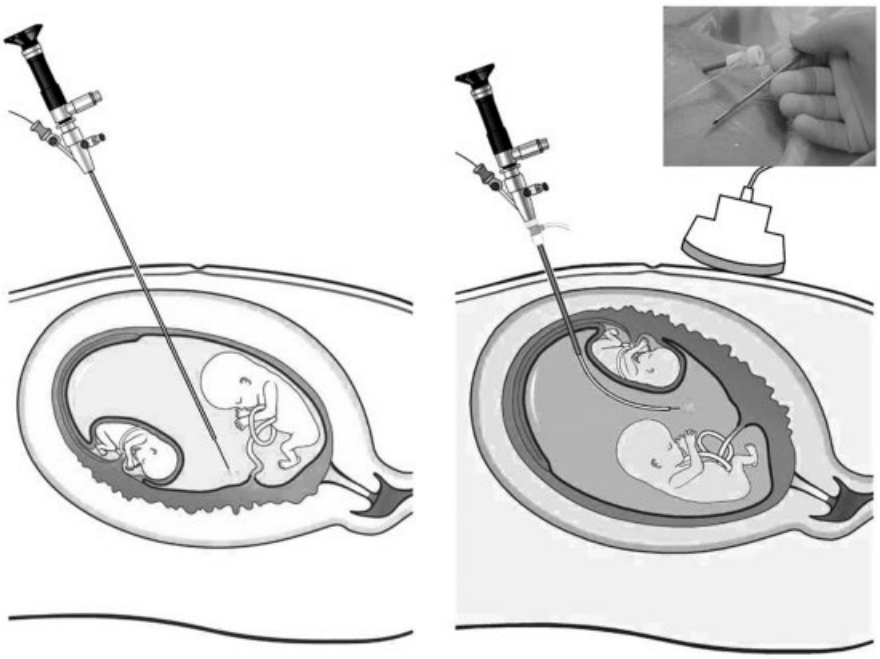


Figure 21.4 Direct insertion of the fetoscope through the sheath – without cannula (*left*). An anterior placenta, with the use of a curved sheath and a flexible cannula (*right*). A photo of the flexible cannula in place (*insert*). Use of a cannula allows change of instruments with only a minimal increase in diameter. *Source*: Reprinted with permission from Deprest et al [222] with permission of Elsevier.

anastomoses on the surface of the placenta are directly visualized and ultrasound can be used to determine directional flow in the vessel. Arteries crossing on top of the veins are a darker red color due to oxyhemoglobin desaturation. Using the fetoscope, chorionic plate vessels that cross the membrane separating the amniotic sacs are visually traced to each fetal umbilical cord insertion. Abnormal vessels traveling between twin cord roots are identified and selectively coagulated with the laser [52]. Due to location of the fetuses, placenta, and cord insertions, many procedures require some small degree of non-selective coagulation. Purely non-selective SFLP is associated with higher rates of intrauterine deaths from acute placental insufficiency [53]. Frequently, some of the abnormal twin–twin anastomoses are not visualized and remain intact after laser therapy. Complete obliteration of all connecting vessels is unnecessary for successful outcomes [54,55]. Following laser ablation, an amnioreduction is often performed when the fetoscope is removed to reduce the polyhydramniotic sac to a normal or slightly lower volume. Fetal monitoring and periodic ultrasound imaging are typically performed for 24–48 h after surgery.

A 2004 multicenter prospective randomized trial compared endoscopic laser surgery to serial amnioreduction for TTTS that was diagnosed before 26 weeks' gestation [56]. The study was stopped early because interim analysis demonstrated a benefit to the laser treatment group. The laser group had a greater likelihood of at least one twin surviving at both 28 days (76% versus 56%, $p < .01$) and 6 months of age (76% versus 51%, $p = 0.002$) [56]. The laser treatment group also had significantly fewer neurological complications at 6 months of life. Another prospective randomized multicenter trial of amnioreduction and SFLP found no difference in 30-day mortality for either the recipient or donor twin [41]. Fetal "recipient" mortality was increased for SFLP but was offset by an increase in neonatal "recipient" mortality in the amnioreduction group [41]. The hypertensive cardiomyopathy of the "recipient" twin was an important factor in survival, which might be the result of vasoactive hormones (renin–angiotensin system) from the "donor" that compromise the recipient.

A recent meta-analysis of the literature from 1995 to 2014 examining laser therapy for TTTS noted that fetal survival rates have improved over time with the most recent studies (2011–2014) demonstrating a mean survival rate of 60% for both twins and 88% for at least one of the twins [57]. The rate of significant long-term neurological morbidity in children previously treated with SFLP is 5–18% [45]. Recent modifications of SFLP include use of sequential ablation of the AV, AA, and VV inter-twin anastomoses [58] and the Solomon technique, which creates a photocoagulated line at the inter-twin vascular equator [59]. There is some limited evidence of benefit of these newer techniques regarding improved survival and prevention of TTTS recurrence [60–62].

The most common complication of laser therapy for TTTS is PPROM and preterm labor, but risks also include transplacental entry of the trocar, infection, and hemorrhage. Rarely membrane perforation can result in limb entrapment and tissue ischemia.

In summary, randomized controlled trials and meta-analysis suggest that fetoscopic laser ablation is superior to serial amnioreduction and should be considered as treatment for TTTS to improve both neonatal survival and outcome.

Fetoscopic cord coagulation

In cases where salvage of the recipient twin is unlikely, fetoscopic cord coagulation (FCC) or ligation can be used. It attempts to significantly improve the outcome of the remaining fetus by stopping twin–twin blood flow and its associated morbidities. FCC has also been used following SFLP if the laser therapy worsened fetal condition [41].

KEY POINTS: TWIN–TWIN TRANSFUSION SYNDROME

- In TTTS, a branch from an umbilical artery connects with an unpaired vein that carries blood to the other twin
- The unbalanced flow of TTTS causes hypovolemia, oliguria, oligohydramnios, and intrauterine growth restriction in the donor twin
- Treatments include serial amnioreduction, surgical microseptostomy, selective fetoscopic laser photocoagulation, and fetoscopic cord coagulation

Twin reversed arterial perfusion sequence

In monochorionic twin pregnancies, retrograde blood flow through arterial–arterial anastomoses allows blood to flow from one twin to the other and is known as the twin reversed arterial perfusion (TRAP) sequence. The twin receiving the retrograde flow has a non-functioning heart or acardia. Less commonly, both twins can have cardiac activity and still have the diagnosis of TRAP if the "acardiac" twin has a malformed cardiac mass without effective pumping. This condition is associated with other lethal anomalies that include acephalus. The acardiac twin receives all of its blood flow from the normal or "pump" twin and has no direct placental connection. Blood flows retrograde to the acardiac twin via the normal twin's umbilical artery branches and returns from the acardiac twin via the umbilical vein. Instead of entering the placenta, this blood bypasses the placenta and flows into the normal twin via a venous–venous connection [63]. This puts the normal twin at risk for high-output congestive heart failure, preterm birth, and polyhydramnios [64]. The incidence of TRAP is about 1 in 35,000 live births, affecting about 1% of monochorionic twins and 3% of monochorionic triplets [65,66]. The risk of death for the pump twin is >50% if the condition remains untreated, and 90% if the acardiac twin is >75% of the size of the normal twin [67,68].

Early diagnosis is beneficial for optimal management and is confirmed by documenting retrograde flow to the acardiac twin by ultrasound Doppler imaging. The primary goal of treatment is to stop blood flow between the twins by interrupting the connecting vasculature. Initially this was accomplished by extracting the acardiac twin through an open hysterotomy (Fig. 21.5). Currently, image-guided bipolar or radiofrequency coagulation of the acardiac twin umbilical cord or placental inter-twin anastomoses are the most common and viable options [69]. Other therapeutic options include either percutaneous endoscopic laser ablation of placental vascular anastomoses, selective delivery of the acardiac twin, percutaneous blockage of the acardiac twin's umbilical cord using coils or ligation, and intrafetal injection of alcohol [69]. TRAP treatment procedures are typically done after 16 weeks' gestation but early intervention is ideal to minimize the morbidity to the normal twin. Optimal timing and mode of treatment are yet to be determined. Absence of flow to the acardiac twin is confirmed by ultrasound color Doppler at the end of the procedure and again at 12 or 24 h post procedure.

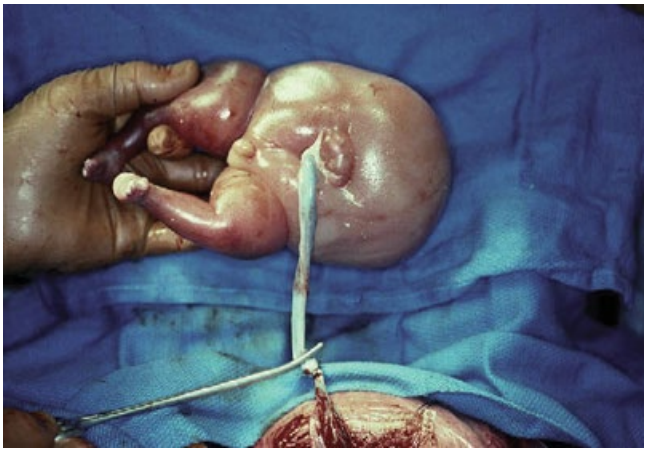


Figure 21.5 Open selective extraction of an acardiac twin. *Source*: Photo courtesy of UCSF Fetal Treatment Center.

A retrospective study of 60 TRAP cases (mean gestational age 18.3 weeks) from three European centers that used fetoscopic laser coagulation of the placental vascular anastomoses or of the umbilical cord reported a 80% survival rate and a mean gestational age at birth of 37.4 weeks for the pump twin [70]. A single-institution retrospective review of 26 cases of monochorionic diamniotic twins who had TRAP and were treated with RFA noted a 92% survival of the pump twin, who on average was born at 35.6 weeks [71]. A 2014 meta-analysis found the normal twin survival rate to be about 80% for most treatment techniques except use of cord coils or intrafetal alcohol injection [69]. Additionally, earlier treatment intervention was associated with a longer gestation.

Interventions for TRAP are typically performed with infiltration of local anesthesia at the percutaneous device insertion site, but neuraxial anesthesia is also used. The most common complication from the treatment procedures is PPROM.

Myelomeningocele

Open spina bifida or myelomeningocele (MMC) is a non-lethal neural tube defect that occurs early in gestation and results in protrusion and exposure of the meninges and spinal cord through a spinal defect. These neural elements may be injured by exposure to amniotic fluid during gestation, making possible early fetal repair attractive. The definitive cause of MMC remains unknown but is likely multifactorial. Taking folate during pregnancy has decreased the incidence of this lesion to 1 in 3000 livebirths.

Animal studies suggest that the ultimate neural damage results not just from failure of the neural tube to form but from chemical neurotoxicity and secondary neural destruction by components of amniotic fluid or meconium [72]. In sheep, covering the MMC neural defect decreased neurological morbidity and increased the likelihood of normal anal sphincter function [73]. Using somatosensory evoked potentials, Julia et al demonstrated decreased neurological sequelae following *in utero* repair of a surgically created MMC in rabbits [74]. Examination of fetuses with MMC early in gestation showed an open but undamaged cord. Direct trauma to the exposed cord and mutations in the *PAX3* gene have also been implicated in causing MMC [75]. α-Fetoprotein screening of maternal

blood detects MMC during the first trimester and improved ultrasonography allows early detection and the option of pregnancy termination. The 5-year mortality of MMC is about 8% of livebirths; surgical closure in the first days of life is required if MMC is not corrected antenatally [76].

Complications from MMC include hydrocephalus, Arnold–Chiari II malformation, motor and sensory nerve deficits (including paraplegia), bowel and bladder incontinence, spinal cord tethering, sexual dysfunction, and cognitive impairment [77]. Approximately 80% of children with MMC require ventriculoperitoneal shunting for the treatment of hydrocephalus [78]. Despite shunting, permanent deficits including central hypoventilation, vocal cord dysfunction, and swallowing dysfunction can occur secondary to the Arnold–Chiari II malformation. The primary purpose of *in utero* treatment of MMC is to cover and protect the fetal neural contents early in gestation to prevent additional damage by prolonged exposure to the uterine environment.

Open myelomeningocele repair

Utilization of the open fetal surgery approach for MMC repair rapidly increased following the publication of the results of the Management of Myelomeningocele repair Study (MOMS Trial) in 2011 [79]. During the open *in utero* repair (Fig. 21.6), the meninges are separated from the fetal skin and soft tissue layers. In a primary closure (Fig. 21.7A), the dura is closed over the neural placode and the paraspinal myofascial flaps are closed over the dura with a final closure of the skin layer. If primary closure is not possible secondary to the size of the defect, an acellular dermal patch is used to cover the defect (Fig. 21.7B).

The many benefits of prenatal repair revealed as a result of the MOMS study [79] included a decreased need for ventriculoperitoneal shunt placement by 1 year of age (68% versus 98%) as well as decreased actual shunt placement rates (40% versus 82%). In addition, there was decreased hindbrain herniation and improved neurofunctional outcome at 30 months of age with the *in utero* open intervention as assessed by an ability to walk without orthotic device assistance in 42% versus 21% of study children. There were two perinatal deaths in each study group. The trial had been stopped early because of demonstrated efficacy in the prenatal group with only 158 of 183 enrolled patients' data analyzed. Recent follow-up studies on the entire data set demonstrate similar beneficial results of *in utero* intervention with only 70% versus 93% meeting criteria for shunt placement, a decrease in actual shunt placement (44% versus 84%), and independent ambulation in 45% versus 24% [80,81]. These findings clearly have a significant positive impact on the prognosis of the child with a prenatal diagnosis of spina bifida. However, the outcomes for the mothers in this study included a variety of significant complications detailed in Table 21.3 [12,79]. Increased thinning of the uterine wall predisposes to increased risk of uterine rupture with subsequent pregnancies. As a result of this, mothers who have undergone open fetal surgery are committed to cesarean delivery prior to the onset of labor for all subsequent pregnancies. This, together with the increased risk of premature delivery (average gestational age at delivery was 34 weeks), has remained the primary negative aspect to prenatal open surgical repair of MMC.

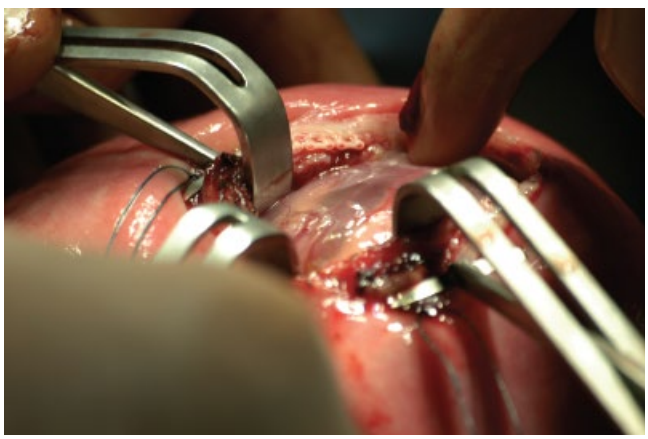
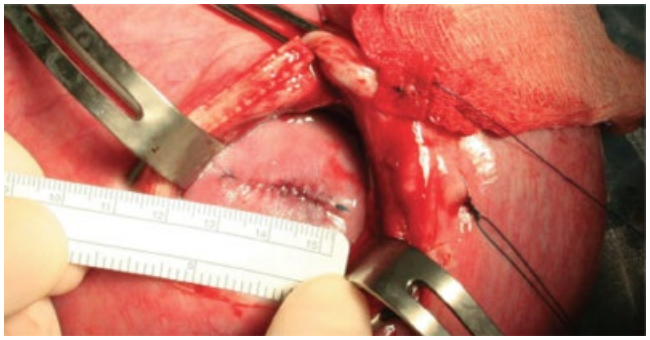
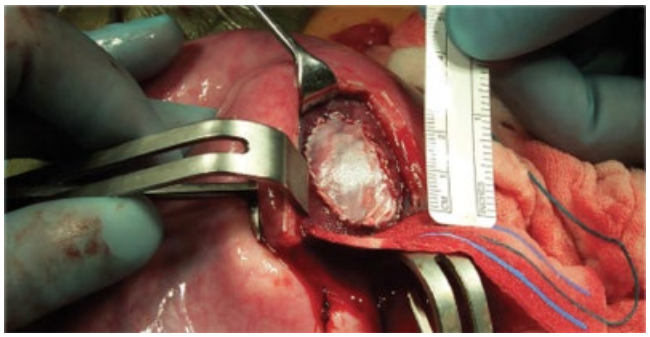


Figure 21.6 Open repair of fetal myelomeningocele. *Source*: Photo courtesy of UCSF Fetal Treatment Center.



(A)



(B)

Figure 21.7 (A) Primary closure of fetal myelomeningocele. (B) Closure of fetal myelomeningocele with dermal patch. *Source*: Photos courtesy of UCSF Fetal Treatment Center.

Fetoscopic myelomeningocele repair

In an attempt to circumvent the undesired consequences of open MMC repair, the fetoscopic approach to MMC repair was explored. The first attempt at fetoscopic repair involved maternal hysterotomy and percutaneous repair through an exteriorized uterus [82]. This was complicated by placental abruption in one case, resulting in abandonment of this approach. Nevertheless, animal studies continued in order to determine the feasibility of this approach [83,84]. Following refinement in animal studies, a few centers are now routinely performing fetoscopic repair of open neural tube defects between 22 and 26 weeks of gestation, either via the percutaneous minimally invasive fetoscopic approach or a "hybrid" procedure involving an initial maternal hysterotomy followed

Table 21.3 Maternal complications for MOMS trial patients*

Maternal outcome	Prenatal (*n* = 78)	Postnatal (*n* = 80)	p
Chorioamniotic membrane separation	30 (33%)	0	<.0001
Pulmonary edema	5 (6%)	0	.03
Oligohydramnios	19 (20%)	3 (3%)	<.001
Placental abruption	6 (7%)	0	.01
Spontaneous rupture of membranes	40 (44%)	7 (8%)	<.0001
Spontaneous labor	39 (43%)	13 (14%)	<.0001
Blood transfusion at delivery	8 (9%)	1 (1%)	.02
Hysterotomy site thin, or partial or complete dehiscence noted at delivery	31 (35%)	N/A	N/A
Mean gestational age at birth (weeks)	34.0 ± 3.0	37.3 ± 1.1	<.0001

* The table lists maternal complications that were significantly different (p <.05) between the prenatal and postnatal repair groups in the Management of Myelomeningocele Study (MOMS) following complete cohort analysis of 183 patients. Other outcomes were evaluated, but only those that were different between the two groups are included. Data for each group are shown as both an absolute number and as a percentage.
N/A, not applicable.
Source: Reproduced from Johnson et al [12] with permission of Elsevier.

by exteriorization of the uterus with trocar insertion and repair of the fetal defect [85–88].

Both the fetoscopic and the hybrid approach to MMC repair are likely to decrease maternal morbidity as the uterus does not have a significant scar that is at risk of dehiscence during labor. Following both of these surgical approaches, the mothers are allowed to labor and have a spontaneous vaginal delivery. The gestational age at delivery for both of these approaches has a wide range (24–40 weeks' gestation) with a mean of 38 weeks or 33 weeks depending on the center [88,89].

Lesions between T1 and S1 are deemed acceptable for fetoscopic repair [85]. Similar to open fetal procedures, pregnant patients with minimal co-morbidities or well-managed chronic disease states are ideal candidates for this fetal intervention.

With the percutaneous minimally invasive endoscopic approach to MMC repair, three or four trocars with an outer diameter of 5 mm each are introduced via the abdominal wall into the maternal amniotic cavity, under ultrasound guidance, using a Seldinger technique. The trocars are carefully positioned to avoid the placenta in the case of an anterior placenta [85]. In the early days of this procedure, partial removal of amniotic fluid was performed followed by partial insufflation of carbon dioxide. However, with refinement of the technique, this has been found to be no longer necessary [85,89]. Fetoscopic repair occurs under partial amniotic carbon dioxide insufflation which helps maintain clear visualization for surgical repair within the uterus.

Humidified carbon dioxide is gradually insufflated into the amniotic cavity, starting at 8 mmHg gas flow pressure, and gradually increased by 2 mmHg increments until an "opening pressure" is attained. The fetus is then properly positioned for surgery and endoscopic repair commences. Depending on the size of the lesion, fetal surgical repair ranges from simple repair with an inert patch to dissection of the placode and closure with one or more collagen and polytetrafluoroethylene patches. Water-tight closure is confirmed by ensuring there is no cerebrospinal fluid leak when gentle pressure is applied to the surface of the repair [85,90].

Although perioperative anesthetic approaches to both minimally invasive and open fetal surgery cases are detailed later in the chapter in the sections "Anesthetic management of fetal procedures" and "Perioperative and procedural considerations," the unique circumstances of this fetoscopic approach to fetal MMC repair warrant the additional description in the following paragraphs.

Anesthetic management and considerations for fetoscopic myelomeningocele repair

On the day of surgery, aspiration prophylaxis is administered and venous compression stockings are also placed on the mother. Prior to commencing the mother's anesthetic, it is important to try to avoid the administration of any maternal anxiolytic or sedative medication as this may result in immobilization of the fetus and may make adequate positioning for surgical repair of the spina bifida lesion challenging. General anesthesia via rapid-sequence induction and endotracheal intubation is routinely required with either the percutaneous or hybrid surgical approach. Monitoring and venous access for the percutaneous minimally invasive approach in the European center that has performed a large number of these particular cases includes insertion of a central venous catheter in addition to standard monitoring of blood pressure, electrocardiography, and non-invasive monitors [91]. Relatively smaller endotracheal tubes compared to those that may be utilized in the non-pregnant female should be considered, due to possible airway edema that may be present in the pregnant woman. For the entirely percutaneous fetoscopic approach, maintenance of anesthesia is accomplished with volatile anesthetic (e.g. desflurane) and an intravenous remifentanil infusion. The opioid remifentanil not only provides analgesia for the mother but also has adequate transplacental passage to provide fetal analgesia and immobility during the procedure compared with diazepam [92]. In addition, an intravenous bolus of the tocolytic agent atosiban is also routinely administered at some European centers prior to induction of anesthesia. An oxytocin antagonist, atosiban is not approved for use in the USA and is only available in Europe. Both routine and invasive monitoring are often employed when this drug is administered and include invasive blood pressure monitoring via an arterial catheter, pulmonary artery catheter assessment of the cardiac output, and estimation of lung water content. The last is utilized to assess the development of or presence of maternal pulmonary

edema during surgery and also in the postoperative phase. Pulmonary artery catheter monitoring is unique to these cases and not a routine part of open approaches to MMC repair.

Intraoperative intermittent assessment of feto-maternal placental circulation and fetal heart rate via ultrasound and echocardiography is frequently employed and this influences surgical maneuvers as well as anesthetic depth. Postoperative pain in patients following percutaneous minimally invasive repair of spina bifida is managed with oral opioid medication.

For the alternative, "hybrid" approach with an initial maternal laparotomy and subsequent fetoscopic repair through trocars inserted into the exteriorized uterus (Fig. 21.8), general and neuraxial anesthesia is administered to the mother. An epidural catheter is placed preoperatively for administration of local anesthetic and opioid infusion after the surgery to manage postoperative pain. General anesthesia is instituted as described previously, with any choice of the volatile anesthetics used for the hybrid approach. The fetus also receives direct intramuscular medication for pain relief and immobility. Implications of the administration of maternal anesthetics are discussed in the sections "Anesthetic implications" for each system.

Once the fetus has been adequately positioned for surgery, intramuscular fetal medications are administered [93]. Most commonly, a combination of analgesic medication (most commonly fentanyl 5–10 μg/kg), muscle relaxant (vecuronium 0.2–0.4 mg/kg) and a vagolytic agent (atropine 0.02 mg/kg) is administered to the fetus prior to commencing the fetoscopic spina bifida repair. Administration of this combination to the fetus may be repeated every 45 min to 1 h depending on the duration of the repair.

Postoperatively, analgesia for the hybrid procedure is routinely accomplished via patient-controlled epidural infusions of a local anesthetic with opioid for 48–72 h, offering both the fetus and mother adequate pain relief. Postoperative tocolysis is achieved with intravenous magnesium sulfate infusion for 24–48 h.

While fetoscopic repair (percutaneous or "hybrid" approach) has potential advantages for both the mother and the fetus with a decreased chance for both uterine rupture and premature delivery, there are still significant areas for concern. A steep learning curve exists for the fetoscopic repair, with the time for completion of these cases being more prolonged than open cases [88,89]. A 2012 study of endoscopic intrauterine MMC repair resulted in a high complication rate for both mothers and fetuses [94]. Of 19 patients, three fetuses died intraoperatively and three procedures were stopped secondary to severe hemorrhage during the procedure. A 2016 phase I trial of endoscopic fetal repair of 10 MMC patients resulted in two of 10 procedures aborted due to loss of uterine access, one fetal and one neonatal demise and PPROM in 100% of cases [95]. Fetal repair in a carbon dioxide-filled environment has also raised concern for fetal hypercarbia and subsequent possible untoward sequelae [96]. Previous fetoscopic studies in sheep have demonstrated significant fetal lamb acidosis; while this has not been directly assessed in human fetuses undergoing surgery in a carbon dioxide-filled uterus, no physiological parameters of the fetus during surgery raise any suspicion of an untoward effect [87]. Absorption of carbon dioxide during this procedure, particularly through open vessels if any occur during surgery, could result in maternal carbon dioxide embolism. However, this has not been reported to date in any of the patients undergoing fetoscopic repair of MMC in the carbon dioxide-filled environment. In some studies, when compared to open MMC repair, fetoscopic MMC repair was associated with increased membrane complications, earlier gestational age at birth, persistent fetal CSF leaks, and increased perinatal demise [77,94,95,97].

Despite these concerns, fetoscopic repair of spina bifida is slowly gaining popularity in different centers. The decreased maternal morbidity, and propensity for vaginal delivery of a near term baby are goals that are difficult to ignore. In addition, the postnatal neurological outcomes are encouraging, with the rate of neurosurgical intervention in children following *in utero* repair being similar to that of the MOMS trial [88,98]; however, assessment of the long-term neurological outcomes of children who have undergone these procedures is needed before definitive proof of benefit of this approach can be conclusively stated. Chapter 25 presents additional detail about postnatal MMC surgery and anesthesia.

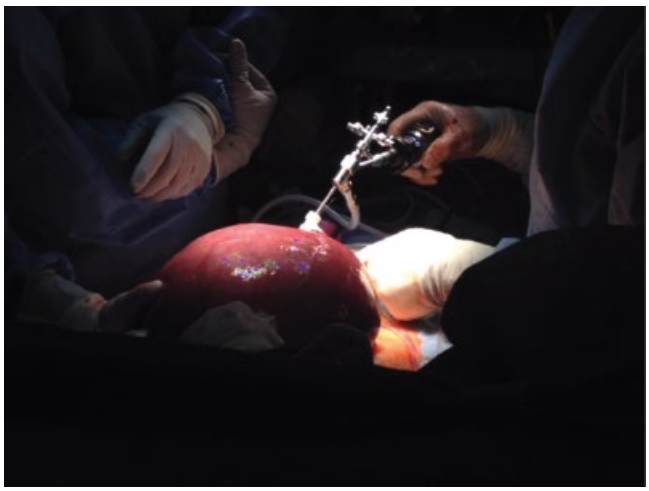


Figure 21.8 Fetoscope inserted into exteriorized uterus during "hybrid" approach to myelomeningocele repair where the mother undergoes an initial maternal laparotomy and subsequent fetoscopic repair. *Source*: Courtesy of Olutoyin Olutoye MD, MSc.

KEY POINTS: MYELOMENINGOCELE

- Open fetal MMC repair significantly decreased the ventriculoperitoneal shunt placement rate and improved neurological outcome in the MOMS study
- Fetoscopic MMC repair reduces the risk of premature labor and requirement for cesarean section for subsequent pregnancies
- For either the open or fetoscopic approach, the fetus receives intramuscular fentanyl, vecuronium, and atropine for analgesia and immobility

Congenital pulmonary airway malformations

A congenital pulmonary airway malformation (CPAM) is a discrete pulmonary mass that contains both solid and cystic components that are <1 mm to several cm in diameter and typically isolated to one lung. These malformations were

previously described as congenital cystic adenomatoid malformations (CCAMs). CPAMs have been classified into two types based on ultrasound imaging and size [99]. Malformations containing single or multiple cysts >5 mm in diameter on ultrasound are termed "macrocystic"; they may develop into large solitary cysts several cm in diameter. Smaller lesions with cysts <5 mm of diameter are termed "microcystic"; they appear as solid images on ultrasound. A second-trimester ultrasound can assist in differentiating CPAM from CDH, peripheral bronchial atresia, neurogenic cysts, bronchopulmonary sequestration, and bronchogenic cysts [99]. A histological classification scheme includes five subtypes based on: (1) cyst size; (2) epithelial lining characteristics; (3) wall thickness; and (4) presence of mucus-secreting cells, cartilage, and muscle [100]. The incidence of CPAM is estimated to be 1 in 25,000 pregnancies [101].

Large tumors can result in mediastinal shift, polyhydramnios, pulmonary hyperplasia, hydrops, and fetal demise. The overall fetal outcome depends on CPAM size, tumor growth characteristics, presence of hydrops, and secondary morbidity from large masses that cause a fetal mediastinal shift, pulmonary hypoplasia, or polyhydramnios [102,103]. Fetuses with untreated lesions and hydrops have a survival rate <5% [104]. Smaller CPAMs detected *in utero* without significant compromising effects are resected after birth, usually by excising the affected pulmonary lobe. The CPAM volume ratio (CVR) is the quotient of the calculated CPAM volume and the fetal head circumference normalized for gestational age as determined by ultrasound imaging [105]. A CVR <0.56 was noted to have no adverse effects, >0.56 was associated with an adverse postnatal outcome one-third of the time, and a CVR >1.6 was associated with greater risk of fetal hydrops [105,106]. Bilateral fetal masses or the presence of hydrops are associated with poor outcomes [105,107]. Periodic ultrasound surveillance of CPAM masses is critical because these tumors can grow rapidly and unpredictably. Depending on the mass and its effects, *in utero* intervention or postnatal resection may be chosen.

Possible fetal surgical strategies include aspiration and drainage of cysts using serial thoracocentesis or shunt placement, percutaneous laser ablation, and CPAM resection during open fetal surgery [108]. Aspiration of cysts may improve the condition of the fetus temporarily, but the fluid often reaccumulates. Placement of shunts can produce sustained decompression and resolution of hydrops *in utero*, and allow definitive treatment after birth [109]. Without intervention, large CPAMs may cause significant pleural effusions and pulmonary hypoplasia. Unfortunately, some cystic lesions are compartmentalized and cannot be successfully drained. Thoracoamniotic shunts may be displaced, malfunction, or occlude, and may cause fetal hemorrhage, placental abruption, PPROM, preterm labor, and chorioamnionitis [105,108]. Administration of betamethasone to fetuses with CPAMs and hydrops can improve outcomes [110]. In a series of macrocytic CPAMs treated with thoracoamniotic shunts, 68% of hydropic and 88% of non-hydropic fetuses survived [111].

Solid microcystic CPAMs or other large masses not amenable to drainage or shunting can be resected during open fetal surgery (Fig. 21.9). The lobe containing the lesion is resected during a hysterotomy and fetal thoracotomy [104]. Anesthetic considerations are described in the section "Open fetal surgical procedures." A retrospective review of 30 fetuses with large CPAMs and hydrops had a 50% 30-day survival after birth following open fetal surgical resection [112]. Only 3% (one of 33) of fetuses with similar CPAMs survived without surgical intervention.

Less frequent options include resection during an EXIT procedure, with ECMO, tumor ablation, or percutaneous sclerotherapy. Improved selection criteria and the potential for minimally invasive video-assisted thoracoscopic RFA of the tumor hold promise for improved outcomes [108]. Chapter 26 contains additional information about postnatal treatment of CPAMs.

Sacrococcygeal teratoma

Fetuses with sacrococcygeal teratoma (SCT) are typically diagnosed in the second trimester of pregnancy; the incidence of SCT is 1 in 20,000 to 40,000 livebirths [113]. The lesions can grow to 500–1000 cm^3 [114]. Perinatal mortality is high due to massive tumor enlargement, hydrops, and placentomegaly. Perinatal mortality is estimated at 25–35% [113]. However in one series, the perinatal mortality of 23 fetuses with SCT was 43% [114]. These tumors also cause significant arteriovenous shunting, and the resultant high-output cardiac failure is often the cause of fetal death. Fetuses with large lesions are at risk for intrapartum dystocia, tumor rupture and hemorrhage, and bladder outlet obstruction. Fetal hydrops may be associated with "mirror syndrome," in which the mother develops a hyperdynamic high-cardiac output state similar to that of the fetus and has superimposed symptoms of pre-eclampsia [115].This syndrome increases the risk of fetal mortality and maternal morbidity, with severe maternal complications occurring in 20% of cases [116].

Several SCTs have been successfully removed *in utero* [117]. Tumors are staged based on location using the Altman criteria [118]. Tumors located entirely outside the pelvis (stage 1) are amenable to *in utero* resection, while those completely within the fetal pelvis (stage IV) are not suitable for *in utero* resection. Successful operations for large SCTs require catheterization of a fetal hand or umbilical cord vein to allow blood and fluid resuscitation during tumor resection. Minimally invasive surgery using RFA, embolization, and thermocoagulation of the tumor or its vasculature attempts to reduce the tumor burden and blood supply, but studies are needed to determine the degree of benefit [119].

Fetal urinary tract obstruction

Urinary tract obstructions are detected by ultrasound in approximately 1% of pregnancies [120]. The great majority of these abnormalities have no significant clinical consequence. Only 1 in 5000 livebirths has a lower urinary tract obstruction [121]. The clinical morbidity from fetal urinary tract obstruction depends on the location of the obstruction, severity, duration, age at onset, and gender of the fetus [120]. Congenital bilateral hydronephrosis from obstruction of the fetal urethra has a worse prognosis than unilateral upper urinary tract obstruction. Although the exact etiology may vary, posterior urethral valves are often the cause of bilateral hydronephrosis in male fetuses. Other possible causes include obstruction of the ureteropelvic junction and ureterovesical junction, ectopic ureter, ureterocele, megacystic megaureter, multicystic kidney,

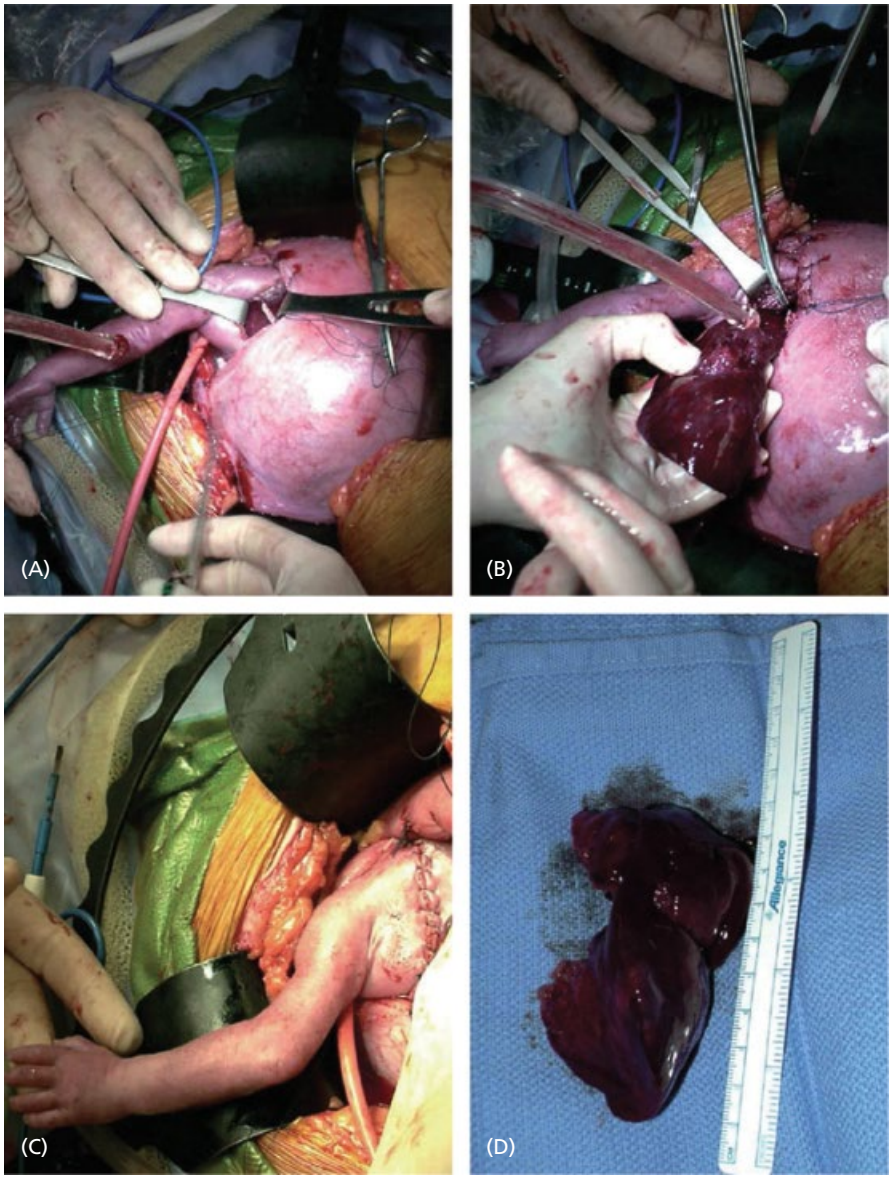


Figure 21.9 (A) Open resection of fetal congenital pulmonary airway malformation (CPAM) with fetal thoracotomy shown. (B) Resected CPAM mass. (C) Primary closure of fetal thoracotomy. (D) Pathology specimen of resected CPAM mass. *Source*: All photos courtesy of UCSF Fetal Treatment Center.

or more complex pathologies [122]. These anomalies are easily detected by ultrasonography and commonly result in oligohydramnios. Before 16 weeks' gestation, a transudate of maternal plasma forms the amniotic fluid; after 16 weeks' gestation, fetal urine is its primary source. An ultrasound grading system based on fetal renal pelvis anteroposterior diameter is used to assess the severity of prenatal hydronephrosis [123]. Not only should an extensive ultrasound evaluation of the entire urinary tract be done, cardiac or neural tube defects should also be sought because they occur more commonly in fetuses with lower urinary tract obstructions [120]. A more recent severity classification system for lower urinary tract obstruction based on amniotic fluid index, renal imaging, and fetal urine chemistry has been proposed [124].

Severe urinary tract obstruction causes oligohydramnios, hydroureteronephrosis, and bladder distension, which in turn cause pulmonary hypoplasia, facial and extremity deformations, renal dysplasia and dysfunction, and deficiencies of abdominal muscle (Fig. 21.10) [125]. These problems significantly reduce postnatal survival, primarily by causing lung hypoplasia. Of livebirths undergoing postnatal correction, more than 25% are dialysis dependent by 5 years of age [126].

Placement of a double pigtail catheter between the fetal bladder and amniotic cavity allows decompression and drainage of the bladder *in utero*. This reduces oligohydramnios and its associated morbidities (pulmonary hypoplasia and umbilical cord compression) and improves renal development. The first intervention for congenital hydronephrosis was performed by open hysterotomy in 1981. The neonate was born at 35 weeks' gestational age and died from lung hypoplasia [125]. Improved selection and placement of vesicoamniotic shunts allowed successful treatment of congenital hydronephrosis [7]. An algorithm with specific criteria was proposed to improve fetal candidate selection and outcome [127]. Components of the algorithm included fetal karyotype, an ultrasound examination searching for additional anatomical abnormalities, and fetal urine sampling to determine the degree of renal dysfunction.

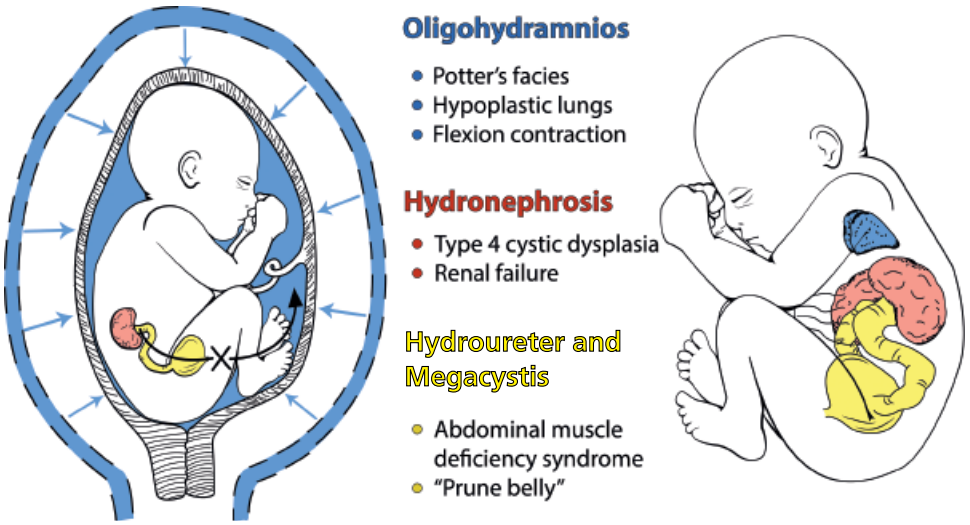


Figure 21.10 Developmental consequences of fetal urethral obstruction. Severe urinary tract obstruction results in significant fetal sequelae that can reduce postnatal survival. Reproduced from Harrison et al [125].

Fetal intervention requires a male karyotype (females often have more complex urinary abnormalities), absence of other structural abnormalities that impact outcome, and the presence of oligohydramnios or decreasing amniotic fluid volume. Serial sampling of fetal urine on three to five occasions, complete bladder drainage, 24–48 h intervals between samples, and assessment of sodium, chloride, calcium, osmolality, protein, and β2-microglobulin improve fetal outcome prediction [120,128]. Increased levels of these components of fetal urine are associated with advanced renal damage and a poor prognosis [129]. Detection of lesions early in gestation, the degree of oligohydramnios, and the presence of additional abnormalities all predict worse outcomes.

Vesicoamniotic catheter shunt (VAS) placement is often difficult because oligohydramnios compromises ultrasound imaging. Potential complications of catheter insertion include catheter occlusion or displacement, chorioamnionitis, PPROM, fetal trauma, abdominal wall defects (gastroschisis), placental separation and hemorrhage, preterm labor, and maternal leakage of amniotic fluid [120]. This minimally invasive intervention requires neuraxial anesthesia or infiltration of local anesthetic into the maternal abdominal wall and uterine musculature. The neonate will require definitive repair of the underlying problem after birth.

A single-institution, retrospective review of 34 VAS placements for heterogeneous causes of obstructive uropathy between 1987 and 1996 reported 50% survival to at least 2 years of age; 43% of survivors had normal renal function [130]. A retrospective review of 20 pregnancies with male fetuses with lower urinary tract obstruction reported overall 1-year survival of 90% and only two neonatal deaths from pulmonary hypoplasia [131]. Eight children had normal renal function, 11 had normal bladder function with spontaneous voiding, and eight had respiratory difficulty [131]. A meta-analysis of studies from 1990 to 2015 noted improved survival with *in utero* shunting compared to conservative management (57% versus 39%) [126]. However, there was no difference in 2-year survival or postnatal kidney function.

Minimally invasive percutaneous cystoscopy with laser ablation of the posterior urethral valves allows direct visualization of the fetal urethra to facilitate diagnosis and provide *in utero* treatment that may reverse pulmonary and renal morbidity, but its efficacy is uncertain at this time [132]. A case-control study compared fetal cystoscopy with VAS and no intervention [133]. Both fetoscopy and VAS improved 6-month survival in severe lower urinary obstruction, and in the subset of fetuses with posterior urethral valves only fetoscopy improved both 6-month survival and renal function. Limited evidence currently supports fetal intervention in lower urinary tract obstruction, as an attempt to reduce pulmonary hypoplasia and improve perinatal survival. Other improvements in kidney and bladder function are also yet to be definitively demonstrated as a result of fetal interventions.

KEY POINTS: CONGENITAL PULMONARY AIRWAY MALFORMATIONS, SACROCOCCYGEAL TERATOMA, AND FETAL URINARY TRACT OBSTRUCTION

- Large CPAMs are treated with cyst drainage, thoracocentesis, thoracoamniotic shunt placement, percutaneous laser ablation, and open fetal surgery
- Sacrococcygeal teratomas outside the pelvis are amenable to *in utero* resection
- Congenital urinary tract obstruction may be treated with vesicoamniotic shunt or fetoscopic laser ablation of posterior urethral valves

Fetal cardiac anomalies

Advances in angioplasty, ultrasound, and maternal–fetal care have allowed for successful fetal cardiac intervention, specifically for cardiac conditions that evolve during the second trimester to early third trimester. Ultrasound imaging provides percutaneous guidance into the left ventricle (for aortic valvuloplasty), right ventricle (for pulmonary valvuloplasty), or atrium (for atrial septostomy), depending on the procedure

required. Percutaneous fetal cardiac intervention has provided benefit for conditions such as aortic stenosis and evolving hypoplastic left heart syndrome (HLHS), established HLHS and restrictive atrial septum, pulmonary artery hypoplasia and hypoplastic right heart syndrome, and also fetal cardiac failure or hydrops fetalis due to structural cardiac disease [134,135]. Fetal aortic valvuloplasty for evolving HLHS, pulmonary valvuloplasty for hypoplastic right heart syndrome, and atrial septostomy for established HLHS are being performed as these procedures have mitigated abnormalities or limitations of cardiac growth and development that may occur *in utero*.

Fetal aortic valvuloplasty is discussed here as a prototype of prenatal cardiac intervention. This percutaneous procedure is performed for critical stenosis of the aortic valve, which results in decreased flow across the transverse aortic arch, reversal of flow across the foramen ovale, and increased left ventricular pressure with resulting myocardial damage. If left untreated, this condition results in HLHS in the postnatal period due to the underdeveloped left heart structures. Fetal aortic valvuloplasty was first described in 1991, but initial reports of successful prenatal intervention were performed in the third trimester [136]. This procedure is now performed during the second trimester or early third trimester and has favorably altered the postnatal course for fetuses with these conditions.

Fetal cardiac interventions are typically performed between 22 and 26 weeks' gestation. Optimal fetal positioning that allows for appropriate access to the necessary valves or area of interest is paramount for the success of this procedure. The most common access for fetal aortic valvuloplasty is through the fetus's anterior left chest wall and left ventricle (Fig. 21.11). The ideal fetal position provides clear access to the left chest wall without any intervening limbs or structures. An 11 cm long, 19 ga needle and stylet is inserted into the maternal abdomen and through the uterine wall, left fetal chest wall, and into the left ventricle. The left ventricle outflow tract should be parallel to the course of the cannula [134]. Inability to adequately position the fetus via external version has resulted in occasional maternal minilaparotomy, exteriorization of the uterus, and manipulation of the fetus to allow an appropriate needle trajectory, although this approach to fetal positioning is rarely employed. After successful entry into the left ventricle, a guidewire is advanced toward the stenotic aortic valve using ultrasound guidance and knowledge of predetermined measurements of the cannula and balloon tip [134].

Technically successful aortic valvuloplasty is described as confirmed insertion of the guidewire across the aortic valve, inflation of the balloon, and immediate observation of increased flow across the aortic valve, plus or minus new aortic regurgitation [137]. The increased flow observed following a technically successful fetal aortic valvuloplasty allows the fetal left ventricle to recover, remodel, and support a biventricular circulation in the postnatal period (i.e. circulation in which the left ventricle is entirely responsible for the baby's cardiac output with no contribution from atrial shunting) [138]. The recent study by Prosnitz and colleagues [138] reported that establishment of partial or exclusive postintervention anterograde flow across the aortic transverse arch was the most significant, independent predictor of postnatal biventricular function. Biventricular function may be present at birth following this prenatal cardiac intervention or may be acquired after a series of operations and/or in the presence of suboptimal diastolic function or pulmonary hypertension. Nevertheless, it is an improvement over the hypoplastic left heart, which is associated with significant morbidity and mortality [139].

Multidisciplinary meetings including the cardiologist, obstetrician, and anesthesiologist are frequently helpful to discuss not only the maternal history and fetal characteristics but also any anticipated difficulty with fetal positioning for

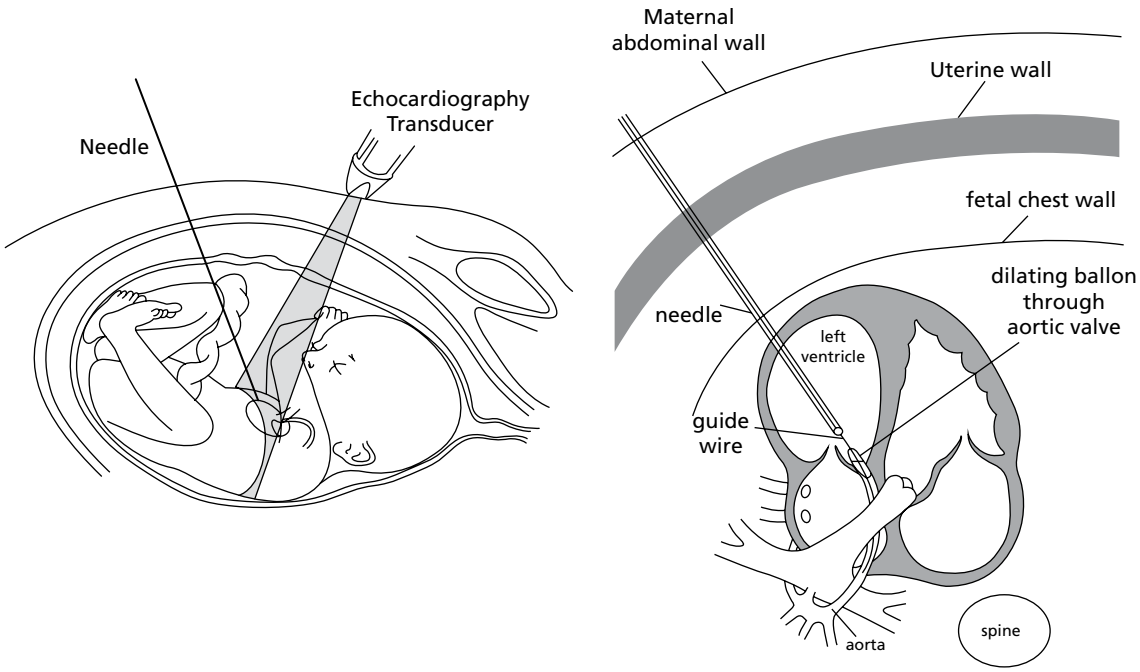


Figure 21.11 Illustration of ideal fetal position and unobstructed course of cannula access for fetal aortic valvuloplasty: through maternal abdomen, uterine wall, fetal chest and into left ventricle of fetus, facing left ventricular outflow tract. *Source*: Reprinted with permission from Tworetzky et al [134] with permission of Wolters Kluwer.

the procedure. Proper fetal position must be ascertained prior to administration of sedatives to the mother in case external version of the fetus would be required. Administration of significant sedation or analgesia to the mother may make fetal positioning more difficult once transplacental passage to the fetus has occurred. As surgical approach and technique for fetal cardiac intervention has been refined, the anesthetic requirement for these procedures has evolved from maternal general anesthesia to neuraxial anesthesia and even local infiltration at the insertion site with minimal intravenous sedation. The last option offers the benefit of easy reversal or discontinuation of sedation for situations in which fetal positioning for the procedure proves problematic. An intravenous remifentanil infusion may be administered to provide maternal sedation for this procedure as with other fetoscopic fetal procedures [92]. It can also potentiate immobilization of the fetus once an adequate fetal position has been ensured and the baby has received intramuscular combination medication of atropine, fentanyl, and muscle relaxant (see section "Minimally invasive and percutaneous procedures").

In some cases, general or regional anesthesia may be chosen to improve the success of external version of the fetus before the procedure starts if initial attempts were unsuccessful. However, avoiding general anesthesia and scheduling the case for a time when the baby is in a better position can also be entertained by the team. This decreases the risks associated with general anesthesia in a pregnant mother.

Traversing the ventricle in particular is associated with an increased risk for fetal hemodynamic instability [135]. Fetal hemodynamic instability, namely bradycardia and ventricular dysfunction, commonly occurs during fetal cardiac intervention. Adequate preparation should therefore be made for fetal resuscitation during the procedure (see section "Minimally invasive percutaneous procedures"). A review of fetal hemodynamic instability during prenatal cardiac intervention procedures revealed that fetal hemodynamics was frequently unstable a few minutes after insertion of the cannula into the heart and also shortly after removal of all instruments from the heart [135]. Hemodynamic instability is to be expected during this procedure due to the nature of the intervention; however, the exact pathophysiology is not clear. One hypothesis includes fetal hypoxia, which may occur due to reduced cardiac output from inferior vena cava compression. Another hypothesis is ventricular dysfunction, which may occur following direct ventricular stretch reflex as a result of cannula-induced depression of the ventricular wall into the ventricular cavity or as a result of cardiac tamponade from hemopericardium. Ventricular dysfunction may also result from torsion of the cannula within the cavity or withdrawal of the dilating balloon from the heart.

Fetal hemodynamic instability may also be related to injury to the fetal conducting system during ventricular access. Reduction in uterine flow due to maternal hypotension could also result in fetal hemodynamic instability, however a review of fetal cardiac intervention cases demonstrated that hemodynamic instability occurred during periods of maternal normotension [135].

In preparation for possible hemodynamic instability during this procedure, several weight-based aliquots of epinephrine (1 μg/kg), epinephrine (10 μg/kg), atropine 20 μg/kg, and calcium gluconate (approximately six syringes each), should be readily available in a sterile fashion for rapid administration by the cardiac interventionalist during the procedure in response to any observed cardiac dysfunction. In some centers, prophylactic atropine is administered at the beginning of the procedure. Prophylactic epinephrine may also be administered through the wire lumen of the balloon after aortic valvuloplasty. Both intramuscular and intracardiac epinephrine concentrations of 1 μg/kg or 10 μg/kg have been utilized depending on the severity of the cardiac dysfunction observed. The latter epinephrine dose appears to have a more rapid and sustained effect.

Hemopericardium has been noted to occur following aortic valvuloplasty; as a result, pericardiocentesis using the valvuloplasty cannula can be attempted prior to withdrawal of the cannula. It is important to note that fetal hemodynamic instability is more common with ventricular access and is observed much less often with transatrial access.

Postnatal biventricular function is the ultimate desired outcome following prenatal cardiac intervention. The ability for this to occur, in the case of aortic stenosis, seems to depend on the size of the left ventricle before the procedure, with a larger preintervention left ventricle predicting better postnatal biventricular function following the procedure. The potential benefits of this procedure must be weighed against possible risks of technical failure, valvular insufficiency, fetal demise, and yet to be determined, potential long-term events. Maternal complications include infection, PPROM, and preterm labor.

An alternative approach to the management of prenatally diagnosed cardiac anomalies is immediate access to postpartum cardiac therapy, otherwise referred to as immediate postpartum access to cardiac therapy (IMPACT) [140]. This approach has been used to manage neonates with prenatally diagnosed HLHS, heart block with associated hydrops fetalis, and giant pulmonary arteriovenous malformation. This multidisciplinary treatment modality typically involves a cesarean delivery in the cardiac operating room suite, and immediate resuscitation of the newborn by pediatric cardiothoracic anesthesiologists, which is quickly followed by surgical or catheter intervention within the first few minutes of life after separation from placental circulation. While this approach to prenatal cardiac lesions has been reported, it has not yet achieved widespread practice, and there are currently no published outcomes on its efficacy. It may be challenging to have this approach widely adopted as the ability to offer newborns such high-level immediate care will vary based on institutional capability.

KEY POINTS: FETAL CARDIAC ANOMALIES

- Fetal aortic valvuloplasty for evolving HLHS, pulmonary valvuloplasty for hypoplastic right heart syndrome, and atrial septostomy for established HLHS are being performed
- Needle and guidewire access through the maternal abdomen and uterus, fetal left chest wall, left ventricle, and across the aortic valve is used for aortic valvuloplasty
- Intramuscular fentanyl, vecuronium, and atropine, continuous echo monitoring, and preparations for resuscitation with epinephrine, atropine, and pericardiocentesis are important for fetal cardiac procedures

Ex utero intrapartum treatment procedure

The *ex utero* intrapartum treatment (EXIT) procedure was originally developed to allow adequate time to manage and secure the airway of fetuses at birth who had undergone *in utero* tracheal occlusion [141]. The EXIT procedure is now widely used for cases in which the neonatal airway may be difficult or impossible to manage, i.e. fetal neck masses and congenital high airway obstruction (CHAOS) [13,142]. The EXIT procedure is also used for other surgical procedures, such as thoracotomy to excise large CPAMs, for separation of conjoined twins, or for transition to ECMO. It is useful for severe lung hypoplasia (e.g. unilateral pulmonary agenesis) and selected cardiac lesions for transition to ventilatory support and/or ECMO, when resuscitation could otherwise be jeopardized by compromised oxygenation [143]. During the EXIT procedure, the neonate is partially delivered by cesarean delivery, and the connection between fetus, placenta, and mother remains intact. This allows gas exchange through the placenta rather than the fetal lungs. Uterine relaxation is necessary to prevent uterine contractions, separation of the placenta from the endometrium, or compromised uterine blood flow. Although most EXIT procedures only require about 30 min, durations of more than 2.5 h have been reported [144]. During this time placental circulation was adequate, as demonstrated by normal umbilical cord blood gases and absence of fetal acidosis at delivery [117].

For fetal surgery to be successful, a multidisciplinary team of fetal surgeons, anesthesiologists, ultrasonographers, maternal–fetal medicine specialists, and dedicated operating room nurses is needed. Maternal considerations, positioning, induction of anesthesia, and tracheal intubation are similar to those with general anesthesia for cesarean deliveries (see section "Open fetal surgical procedures").

Often >2 minimal alveolar concentration (MAC) of maternal volatile anesthetic agent is required to maintain profound uterine relaxation and prevent placental separation from the uterine endometrium. In some cases, periodic boluses of intravenous nitroglycerine (50–200 μg) or a continuous infusion of nitroglycerine (1–20 μg/kg/min) are required in addition to or instead of volatile anesthetic to provide adequate uterine relaxation. In certain cases, EXIT has been successfully accomplished with neuraxial blockade and nitroglycerine [145].

The use of high volatile anesthetic levels often decreases maternal cardiac output and uteroplacental blood flow and results in vasodilation and hypotension. Close hemodynamic monitoring is therefore required. Vasopressors such as phenylephrine and/or ephedrine are administered as needed and are preferred to excessive intravascular volume expansion, which may cause maternal pulmonary edema.

The uterus must be flaccid and atonic for hysterotomy. The location of the placenta and fetus are determined by ultrasound, the uterine incision avoids the placenta, and a stapling device is used to ensure hemostasis [144]. Following hysterotomy, the fetal head and upper torso are partially delivered outside the uterus. Keeping part of the fetus *in utero* helps maintain uterine volume and facilitates fetal warmth. A sterile pulse oximeter probe is applied to the fetal hand for monitoring heart rate and oxygen saturation. Occasionally partial delivery of the fetus causes fetal bradycardia from occult umbilical cord compression; full delivery of the fetus is then necessary. Partial delivery allows placental–fetal gas exchange to continue while the airway is secured or surgery is performed (Fig. 21.12). Volatile anesthetic is transferred to the fetus via the placenta; muscle relaxant, opioid, or resuscitation drugs are given by fetal intramuscular injection (see section "Open fetal surgical procedures"). Fetal well-being is continuously monitored by pulse oximetry (Fig. 21.12) and by periodic echocardiography. The mother breathes at least 50% inspired oxygen to improve fetal oxygenation. Typical fetal saturations prior to intubation are 40–65%. Despite maternal PaO_2 >500 mmHg, fetal arterial PaO_2 is <60 mmHg due to the nature of placental oxygen transfer [146]. Decreases in fetal heart rate or arterial saturation can result from maternal hypotension, placental abruption, umbilical cord compression or kinking, or loss of uterine relaxation. Anesthesiologists play a key role in monitoring the fetus and ensuring its safety by maintaining adequate uterine relaxation and appropriate maternal hemodynamic status.

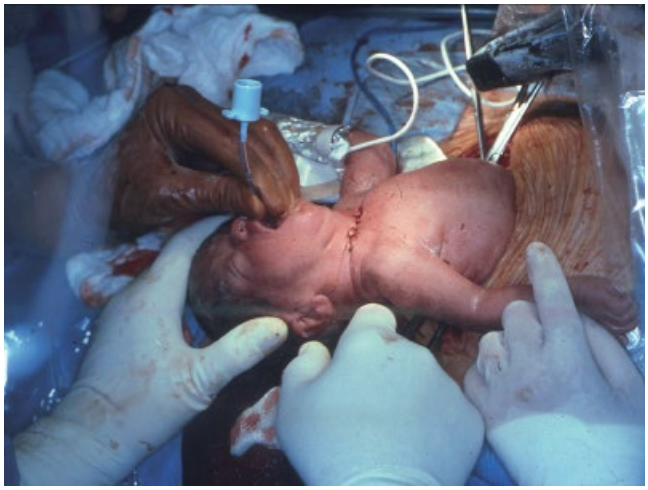


Figure 21.12 Partial delivery during EXIT procedure with airway secured and pulse oximeter monitor placed on left hand and occluded from light with foil. *Source*: Photo courtesy of UCSF Fetal Treatment Center.

Oral fetal intubation is accomplished by direct laryngoscopy, bronchoscopy, or video-assisted devices using a 3.0–3.5 mm internal diameter (ID) tracheal tube. After the trachea is intubated, pulmonary surfactant is often administered, and the lungs are ventilated. Peak inspiratory pressures are monitored with a manometer and maintained at the lowest pressures required for adequate pulmonary ventilation. Typically, a positive end-expiratory pressure of 5 cmH_2O is used to increase functional residual volume. Before delivery and termination of "placental support," endotracheal tube placement is confirmed by direct observation, auscultation of breath sounds, an increase in fetal SpO_2, and presence of end-tidal CO_2. Fetal pulmonary ventilation typically increases arterial oxygen saturation to >90%. After the baby's oxygen saturation increases, the cord is clamped, the baby is delivered, and neonatologists provide further resuscitation as needed.

Failure of fetal arterial oxygen saturation to rise above 90% with pulmonary ventilation is an indication to initiate ECMO before delivery [147]. This allows time to insert vascular cannulae and initiate ECMO flow before the fetus is removed from placental gas exchange. In other cases, fetal ascites or cystic masses can be decompressed before securing the airway, making it easier to manipulate the head and upper

airway and ventilate the fetal lungs. For longer surgeries, or when intravascular fetal volume or red blood cell mass must be increased, a fetal intravenous catheter is inserted into an upper extremity vein.

Immediately after cord clamping and fetal delivery, the volatile anesthetic is reduced or discontinued and oxytocin is administered to maintain normal postpartum uterine tone. Other agents, such as methylergonovine, prostaglandin-F2α or prostaglandin-E, are used if uterine atony persists. As the concentration of volatile anesthetic is reduced or discontinued, intravenous opioids, propofol, and/or nitrous oxide are administered to provide maternal anesthesia while maintaining uterine tone to complete surgery.

Six case series (4–52 patients) of EXIT determined neonatal outcome [148]. Ninety-seven to 100% of infants were born alive. Average blood loss was 850–1150 mL and the mean time on uteroplacental circulation was 28–45 min. Long-term outcomes of these neonates depended on the severity of the pathology necessitating the EXIT procedure.

Maternal outcomes after EXIT procedures have been excellent. Whenever possible, low transverse uterine incisions are used to decrease the risk of uterine rupture with subsequent pregnancies. Noah et al compared complications in 34 mothers who underwent EXIT procedures to 52 women who underwent cesarean delivery prior to labor [149], and found small increases in both wound complication rates and estimated blood loss in the EXIT procedure group, but no difference in transfusion requirements, postoperative hematocrit levels, and length of hospital stay [149].

KEY POINTS: *EX UTERO* INTRAPARTUM TREATMENT PROCEDURE

- The EXIT procedure is used for fetal neck masses and congenital high airway obstruction, thoracotomy for cystic adenomatoid malformations, separation of conjoined twins, or transition to ECMO
- The neonate is partially delivered by cesarean delivery, and the connection between fetus and placenta remains intact, allowing gas exchange through the placenta rather than the fetal lungs
- Uterine relaxation with >2 MAC volatile anesthetic and/or nitroglycerine is key to anesthesia for the EXIT procedure

Anesthetic management of fetal procedures

Anesthetic management of fetal surgical procedures is similar to anesthesia for non-obstetric surgery during pregnancy. Although the anesthesiologist must optimize fetal well-being and the conditions required for successful surgical and fetal outcomes, the anesthesiologist's paramount focus must be maternal safety. Consequently, anesthesiologists must participate in determining potential maternal risk compared to potential fetal benefit and exclude women in whom the benefit:risk ratio is low. Pregnancy-induced hormonal changes, mechanical effects of a growing uterus, and changes in maternal physiology have important implications for administration of anesthesia. To ensure maternal and fetal safety, the anesthesiologist must understand these physiological changes and how they affect anesthetic management, and must take an active role in perioperative management of both patients.

Unlike other surgical procedures performed during pregnancy for maternal indications (e.g. appendectomy) where the fetus is an innocent bystander, fetal surgery involves two surgical patients, and the anesthesiologist must balance the needs of both. For fetal procedures, the anesthesiologist must consider the fetus' requirements for anesthesia and the perioperative control of uterine tone.

Physiological changes in pregnancy and anesthetic implications

During pregnancy women undergo fundamental changes in anatomy and physiology [150–152]. These physiological changes and the associated morbidities of the fetal procedure place mothers at significantly greater risk for complications during anesthesia than non-pregnant patients. A detailed understanding of these changes and their anesthetic implications is required to prepare for and respond immediately to complications such as fetal distress and maternal hemorrhage. Although the physiological changes of pregnancy affect all organ systems, this section focuses only on cardiovascular, respiratory, and gastrointestinal changes and the anesthetic considerations for these changes in the perioperative period. A more detailed discourse on this subject is found in obstetric anesthesia texts [152].

Maternal cardiovascular system

Hematology

Maternal intravascular volume begins to increase in the first trimester of pregnancy. Larger increases in plasma volume (45–55% at term) than in erythrocyte volume (20–30% at term) cause both an increased intravascular volume and physiological (dilutional) anemia of pregnancy. Although decreased, typical hemoglobin levels are 11 g/dL or greater during pregnancy [152].

Pregnancy induces a hypercoagulable state. Factors I, VII, VIII, IX, X, XII, vWF increase, and factors XI, XIII, and antithrombin III decrease. These changes reduce both prothrombin (PT) and partial thromboplastin time (PTT) by 20%. Platelet levels are normal or reduced by 10%, and the leukocyte count is commonly elevated.

Cardiac output

Cardiac output increases 10% above the pre-pregnant state by 10 weeks of gestation and by about 45% by the third trimester. Increases in both heart rate and stroke volume are responsible for this increase. During labor, maternal cardiac output increases further. Each uterine contraction autotransfuses 300–500 mL of blood into the maternal central circulation. The greatest increase in cardiac output occurs immediately after delivery, when it is elevated by as much as 80% above pre-delivery levels. This abrupt increase in cardiac output is secondary to removal of aortocaval compression, autotransfusion from the contracted uterus, and decreased venous pressure in the lower extremities. These changes in cardiac output are a significant

risk for patients with major cardiac disease, e.g. fixed valvular lesions or left ventricular outflow tract obstruction.

Aortocaval compression

The gravid uterus may decrease preload, cardiac output, and maternal blood pressure by compressing the vena cava of supine pregnant women, especially at term. Venous blood from the lower extremities is redirected to the heart via the azygos, epidural, and vertebral veins. Some degree of vena caval compression is universal and occurs as early as 13–16 weeks of gestation. Approximately 15% of women experience significant hypotension in the supine position late in gestation. In addition, symptoms of nausea, vomiting, diaphoresis, and decreased mental status may accompany the reduction in blood pressure.

Anesthetic implications for the cardiovascular system

The majority of pregnant women experience little supine hypotension because they increase systemic vascular resistance to compensate for reduced venous return. Anesthetic interventions that diminish sympathetic tone (e.g. neuraxial blockade, general anesthesia) exacerbate the effects of vena cava compression and hypotension in supine mothers. Compression of the abdominal aorta by the gravid uterus can also produce lower extremity hypotension and reduced uterine and fetal blood flow that may not be reflected by upper extremity maternal blood pressures. Therefore, supine positioning is to be avoided during the perioperative period in the second and third trimesters of pregnancy. To help preserve uterine blood flow and fetal circulation, the right hip is elevated with a wedge or lateral table tilt. A >25% decrease in maternal blood pressure for >10–15 min may lead to progressive fetal acidosis.

Vena caval compression contributes to lower extremity venous stasis and increases the risk of venous thrombosis and pulmonary embolus. The venous stasis and hypercoagulable state of pregnancy require deep venous thrombosis prophylaxis in the postoperative period (sequential compression devices, low-molecular-weight heparin, increased mobility). In addition, vena cava compression causes epidural veins to dilate, and this increases the risk of accidentally placing an epidural catheter in a vein and injecting local anesthetic intravenously. Consequently, a "test dose" (e.g. 3 mL of 1.5% lidocaine with 1:200,000 epinephrine) is injected in the epidural catheter prior to administering larger (therapeutic) doses of local anesthetic. Increases in heart rate and blood pressure in excess of 20% (intravascular injection), or a rapid loss of lower extremity sensation and onset of motor block (intrathecal injection), are evidence of a misplaced epidural catheter.

Maternal airway and pulmonary system

Upper airway

During pregnancy, the pharynx, larynx, and trachea have increased capillary engorgement and tissue friability, making both laryngoscopy and intubation more challenging. It is frequently appropriate to use smaller cuffed endotracheal tubes (6.0 and 6.5 mm ID) because the larynx may be edematous and narrowed. Because of increased tissue friability, oropharyngeal suctioning and airway instrumentation may induce bleeding.

Ventilation and oxygenation

At term, minute ventilation is increased 45–50% and oxygen consumption more than 20%; functional residual capacity is decreased 20%. Resting maternal arterial CO_2 decreases from 40 mmHg to 30–32 mmHg in the first trimester of pregnancy. Arterial pH is slightly alkalotic (7.42–7.44) due to decreased concentrations of bicarbonate (compensatory metabolic acidosis).

Anesthetic implications for the respiratory system

Airway management by facemask, laryngeal mask, or tracheal intubation can be technically difficult in pregnant women because of their increased anteroposterior chest diameter, enlarged breasts, and laryngeal narrowing. The increased oxygen consumption and decreased oxygen reserve allow more rapid oxygen desaturation during hypoventilation, apnea, and general anesthesia. Obesity exacerbates this desaturation. Pregnancy-induced changes in both airway and respiratory physiology make ventilation and tracheal intubation more difficult and increase the potential for complications. During general anesthesia and controlled ventilation for fetal surgery, the maternal arterial CO_2 should be maintained at physiological levels (30–32 mmHg). Significant additional alkalosis reduces uterine blood flow and causes fetal acid–base abnormalities. Excessive positive pressure ventilation can increase the mean intrathoracic pressure of the mother and decrease cardiac preload, cardiac output, and uterine blood flow [153]. Lastly, an arterial $PaCO_2$ of <20 mmHg can decrease umbilical blood flow [154] and jeopardize the fetus.

Maternal gastrointestinal system

Women beyond 20 weeks' gestation are at risk for regurgitation and aspiration of gastric contents during the induction of anesthesia or with deep sedation. The gravid uterus displaces the stomach cephalad and anteriorly and the pylorus cephalad and posteriorly. The normally intra-abdominal portion of the esophagus is elevated into the thorax, decreasing the competence of the esophageal sphincter. Elevated progesterone and estrogen levels during pregnancy reduce esophageal sphincter tone. The gravid uterus increases gastric pressure, and placental gastrin secretion lowers gastric fluid pH. Consequently, maternal symptoms of gastric reflux increase with increasing duration of pregnancy in most pregnant women. Although gastric emptying is not delayed until the onset of labor, systemic or neuraxial boluses of opioids during surgery can delay gastric emptying and increase the risk of aspiration [155].

Anesthetic implications for the gastrointestinal system

Beyond mid-gestation, or earlier if there are symptoms of gastric reflux, women are at increased risk for pulmonary aspiration of acidic gastric contents and considered to have a full stomach. Current American Society of Anesthesiologists (ASA) guidelines recommend the "timely administration of oral nonparticulate antacids, intravenous (IV) H_2 receptor antagonists, and/or metoclopramide for aspiration prophylaxis" prior to the induction of anesthesia in pregnant women [156]. Rapid-sequence induction of anesthesia and tracheal intubation, utilizing cricoid pressure and a cuffed tracheal tube, are routinely employed during induction of general

anesthesia in pregnant women after mid-gestation. The risk of aspiration during tracheal extubation is similar to that during induction of anesthesia. Consequently, the trachea is not extubated until protective airway reflexes have returned. Nonparticulate antacids (30 mL sodium citrate) work rapidly. Metoclopramide (10 mg IV) when given at least 15 min before the start of anesthesia decreases the risk of aspiration. However, prior opioid administration reduces the effectiveness of metoclopramide [157]. H_2 receptor antagonists also effectively increase gastric pH but require significant time for efficacy.

Maternal central nervous system

The MAC of volatile anesthetics decreases during pregnancy based on studies demonstrating a 40% reduction in animals and a 28% reduction in humans [151,152,158,159]. However, an electroencephalographic study found anesthetic effects of sevoflurane on the brain were similar between pregnant and non-pregnant patients [160]. Additionally, intraoperative awareness rates are increased during cesarean delivery under general anesthesia, and reducing typical anesthetic levels in obstetric patients may not be prudent [161]. The decreased MAC in pregnant women increases the possibility of anesthetic oversedation.

Pregnant women are more sensitive to local anesthetics, which decreases the local anesthetic dose requirement for epidural or spinal anesthesia. This increased sensitivity begins in the first trimester, suggesting a role for biochemical changes (progesterone mediated). Engorgement of epidural veins and the corresponding decrease in the size of the epidural space with advancing gestation may facilitate the spread of local anesthetics.

Uteroplacental and fetal physiology

Uterine blood flow

Uterine blood flow (UBF) increases from approximately 100 mL/min in the non-pregnant state to about 700 mL/min (about 10% of cardiac output) at term. The placenta receives approximately 80% of the UBF and the myometrium 20%. The uterine vasculature has limited autoregulation and is essentially maximally dilated throughout pregnancy. Reduced uterine perfusion pressure, reduced cardiac output, or increased arterial resistance reduces maternal UBF. Decreased perfusion pressure results from systemic hypotension (e.g. hypovolemia, aortocaval compression) and neuraxial or general anesthesia. Decreases in uterine perfusion may result in placental hypoperfusion and fetal hypoxemia and acidosis.

Placental exchange and fetal circulation

The placenta is the interface between the fetal and maternal circulatory systems. Maternal blood is delivered to the placenta by the uterine arteries. Oxygen-poor fetal blood arrives at the placenta via two umbilical arteries, and oxygen- and nutrient-rich blood returns from the placenta to the fetus through a single umbilical vein.

Oxygen transfer to the fetus depends on a variety of factors including: (1) ratio of maternal UBF to fetal umbilical blood flow; (2) oxygen partial pressure gradient; (3) respective hemoglobin concentrations and affinities; (4) placental diffusing capacity; and (5) acid–base status of the fetal and maternal blood (Bohr effect). The fetal oxyhemoglobin dissociation curve is left-shifted (greater oxygen affinity) while the maternal hemoglobin dissociation curve is right-shifted (decreased oxygen affinity). This facilitates oxygen transfer to the fetus. After the first trimester, the fetal–placental blood volume is 120–160 mL/kg, depending on the gestational age [162].

Fetal hypovolemia reduces fetal organ perfusion because the immature sympathetic nervous system and baroreceptor activity are unable to compensate by vasoconstriction. The fetus also has limited capacity to increase cardiac output in response to stresses. Fetuses become rapidly hypothermic when outside the uterus because of transdermal heat loss and immature thermoregulatory vasoconstriction. Fetuses produce their own coagulation factors (which do not cross the placenta). The concentration of these factors increases with gestational age. Despite this increase, fetal blood clotting is less efficient than that in adults.

Maternal–fetal exchange of most drugs and other substances of <1000 Da is principally by diffusion. Transfer of substances across the placenta to the fetus depends on: (1) maternal–fetal concentration gradients; (2) maternal protein binding; (3) molecular weight of the substance; (4) lipid solubility; and (5) the degree of substance ionization. In most instances, the drug concentration in maternal blood is the major determinant of how much drug ultimately reaches the fetus.

Non-depolarizing neuromuscular blockers (large molecular weight and poorly lipid-soluble) and succinylcholine (highly ionized and poorly lipid-soluble) have limited ability to cross the placenta unless given in large doses. Similarly, unfractionated heparin, low-molecular-weight heparins, and glycopyrrolate are highly ionized and do not cross the placenta in significant amounts. In contrast, volatile anesthetic agents, benzodiazepines, local anesthetics, and opioids all have relatively small molecular weights and readily cross the placenta. Weakly basic drugs (e.g. local anesthetics) that cross the placenta in the non-ionized form are ionized in the more acidic fetal circulation and accumulate against a concentration gradient (ion trapping). Therefore, distressed, acidotic fetuses can accumulate high concentrations of local anesthetic. If there is an inadvertent maternal intravascular local anesthetic injection, the fetus often develops bradycardia, ventricular arrhythmia, acidosis, and severe cardiac depression.

The anatomy of the fetal circulation helps decrease fetal exposure to potentially high concentrations of drugs in umbilical venous blood. Approximately 75% of umbilical venous blood initially passes through the fetal liver, which may result in significant drug metabolism before the drug reaches the fetal heart and brain (first-pass metabolism) if the enzymes for metabolism are present (see Chapters 9 and 10). Fetal/neonatal enzyme system activities are lower than those of adults, but most drugs can be metabolized. In addition, drugs entering the fetal inferior vena cava via the ductus venosus are initially diluted by drug-free blood returning from the fetal lower extremities and pelvic viscera. These characteristics of the fetal circulation markedly decrease initial fetal plasma drug concentrations compared to maternal concentrations.

Anesthetic considerations

Adequate uterine blood flow and oxygenation are critical to fetal well-being. Because asphyxiated fetuses cannot increase oxygen extraction, they compensate by redistributing blood flow from the periphery to vital organs. Both hypercapnia and

hypocapnia reduce uterine blood flow, which causes fetal acidosis. In addition to left uterine displacement, normocarbia for the mother (30 mmHg end-tidal CO_2) should be maintained during general anesthesia. When regional or general techniques are used, a FiO_2 of 0.5 or higher is recommended during the procedure. In addition, maintenance of maternal blood pressure near baseline values is critical to fetal well-being. Use of vasopressors and judicious fluid administration are frequently required to maintain normal maternal blood pressure. Despite the historical use of ephedrine, phenylephrine (α-adrenergic) has proven to be a first-line treatment of maternal hypotension when reasonable dosing parameters are used and maternal heart rate is maintained [163].

Impact of anesthesia on the fetus

Of note is the concern for the possible detrimental effect of anesthetic agents on the developing fetal brain. In December 2016, the United States Food and Drug Administration (FDA) issued a safety warning for anesthetic agents that are either γ-aminobutyric acid (GABA) agonists or N-methyl D-aspartate (NMDA) receptor antagonists. The warning specifically states, "repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains" [164,165]. This warning is based primarily on animal data which suggest there may be a detrimental effect on the developing brain. To date, prospective studies in humans have not definitively supported these findings [166,167]. All volatile anesthetics as well as some intravenous sedatives such as benzodiazepines exert their action by their effect on the GABA receptors. While this warning highlights use of these drugs in pregnant women in the third trimester, the implications for the pregnant mother with a midgestation fetus undergoing *in utero* surgery during which these agents are administered are not clear based on the limited animal studies. As such, some centers that offer fetal intervention or surgery in mid-gestation discuss the FDA warning and the use of inhalational agents with families during the consent process. In addition, based on this warning, attempts are made in some, but not the majority of US fetal treatment centers, to minimize the time of exposure of the mother (and subsequently the fetus) to general anesthesia. Additional intravenous lines, arterial and urinary catheter placement, as well as prepping and draping of the patient, all occur while patient is awake or mildly sedated with non-implicated intravenous agents such as dexmedetomidine or fentanyl. However, it could be argued that the increased maternal pain and stress of performing these procedures prior to induction could also have an impact on both fetal blood flow and chance of preterm labor [168]. Additional discussion of potential anesthetic neurotoxicity in the developing brain is presented in Chapter 46.

KEY POINTS: PHYSIOLOGICAL CHANGES OF PREGNANCY AND ANESTHETIC IMPLICATIONS

- Anesthetic management considerations for fetal surgical procedures are similar those of anesthesia for non-obstetric surgery during pregnancy
- Cardiac output increases 45% by the third trimester, and left uterine displacement is needed to reduce aortocaval compression and improve maternal cardiac output by mid-gestation
- The upper airway has increased capillary engorgement and tissue friability, and minute ventilation is increased by 45–50% at term
- Uterine vasculature has limited autoregulation and is essentially maximally dilated throughout pregnancy

Fetal pain and anesthesia

Whether or when fetuses experience pain and whether fetuses require or benefit from anesthesia for surgical intervention are inadequately understood and remain controversial. Surgical pain is defined as an unpleasant sensory and emotional response to tissue damage and a subjective experience involving cognition, sensation, and affective processes [169]. Although pain is commonly associated with physical noxious stimuli, it is clearly more than nociception or the simple reflex activity of a withdrawal response [170]. Pain is fundamentally a psychological construct that can exist in the absence of physical stimuli (e.g. phantom limb pain). The psychological nature of pain distinguishes it from nociception, which involves activation of nociceptive pathways without the subjective emotional experience of pain. Most definitions of pain suggest the experience is subjective, organized into a conceptual framework, and based on previous painful injuries [169]. While the ability to experience pain must begin at some point and is clearly present in neonates, it is unclear when fetuses actually first feel pain.

Reflex movements and biochemical evidence of a "stress response" can be triggered by a noxious stimulus without involving the cerebral cortex and without conscious pain perception. An example is withdrawal from a noxious stimulus mediated in the spinal cord without conscious perception of pain (Fig. 21.13). This occurs by about 18 weeks' gestational age. Peripheral sensory receptor nociception is transmitted by afferent fibers that synapse on interneurons in the spinal cord and then synapse on spinal cord motor neurons. These motor neurons trigger muscle contractions that cause limb flexion and movement. The stress response can be mediated in the spinal cord, brainstem, or basal ganglia without cortical involvement.

It is generally accepted that experiencing pain requires higher cognitive functioning and cortical recognition that the stimulus is unpleasant. This requires intact neural pathways from the periphery, through the spinal cord, to the thalamus, which relays the stimulus to the primary sensory cortex, the insular cortex, and the anterior cingulated cortex (Fig. 21.14). Peripheral sensory receptor afferents also synapse on spinal cord neurons that project to the thalamus, which relays afferent stimuli to the cerebral cortex and activates many different cortical regions. Sensory receptors and spinal cord synapses required for nociception develop earlier than the thalamocortical pathways required for conscious perception of pain. It is unlikely that fetal perception of pain is possible before pathways from the periphery to the brain and before cortical structures develop. However, the gestational age when pain perception is possible remains unknown.

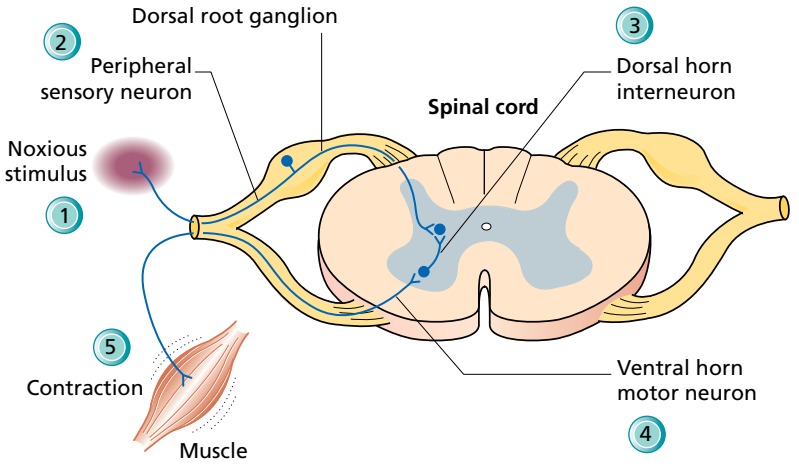


Figure 21.13 Early in development. Reflex responses to noxious stimuli occur before thalamocortical circuits are functional; noxious stimuli trigger reflex movement without cortical involvement. Activated by a noxious stimulus (1), a peripheral sensory neuron (2) synapses on a dorsal horn interneuron (3) that in turn synapses on a ventral horn motor neuron (4), leading to reflex muscle contraction and limb withdrawal (5). *Source*: Reprinted from Lee et al [170] with permission of JAMA.

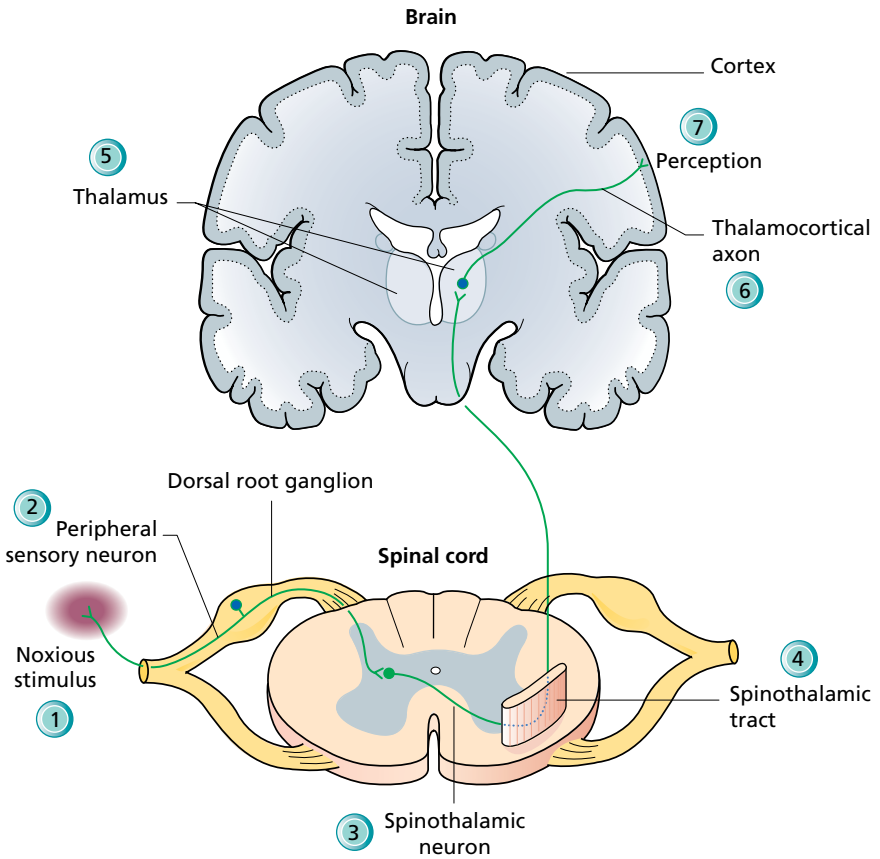


Figure 21.14 Later in development. Noxious stimuli (1) activate peripheral sensory neurons (2) that synapse on spinothalamic tract neurons (3), the axons of which extend up the spinal cord as the spinothalamic tract (4) to synapse on neurons of the thalamus (5). From here, thalamocortical axons (6) synapse on cortical neurons, resulting in the conscious perception of pain (7). *Source*: Reprinted with permission from Lee et al [170] with permission of JAMA.

Nerve terminals for detection of touch, temperature, and vibration (not pain) are present in deep human skin by 6 weeks' gestation and have extended towards the skin surface by 10 weeks [171]. Immature skin nociceptors are likely present by 10 weeks and definitely present by 17 weeks [172]. Nociceptors develop slightly later in internal organs.

Peripheral nerve fibers that control movement first grow into the spinal cord at about 8 weeks' gestation. When these fibers connect with nociceptors is unknown, but in other mammals this is more delayed than other sensory inputs. One human study suggests that nerve fibers from nociceptors do not enter the spinal cord before about 19 weeks [173]. The cerebral cortex develops after the fetal spinal cord and brainstem.

The developing cerebral wall consists of transient fetal zones where neuronal proliferation, cell migration, apoptosis, axonal outgrowth, and synaptogenesis occur according to a highly

specific timetable. Early in development the cerebral cortex is a smooth layer without sulci and gyri and, like the thalamus, has no internal cellular organization [171]. The insular cortex starts developing in humans around 15 weeks' gestation, and the cortical subplate develops at about 13 weeks. The subplate is a temporary structure located one layer deep to the cortical plate. The subplate recedes after 32–34 weeks' gestation, and the cortical plate develops into the six layers of the cerebral cortex [174–176]. The subplate is crucial in cortex development because it serves as a waiting zone for various afferents, including thalamic afferents that are en route to the developing cortex. The subplate is also critical for establishing connections between the thalamus and cortex and for precise organization and laminar relocation of these afferent pathways.

The first fibers from the thalamus reach the subplate by 12 and 18 weeks' gestation and remain in the subplate until cortical plate maturation. By 24 weeks, substantial thalamocortical fibers have amassed in the subplate and have grown into the maturing cortex between 24 and 32 weeks. The gestational age at which thalamic pain fibers reach the human cortex can only be estimated from histological studies of other thalamocortical circuits. Thalamic projections reach the visual subplate at 20–22 weeks [175,177], the visual cortex at 23–27 weeks [178], and the auditory cortical plate at about 26–28 weeks' gestation [179]. The subplate thins in the insula and in areas of the brain where cortical folding occurs early. It disappears after a period of rapid relocation of fibers to the cortex at around 34 weeks' gestation. Massive brain growth and maturation occur after 34 weeks' gestation. This results in the typical cortical sulci and gyri and in development of extensive intracortical pathways and pathways from the cortex to the thalamus, midbrain, and spinal cord.

Given the development of pain pathways and interpretation of cortical function, it is unlikely fetuses experience pain before 24 weeks' gestation (and perhaps significantly later) because the cortex must subsequently undergo considerable development and establish enormously complex and highly integrated neural networking, with dendritic and synaptic rearrangements that occur during late fetal life and infancy and continue into early childhood.

Although development of neural pathways from the periphery to the cortex is important, development of the cortex itself is probably necessary for fetuses to experience pain. The neural networking must also be functional. Although there are no specific electroencephalographic patterns for fetal pain, EEG studies provide some evidence for functionality. Studies at 24 weeks' gestation show the presence of cortical electrical activity only 2% of the time [180]. By 30 weeks, EEG patterns are similar to those of wakefulness and sleep, but they are not continuous and are discordant with fetal behavior. By 34 weeks, electrical activity is present 80% of the time and EEG patterns become more distinct [181–184].

Can the fetus experience pain before there are connections from the periphery to cortex or before there is significant brain electrical activity? Some investigators have postulated that nociceptive information may be transmitted earlier through neurological connections from peripheral tissue through the brainstem and thalamus to the subplate. They argue that the midbrain reticular system is responsible for "consciousness" rather than the thalamocortical system [185]. Although midbrain systems are crucial for the waking state, instincts, orienting, and purposeful behavior, consciousness is widely regarded as a very complex phenomenon for which the cerebral cortex is indispensable. Awareness and wakefulness are different phenomena.

Preterm neonates who undergo surgery with minimal anesthesia have circulatory, sympathoadrenal, and pituitary adrenal responses that are characteristic of stress. These include release of catecholamines, growth hormone, glucagon, cortisol, aldosterone, and other corticosteroids, as well as decreased insulin secretion [186,187]. Anesthesia blunts the neonatal stress response [188]. Opioids also improve the outcome of preterm neonates by attenuating the stress response [189].

In the human fetus, needling of the intrahepatic vein for blood transfusion induces the stress response while needling the insensate umbilical cord does not. This response includes increased plasma β-endorphin and cortisol concentrations and decreased Doppler-determined middle cerebral artery pulsatility index, consistent with redistribution of blood flow to vital organs, including the brain [190,191]. The stress response to intrahepatic vein needling is blunted by 10 μg/kg of fentanyl [192]. Human fetuses elaborate pituitary–adrenal, sympathoadrenal, and circulatory stress responses to noxious stimuli as early as 16–18 weeks' gestation [193,194]. During late gestation, fetuses respond to environmental stimuli (e.g. noises, light, music, pressure, touch, and cold) [195]. However, these physiological stress-related responses or reflexive responses to external stimuli are not necessarily equivalent to the multidimensional, subjective phenomenon we call pain. Reduction in stress hormones is not necessarily indicative of adequate analgesia [196]. The stress response is largely mediated in the spinal cord, brainstem, or basal ganglia, not the cortex.

Two studies used near-infrared spectroscopy to measure changes in cerebral oxygenation over the somatosensory cortex and demonstrated that noxious stimulation of preterm infants caused cortical responses that differed from those of non-noxious stimulation. They concluded that noxious information can be transmitted to the infant cortex from 24 weeks' gestation onward [197,198]. Preterm neonates have cortical evoked potentials after heel lance [199]. Although these studies provide evidence of functional neural activity in the sensory cortex of 24-week-old preterm neonates, the primary sensory cortex is not the only brain area that mediates painful experiences; continued development and organization of the cortex is likely necessary. These were preterm neonates, not fetuses. *In utero*, the low level of oxygen alone may preclude awareness and the ability to experience pain. Furthermore, endogenous neuroinhibitors produced in the placenta (e.g. adenosine, allopregnanolone, pregnanolone, prostaglandin D2, various placental peptide inhibitors) sustain fetal sleep and suppress fetal awareness [200]. Late-gestation fetuses oscillate between REM and NREM sleep 95% of the time. Data suggest that the other 5% of the time they are in a form of indeterminate transitional sleep, suggesting that the fetus is always asleep [201]. Unlike neonates, noxious stimuli do not appear to cause cortical arousal to a wakeful state in fetuses. Wakefulness is a state of arousal mediated by the brainstem and thalamus in communication with the cortex. It must be understood that wakefulness does equal awareness. Thus, the intrauterine environment might keep the fetus from being awake or aware, and from experiencing pain. Maybe awareness is only possible after birth.

Although noxious stimulation might not affect fetal consciousness, it might influence neurological or behavioral development. Circumcision of a non-anesthetized neonate increases the infant's pain response to injections 6 months later, and fetal stress has long-term adverse hormonal effects in young monkeys [202,203]. Consequently, it is possible that noxious stimuli can have adverse long-term neurodevelopmental consequences that could be attenuated or blocked by anesthesia [185], although these effects later in life do not prove that the causal event was experienced as pain.

Anesthetic considerations

Because it is unclear when fetuses feel pain, it seems best to err on the side of providing adequate fetal anesthesia at all gestational ages [204]. Altogether, clinical observations of fetal and neonatal behavior, information about the development of mechanisms of pain perception, and studies of fetal and neonatal responses to noxious stimuli provide a compelling physiological and philosophical rationale for providing adequate fetal anesthesia, especially after 24–26 weeks' gestation. Although we do not know whether or when fetuses experience pain, noxious stimulation causes a stress response, clear evidence that the fetal nervous system is reactive, which could have short- and long-term adverse effects on the developing CNS [205].

Despite unknown fetal capacity for pain perception, fetal anesthesia and analgesia are warranted for fetal surgical procedures. Evidence of fetal pain is unnecessary to justify providing fetal analgesia or anesthesia because doing so serves other purposes, including: (1) inhibition of fetal movement during a procedure; (2) prevention of hormonal stress responses associated with poor surgical outcomes in neonates; (3) prevention of possible adverse effects on long-term neurodevelopment and behavior; and (4) ensuring profound uterine relaxation to prevent contractions and placental separation during open procedures. Anesthesia has been administered to fetuses undergoing surgery since the inception of fetal surgery and continues worldwide.

KEY POINTS: FETAL PAIN AND ANESTHESIA

- Studies as to when fetuses experience pain are not definitive; noxious information can be transmitted to the infant cortex from 24 weeks gestation onward
- Because it is unclear when fetuses feel pain, it seems best to err on the side of providing adequate fetal anesthesia at all gestational ages
- Fetal anesthesia serves other purposes, including inhibition of fetal movement, prevention of hormonal stress responses, prevention of possible adverse effects on long-term neurodevelopment, and ensuring profound uterine relaxation

Perioperative and procedural considerations

Preoperative assessment and considerations

The anesthesiologist should conduct a thorough preoperative assessment of both the mother and fetus. In addition to a standard preoperative history and physical examination, specific details should be obtained regarding how the pregnancy is affecting the mother. The evaluation should include questions about shortness of breath, episodes of syncope or feeling lightheaded, and severity of gastric reflux. Imaging studies should be reviewed because they provide placental location, anatomical information about the fetal lesion, and estimated fetal weight. This information may alter the surgical approach and patient positioning and modify the anesthetic plan. Occasionally general anesthesia might be chosen because maternal position compromises patient safety or the duration of the surgery will be protracted. Most minimally invasive procedures can be performed with just a maternal type and screen, whereas readily available, cross-matched blood is required for open procedures because the risk of hemorrhage is greater. In addition, O-negative, leukocyte depleted, irradiated, CMV-negative blood that is cross-matched against the mother should be readily available for fetuses undergoing open procedures. Maternal IgG antibodies cross the placenta.

Risks and benefits

The primary goal of *in utero* surgery is to improve neonatal outcome compared to interventions performed after birth. The intrauterine environment offers quicker wound healing, decreased scar formation, and an ideal postoperative recovery environment because the placental/fetal circulation provides all of the fetus's nutritional, metabolic, and oxygen requirements.

Risks to the fetus (renal failure, CNS injuries, hemorrhage, chorioamnionitis, demise, postoperative amniotic fluid leaks, membrane separation, abruption, PPROM, preterm labor and delivery) are relatively high. Chorioamniotic membrane separation can cause amniotic bands, umbilical cord strangulation, and fetal demise. Preterm delivery carries significant morbidity and mortality for fetuses that might otherwise benefit from therapeutic interventions if they were born at term.

Maternal safety is of primary concern when developing a fetal management plan. The vast majority of fetal conditions amenable to *in utero* treatment pose no direct maternal risk, but the procedure itself, medications, and possible postoperative complications all carry potential morbidity. Fortunately, serious maternal morbidity is relatively minimal or uncommon [10]. Maternal risks include hemorrhage, wound infection or chorioamnionitis, placental abruption, uterine rupture, and side-effects of tocolytics, including pulmonary edema. In addition, the risks of pulmonary aspiration, difficult ventilation/tracheal intubation, and hemodynamic compromise are increased during pregnancy. Open fetal procedures typically involve a hysterotomy incision that is away from the lower uterine segment, necessitating cesarean delivery for open procedures and all future pregnancies. Future reproductive capabilities do not seem to be compromised [206]. Maternal safety and welfare must be balanced against the risk of fetal death or of caring for a child with a significant morbidity.

Interdisciplinary team

Perioperative care by a multidisciplinary team is essential for success of fetal surgical procedures and care of the mothers. In addition to the anesthesiologist's preoperative assessment, a typical case requires input from ultrasonographers and

radiologists regarding ultrasound and MRI imaging to confirm the diagnosis, detail the abnormal anatomy, and rule out other pathological lesions. Maternal–fetal medicine physicians, geneticists, and neonatologists provide patient counseling, fetal karyotyping, and information about the likely condition of the newborn with or without *in utero* intervention. Fetal surgeons provide details of the procedure and associated risks and outcome potential to the family, and social workers and nurse coordinators address unique family situations, logistics and concerns, and potential psychological issues. Maternal partners are often involved in the process to alleviate potential perceptions of guilt or coercion, depending on the mother's final decision. Regular interdisciplinary meetings with obstetric anesthesiologists, obstetricians, fetal surgeons, neonatologists, maternal–fetal medicine experts, ultrasonographers, operating room staff, nurse coordinators, and social workers allow team communication and provide awareness of patient developments by all caregivers. This maximizes the chances for successful outcomes for both mothers and fetuses. Before undertaking any fetal procedure, members of all disciplines should meet to ensure a complete, detailed, and appropriate plan is in place and needed equipment and personnel are available.

General intraoperative and postoperative considerations

Maternal analgesia and anesthesia for fetal surgery can be provided with local infiltration of the skin and uterine wall, intravenous maternal sedation, neuraxial anesthesia, general anesthesia, or a combination of these techniques.

In addition to the maternal anesthetic plan and the fetal surgical procedure, strategies must be developed for fetal monitoring, fetal analgesia and/or neuromuscular relaxation, management of unanticipated fetal or maternal distress, postoperative fetal and uterine monitoring, and maternal postoperative analgesia. The anesthesiologist must consider the anesthetic requirements of the fetus and appropriate intraoperative fetal monitoring (e.g. fetal heart rate, fetal oximetry, fetal echocardiography, ductus arteriosus flow, umbilical artery flow), and the potential need for fetal intravenous access for fluid resuscitation or blood transfusion. Fetal analgesia and anesthesia can be provided by direct intravenous or intramuscular administration of drugs to the fetus or placental transfer of maternal intravenous agents or general anesthetics. Many anesthetic compounds readily cross the placenta (e.g. induction agents, inhaled anesthetics, opioids, benzodiazepines), but muscle relaxants do so only in small amounts.

Profound uterine relaxation is required for open procedures. Concern for increased uterine tone and initiation of premature labor requires continuous or intermittent postoperative fetal heart rate and uterine activity monitoring, sometimes for days. Maternal postoperative analgesia options include neuraxial opioids, continuous epidural analgesia, patient-controlled intravenous analgesia (PCA), and oral medications.

The anesthesiologist should always be prepared for emergent fetal delivery or uterine evacuation. If maternal cardiac arrest is precipitated by local anesthetic overdose, total spinal anesthesia, or severe hemorrhage, and resuscitation cannot be accomplished in 4 min, the fetus should be delivered emergently even if not viable [207,208]. Emergent cesarean delivery relieves aortocaval compression, improves the effectiveness of resuscitation, and increases the mother's and possibly the fetus's chances for survival.

The following sections are generic descriptions of anesthetic approaches for both minimally invasive and open fetal procedures, and of postoperative management. Approaches vary between fetal treatment centers. The EXIT procedure has been described in the section "*Ex utero* intrapartum treatment procedure" and in the case study at the end of this chapter. Basic anesthetic considerations are similar to those for any woman undergoing surgery during pregnancy [209].

Minimally invasive and percutaneous procedures

Amniocentesis, cordocentesis, intrauterine blood transfusion, needle aspiration of cysts, shunt placement into the fetal bladder or thorax, RFA, and selective fetoscopic laser photocoagulation for TTTS are examples of minimally invasive treatments. These procedures are performed using an ultrasound-guided needle or by inserting a single, small-diameter percutaneous sheath or cannula that allows insertion of an endoscope. Local anesthetic infiltration of the abdominal wall or neuraxial anesthesia is usually adequate. If the procedure involves multiple needle punctures at various locations, large instruments, or a minilaparotomy, neuraxial anesthesia often provides better maternal comfort. Choice of anesthesia technique is based on the surgical approach, anticipated duration of the procedure, and need for postoperative analgesia. Often, the anesthetic is supplemented by minimal or conscious sedation. General anesthesia is rarely necessary. Before the procedure starts, the mother should be appropriately fasted, receive aspiration prophylaxis, have adequate intravenous access, and be fully monitored.

Use of local or neuraxial anesthesia does not provide fetal analgesia or immobility. Supplemental analgesia (opioids), anxiolysis (midazolam), and sedation (low-dose propofol infusion) provided to the mother will sedate her and may provide some fetal immobility and analgesia following placental transfer. A randomized, blinded, controlled trial demonstrated that remifentanil (0.1 μg/kg/min) resulted in more fetal immobility and better surgical operating conditions compared to diazepam [92]. Any maternal sedation regimen must ensure that the mother remains within a level of "conscious sedation" to minimize maternal respiratory depression, loss of maternal airway reflexes, and pulmonary aspiration risk.

Fetal immobilization is unnecessary for certain minimally invasive fetal procedures, such as laser surgery of the chorionic plate (e.g. SFLP for TTTS). However, fetal movement may compromise the success of certain procedures by making them technically difficult or impossible. As an example, in the case of cordocentesis or intrauterine transfusion, fetal movement may be hazardous because displacement of the needle may cause trauma and bleeding, compromise procedure success, and even necessitate emergent delivery. If the procedure requires fetal immobility, muscle relaxants can be administered directly to the fetus. Non-depolarizing neuromuscular blocking agents can be administered to the fetus by ultrasound-guided intramuscular or umbilical venous

administration of rocuronium (2.5 mg/kg IM, 1 mg/kg IV) or vecuronium (0.2 mg/kg IM, 0.1 mg/kg IV). Fetal paralysis with either agent occurs in 2–5 min, with a 1–2 h duration. For long procedures, redosing may be necessary.

For procedures involving noxious stimulation of the fetus (e.g. shunt catheter placement, cardiac septoplasty), intramuscular or intravascular opioid (e.g. fentanyl 10–20 μg/kg) can be administered to the fetus [192]. If general anesthesia is administered to the mother, placental transfer of inhaled anesthetic is sufficient to adequately immobilize and anesthetize the fetus. However, fetal muscle relaxant is often administered if fetal immobility is critical for procedure success.

A plan should be in place for treatment of fetal distress and should include having available weight-appropriate doses of drugs on the sterile field for fetal resuscitation (e.g. atropine 20 μg/kg, epinephrine 1 μg/kg and 10 μg/kg). Persistent fetal bradycardia during minimally invasive procedures may require an emergency cesarean section if the gestational age is compatible with extrauterine viability. Consequently, the anesthesiologist must be prepared to emergently provide general anesthesia for cesarean delivery.

Open fetal surgical procedures

In utero procedures that require a maternal laparotomy and hysterotomy (e.g. open MMC repair, sacrococcygeal teratoma resection) are typically performed under general anesthesia. In addition to the anesthetic considerations required for minimally invasive fetal surgery and for maternal surgery during pregnancy, open fetal procedures have unique considerations. These include: (1) the need for profound uterine relaxation; (2) increased potential for significant maternal or fetal blood loss or fluid shifts; (3) intraoperative fetal monitoring, fetal anesthesia, and the potential need for fetal resuscitation; and (4) postoperative maternal analgesia and prevention of preterm labor. Box 21.2 details specific considerations to be addressed before undertaking open fetal surgery. The majority of these items are also useful when planning for minimally invasive and EXIT procedures.

A non-particulate oral antacid is administered preoperatively for aspiration prophylaxis, indomethacin is administered for tocolysis, and an epidural catheter is placed for postoperative analgesia. Type and cross-matched blood products are obtained for both mother and fetus. Sequential compression devices are placed on the mother's lower extremities to minimize the risk for deep venous thrombosis. Similar to what occurs when any general anesthetic is administered after about 20 weeks of gestation, the patient is positioned with left uterine displacement, adequately preoxygenated, and rapid-sequence induction and tracheal intubation are performed during cricoid pressure. Prior to incision, anesthesia is typically maintained with low concentrations of volatile agent and/or a propofol infusion. During this time, the ultrasonographer determines fetal presentation and placental

Box 21.2: Considerations for open fetal surgery

Preoperative considerations

1. Maternal counseling by multidisciplinary team
2. Complete maternal history and physical examination
3. Imaging studies to define fetal lesion and placental location
4. Complete fetal work-up to exclude other anomalies or karyotype abnormalities
5. Surgical meeting or "time-out" with all team members prior to starting
6. Prophylactic premedication: non-particulate antacid (aspiration) and rectal indomethacin (tocolysis)
7. Blood products typed and cross-matched for potential maternal and fetal transfusion
8. High lumbar epidural catheter placement for postoperative analgesia
9. Sequential compression devices on lower extremities for thrombosis prophylaxis
10. Fetal resuscitation drugs transferred to scrub nurse in unit doses
11. Emergent delivery plan if fetus considered viable for birth

Intraoperative considerations

1. Left uterine displacement and standard monitors
2. Fetal assessment prior to maternal induction
3. Preoxygenation for 3 min prior to induction
4. Rapid-sequence induction and intubation
5. Maintain maternal FiO_2 at ≥50% and end-tidal CO_2 at 28–32 mmHg
6. Ultrasonography to determine fetal and placental positioning
7. Urinary catheter placed and additional large-bore intravenous access obtained
8. Administer prophylactic antibiotics
9. Following incision, initiate high concentrations of volatile anesthetics (2–3 MAC) to achieve uterine relaxation, or an alternate SIVA technique relying on remifentanil and propofol infusions with a reduced volatile anesthetic (1–2 MAC).
10. Consider intravenous nitroglycerine if uterine tone remains increased
11. Maintain blood pressure near baseline with intravenous phenylephrine or ephedrine
12. Intramuscular administration of fetal opioid and paralytic with ultrasound guidance or by direct vision
13. Place fetal pulse oximeter and use periodic ultrasound for fetal monitoring
14. Obtain fetal vascular access if significant fetal blood loss is expected
15. Restrict maternal fluids to <2 L to decrease risk of pulmonary edema
16. Administer loading dose of intravenous magnesium sulfate when uterine closure begins
17. Discontinue halogenated agents after magnesium sulfate bolus complete
18. Activate epidural for conclusion of surgery and postoperative analgesia
19. Administer nitrous oxide and opioids to supplement epidural anesthesia during fascia and skin closure
20. Close monitoring of neuromuscular blockade due to potentiation of magnesium sulfate
21. Extubate trachea when patient is fully awake

Early postoperative considerations

1. Postoperative debrief with team members
2. Continue tocolytic therapy
3. Patient-controlled epidural analgesia
4. Monitor uterine activity and fetal heart rate
5. Ongoing periodic fetal evaluation

MAC, minimum alveolar concentration; SIVA, supplemental intravenous anesthesia.

location, additional large-bore vascular access is obtained, the urinary bladder is catheterized, and prophylactic antibiotics are administered.

For both open and EXIT procedures, 2–3 MAC of volatile anesthetic agent is frequently used to provide maternal and fetal anesthesia and the surgical tocolysis (uterine atony) required for the procedure. Volatile anesthetic agents inhibit myometrial contractility by calcium-sensitive potassium channel modulation [210]. The human uterus has a thick, muscular layer that is sensitive to stimulation or manipulation, and stimulation may produce strong uterine contractions. Complete uterine relaxation is essential because increased uterine tone compromises uterine perfusion and increases the risk for partial placental separation. Because high levels of volatile anesthetic are associated with abnormal fetal cardiac function, some fetal centers use supplemental intravenous anesthesia with a lower MAC of halogenated agent (1–1.5 MAC) combined with propofol and remifentanil infusions [211–213]. High intravenous doses of nitroglycerine may also be used as a supplemental or primary agent for intraoperative uterine relaxation [214].

Prior to hysterotomy, the uterus is assessed for increased tone. If increased uterine tone is noted before or after incision, the halogenated agent can be increased (up to 3 MAC) or additional intravenous nitroglycerin can be given in small boluses (50–200 μg IV) or by continuous infusion. If nitroglycerine is used without high concentrations of volatile anesthetic, an intravenous infusion of up to 20 μg/kg/min may be required [214]. Arterial blood pressure is maintained with intravenous phenylephrine or ephedrine as needed to maintain adequate mean arterial pressures near maternal baseline. Maternal monitoring by arterial line and central venous catheter is not typically required, but may be used at some centers. Cross-matched blood for the mother and O-negative, CMV-negative, leukocyte-reduced, irradiated blood for fetal transfusion should be readily available in the operating room. For open procedures with the potential for significant fetal blood loss (e.g. sacrococcygeal teratoma resection), close attention to fetal monitoring and estimated fetal blood loss is required. It may be necessary to insert a fetal intravenous catheter to transfuse blood. Vascular access is obtained in a fetal hand or arm vein, or by surgical cut-down on the internal jugular vein.

Intraoperative ultrasound is used to determine placental location and fetal position. The uterine incision is made away from the placenta, but in a position that allows for appropriate exposure of the fetal part. A stapling device with absorbable lactomer staples is used to prevent excessive bleeding and seal the membranes to the endometrium [215]. During surgery, the exposed fetus and uterine cavity are bathed with warm fluids.

With ultrasound guidance or direct vision, opioid (e.g. fentanyl 10–20 μg/kg) and muscle relaxant (e.g. rocuronium 2.5 mg/kg) are administered to the fetus intramuscularly before the fetal incision is made [93]. Drugs for fetal resuscitation (atropine 20 μg/kg, epinephrine 1 μg/kg and 10 μg/kg) are transferred to the scrub nurse in sterile fashion for administration by the surgeon (if needed) under the direction of the anesthesiologist. Each syringe is prepared with a single, unit weight-based dose and appropriately labeled.

Maternal and fetal anesthesia, uterine incision, fetal manipulation, and surgical stress may adversely affect uteroplacental and fetoplacental circulation by several mechanisms. Maternal hypotension increases uterine activity and causes maternal hyperventilation and hypocarbia, which impair uteroplacental and/or umbilical blood flow. Manipulation of the fetus may affect cardiac output, regional distribution of cardiac output, and/or umbilical blood flow. Direct compression of the umbilical cord, inferior vena cava, and/or mediastinum adversely affects fetal circulation. Fetal well-being is assessed by continuous fetal pulse oximetry, periodic fetal heart rate (FHR) monitoring by intraoperative ultrasonography, and fetal echocardiography for assessment of ventricular contractility, flow in the ductus arteriosus, and/or umbilical artery flow.

During surgical closure, a loading dose of magnesium sulfate is administered (4–6 g) intravenously over 20 min and is followed by an intravenous infusion of 1–2 g/h to maintain uterine quiescence and prevent postoperative contractions. Intraoperatively, maternal intravenous fluids are restricted to minimize the risk of postoperative pulmonary edema, which is associated with the use of tocolytic agents [12,216,217]. Inspired concentrations of volatile agents are significantly decreased or discontinued once the magnesium sulfate bolus has been administered. Maternal anesthesia can be maintained with a combination of fentanyl, propofol, and/or nitrous oxide, and activation of epidural anesthesia. This regimen facilitates timely tracheal extubation of a fully awake patient and minimizes the likelihood of coughing or straining and jeopardizing the integrity of the uterine closure. If neuromuscular agents are utilized, the absence of neuromuscular blockade should be determined prior to tracheal extubation, since magnesium sulfate potentiates neuromuscular blockade.

Whatever anesthetic technique is used for open fetal surgery, it must ensure adequate uteroplacental perfusion, profound uterine relaxation, maternal hemodynamic stability, fetal anesthesia and immobility, and minimal fetal myocardial depression and compromise.

Postoperative management

Management of postoperative preterm labor has been one of the most difficult aspects of fetal surgery, but prevention and treatment of uterine contractions is essential for optimal fetal outcomes. Postoperative tocolysis has included a variety of agents, including magnesium sulfate, β-adrenergics, indomethacin, and calcium-entry blockers. Magnesium likely competes with calcium at voltage-operated calcium-sensitive potassium channels by an action similar to volatile anesthetics [210]. Indomethacin blocks the synthesis of prostaglandins, and β-adrenergic agents act directly on the uterus by activating adenylate cyclase and thereby reducing intracellular calcium. The relative inefficacy of tocolytic agents and their adverse side-effects have made this aspect of postoperative management challenging. Tocolysis is normally unnecessary after cordocentesis or intrauterine transfusion, but tocolytics are used at most centers for more invasive percutaneous procedures (e.g. shunt catheter placement, endoscopic techniques). With open fetal procedures, early postoperative uterine contractions are expected and tocolysis is provided by a continuous infusion of magnesium sulfate for approximately 24 h. This is supplemented with indomethacin and occasionally with terbutaline or nifedipine as indicated.

Postoperative analgesia can be provided for several days by continuous epidural analgesia or by intravenous opioids by

PCA. Effective analgesia may help prevent preterm labor by decreasing plasma oxytocin levels [218]. Other postoperative concerns include preterm labor, PPROM, infection, and fetal complications that include heart failure, intracranial hemorrhage, chorioamnionitis, indomethacin-induced constriction of the ductus arteriosus, and fetal demise. Uterine activity and FHR are monitored closely during the first few postoperative days. The fetus is typically evaluated daily by ultrasonography and echocardiography looking for ductal narrowing, cardiac valvular function, and oligohydramnios. In rare cases MRI is used to determine the presence of fetal intracranial hemorrhage.

KEY POINTS: PERIOPERATIVE AND PROCEDURAL CONSIDERATIONS

- Thorough preoperative assessment and multidisciplinary planning is necessary for all fetal interventions
- Anesthetic techniques vary from local anesthesia with or without sedation to neuraxial anesthesia to general anesthesia to a combination of these techniques.
- Profound uterine relaxation is necessary for open procedures

Future of fetal therapy and surgery

The future of fetal diagnosis and therapy is bright and provides many opportunities for advances that benefit the fetus and perhaps adults with diseases that originate during fetal development. In the future, prenatal fetal stem cell and gene therapy hold promise for possible treatment of hemophilia disorders, cystic fibrosis, and muscular dystrophy [219].

In the future it is likely that the majority of fetal surgical interventions will be performed percutaneously, using imaging or endoscopic guidance. Although use of minimally invasive techniques will simplify anesthetic management, many issues remain unresolved because research in this area is difficult. The potential neurotoxicity of anesthetic agents in the fetal and neonatal brain, impact of surgical stress on the fetus and/or later in life, prevention of preterm labor, standards of intraoperative fetal monitoring, and optimal anesthetic techniques are among the many issues that require further evaluation. Future advances in fetal therapy and surgery require careful consideration of potential fetal benefit and fetal risk and, most importantly, maternal risk. Maternal safety remains a paramount concern for the anesthesiologist.

CASE STUDY

An ultrasound diagnosis of a large (>6 cm) fetal neck mass, consistent with a cervical teratoma, was made in 25-year-old, gravida 1 woman at 32 weeks' gestation. The mother was otherwise healthy, and no other anatomical abnormality was detected in the fetus. The ultrasound images and patient's history were discussed at the weekly multidisciplinary fetal treatment conference, and it was decided to re-evaluate the fetus in 2 weeks. The planned delivery strategy was by EXIT procedure at 38 weeks' gestation after confirming fetal lung maturity by amniocentesis. Concern was expressed that it would not be possible to intubate the trachea by direct laryngoscopy during the EXIT procedure, given the massive size of the lesion. No significant changes occurred in the mother during the ensuing 2 weeks, and she was admitted at 38 weeks' gestation for amniocentesis. The EXIT procedure was scheduled for the following morning. All team members were notified and their availability confirmed by the perinatologists who performed amniocentesis for fetal lung maturity.

Before entering the operating room, all team members participated in a pre-procedure conference to ensure the availability and readiness of all necessary equipment and personnel, and to discuss the surgical plan, issues specific to the case, and potential complications that might arise. In preparation for the procedure, the anesthesiologists checked maternal and fetal drugs and their doses, and ensured a manometer, sterile manual ventilation system, and separate source of oxygen supply were available for ventilating the fetal lungs once an airway was established. The anesthesiologists had a second pulse oximeter and sterile probe for fetal monitoring. They also prepared a combination of paralytic agent and opioid to administer to the fetus and transferred the sterile drugs in one labeled syringe to the scrub nurse. Similarly, with an estimated fetal weight of 3 kg, two doses of atropine 60 μg each, two doses of epinephrine 30 μg each, and two doses of epinephrine 3 μg each were prepared in labeled syringes for emergent administration to the fetus, if needed. The scrub nurse ensured the appropriate surgical equipment was available, as well as sterile laryngoscopes, bronchoscopes, a Jackson Rees non-rebreathing circuit, endotracheal tubes, cables and sensors for pulse oximetry, including transparent adhesive medical dressing to secure the oximeter and an opaque cover to shield the oximeter sensor from the surgical lights.

The mother was premedicated with 30 mL of sodium citrate before entering the operating room. A preinduction "time-out" was completed, and a high lumbar epidural catheter was placed for postoperative pain control. She was then positioned supine and left uterine displacement was initiated to prevent aortocaval compression by the gravid uterus; 100% oxygen was administered by tight-fitting facemask while pulse oximeter, arterial blood pressure cuff, and electrocardiogram leads were applied. The fetus was evaluated by ultrasonography and was noted to be in a cephalic presentation; the fetal heart rate was 130 beats per minute with appropriate variability. After denitrogenation of the mother's lungs and application of cricoid pressure, rapid-sequence induction of anesthesia was performed with propofol and succinylcholine and the trachea was rapidly intubated. Once tracheal intubation was confirmed by auscultation and by normal-appearing carbon dioxide end-tidal waveform tracings, sevoflurane was

administered. A urinary catheter and a second large-bore intravenous catheter were placed. Prophylactic antibiotics were administered, and her abdomen was prepped and draped. The fetal surgeon, perinatologist, and neonatologist positioned themselves around the surgical table and the equipment was readied. The neonatologist passed the oxygen supply line to the fetal breathing circuit and an additional catheter for connection to the manometer over the drape to the anesthesiologist. Together they ensured the integrity and dynamics of the circuit, with a pop-off valve set for 15 cm water pressure to avoid iatrogenic pneumothorax when fetal ventilation was initiated. The pulse oximeter cable was passed over the drape and connected to the second oximeter. The sensor was tested to ensure all connections were intact.

Following a Pfannenstiel incision, the sevoflurane concentration was increased and was 1.9 MAC at the time of the hysterotomy. No vasopressor support was required to maintain the mean arterial pressures above 65 mmHg (maternal baseline). The uterus was visualized and palpated to assess tone. Since it was not sufficiently relaxed, the inspired concentration of sevoflurane was increased. The ultrasonographer determined the location of the placenta so the surgeons could avoid it during hysterotomy. After 5 min, the end-tidal sevoflurane concentration was 2.6 MAC, the mother's vital signs were stable, the fetal heart rate was 130 beats/min, and the uterus was appropriately relaxed. A purse string suture was placed in the uterine wall and an incision was made that was just large enough to insert a uterine stapler to divide the myometrium and membranes and to apply absorbable staples to seal the edges of the hysterotomy and provide hemostasis. Given the somewhat anterior location of the placenta, the hysterotomy was performed near the uterine fundus using the "classical" uterine incision, which will require all future babies to be delivered by cesarean section without a trial of labor.

Once the uterus was opened, a mixture of 30 μg fentanyl and 7.5 mg rocuronium was administered into the fetus' left triceps muscle. The fetal head and upper thorax were delivered, and the pulse oximeter was placed across the fetus' left palm, secured with a transparent adhesive dressing, and covered with an opaque dressing to shield the sensor from the surgical lights. The pediatric surgeon, neonatologist, and anesthesiologist were unable to visualize airway structures by laryngoscopy and bronchoscopy (Fig. 21.15). Initially, a decision was made to perform a tracheostomy, but this was considered unwise given the enormity of the neck lesion. Instead, during the next 2 h the teratoma was excised while the fetus was maintained on placental support and monitored by pulse oximetry. Peripheral venous access was obtained in the left arm (Fig. 21.16). After the teratoma was resected, it was necessary to perform a tracheostomy. After the airway was secured, positive pressure ventilation was initiated with peak pressures of 15 cmH_2O and a positive end-expiratory pressure of 4 cmH_2O. The fetal oxygen saturation rapidly increased, and when it exceeded 90% the umbilical cord was clamped and cut and the newborn was delivered to the awaiting neonatal resuscitation team for further care. Blood gases from a doubly clamped segment of the umbilical cord were normal and showed no evidence of acidosis.

After cord clamping, sevoflurane was discontinued, an infusion of oxytocin was started, intravenous fentanyl (150 μg) was administered, and a propofol infusion (125 μg/kg/min) was initiated. A test dose was administered through the epidural catheter. Following the negative test dose, epidural bupivacaine (0.125%) with 2 μg/ml fentanyl was administered. Following closure of the uterus and abdomen, the patient awakened, was extubated, and had no significant pain. She received 2 L of crystalloid, no colloid or blood, and had 200 mL of urine output and an estimated blood loss of 650 mL. Over the first 36 postoperative hours, analgesia was provided with epidural analgesia.

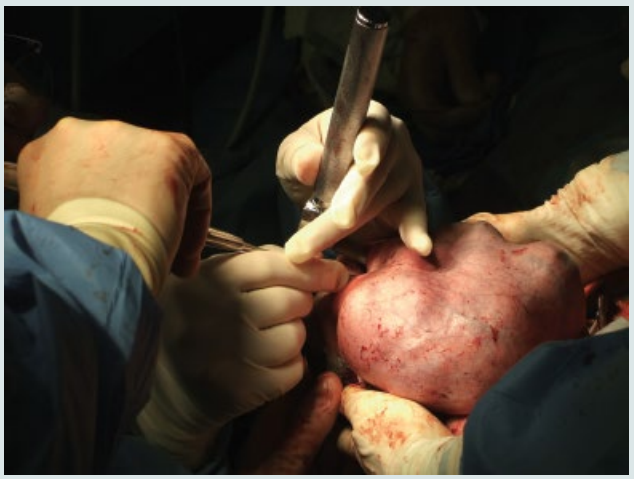


Figure 21.15 Laryngoscopy-assisted bronchoscopy of a fetus with a large neck mass during the EXIT procedure. *Source*: Photo courtesy of UCSF Fetal Treatment Center.

Figure 21.16 Preparation of fetus for neck mass resection. The fetus is maintained on placental support with pulse oximetry monitoring (right hand) and peripheral venous access (left arm). *Source*: Photo courtesy of UCSF Fetal Treatment Center.

The mother did well without any perioperative complications. The pathology confirmed a teratoma, and the neonate had an excellent outcome.

KEY POINTS

- Most fetal malformations diagnosed *in utero* are not appropriate for fetal intervention
- Detailed anatomical information regarding airway mass and placental position is needed for appropriate patient selection and optimal outcome
- Thorough preparation and planning for unanticipated emergent events (e.g. fetal bradycardia, maternal hemorrhage) is critical for a successful outcome
- Maternal safety is a primary consideration and maternal risks must be weighed against potential fetal benefit
- Successful fetal procedures require a multidisciplinary team effort in which detailed preoperative planning and discussion among all team members is crucial
- Preterm PROM and preterm labor remain significant obstacles to ideal outcomes from fetal surgery

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 22
Anesthesia for Premature Infants

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Introduction

Preoperative evaluation of premature neonates is the most important part of anesthesia. During this time the anesthetist determines what abnormalities are present, gathers information from the intensive care nursery (ICN) team, and makes plans to care for the infant during the perioperative period. This chapter provides information about premature infants, preoperative evaluation, and provision of anesthesia. This information is the basis for understanding the physiology and pathophysiology of preterm neonates, which is necessary for effective evaluation of these patients for surgery and for providing appropriate care for them.

Background

About 10% of infants are born prematurely, i.e. <37 weeks' gestation [1]. The more immature they are at birth, the more likely they are to die during the neonatal period and to have serious complications, especially neurological complications. Great strides have been made in reducing the mortality rate, even in very small infants. It is now expected that at least 60–70% of infants weighing <750 g at birth will survive [2]. With this increased survival has come a host of complications that often require surgery, including patent ductus arteriosus (PDA), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH) with hydrocephalus, and inguinal hernias, to name a few.

Most body organs undergo continuous structural and functional development during the last 3 months of gestation. Infants born prematurely have inadequately developed organs that are required to perform functions that may be beyond their capacity. Consequently, preterm infants are less able to maintain their body temperature, suck, swallow, eat, and sustain breathing. Many of them experience asphyxia at or just before birth, predisposing them to central nervous system injury, IVH, NEC, myocardial dysfunction, and the respiratory distress syndrome (RDS).

Preterm infants can be divided into three groups: borderline premature (34–37 weeks' gestation); moderately premature (32–33 weeks' gestation); and severely premature ("micropremies," 28–31 weeks' gestation). The problems of each group increase in number and severity with decreasing gestational age [3].

Late preterm

Seven percent of all livebirths and 71% of preterm births are late preterm infants (34^0–$36^{6/7}$ weeks' gestation) and can often be cared for in the normal neonatal nursery [1]. However, they do require close observation for the first 12 h of life, because, as a group, they have more difficulty maintaining their body temperature without added external heat, and they may not suck and feed well. Those born at 34 weeks' gestation require neonatal intensive care unit (NICU) admission 50% of the time for maintenance of body temperature, cardiorespiratory monitoring, and management of complications of prematurity (RDS, transient tachypnea of the newborn (TTN), and apnea). If feeding is a problem, gavage feeding may be required for a few days, and these infants may be slow to regain their birthweight, especially if they have RDS. Eight percent of borderline premature infants born by cesarean section have RDS versus 1% of those born vaginally, probably because vaginal birth more effectively removes water from the lungs [4,5].

Because they are predisposed to respiratory distress, the respiratory system of near-term infants must be carefully evaluated during the preoperative visit. Intercostal

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

retractions, tachypnea, grunting respirations, and cyanosis suggest RDS but also may be signs of meconium aspiration, pneumothorax, or pneumonia in these large preterm infants. Temperature instability and hyperbilirubinemia suggest sepsis but are usually just manifestations of prematurity.

Moderate prematurity

Moderately premature infants (32–33 weeks' gestation) account for about 1.2% of all births [1]. The neonatal mortality of infants born at 32 weeks' gestation is below 5%, whereas it is nearly zero at 36 weeks' gestation when there are no congenital anomalies. The major causes of death are intracranial hemorrhage, sepsis, and RDS. As in late preterm infants, the incidence of RDS, TTN, pneumonia, and pulmonary hypertension is higher in moderate prematurity. Apnea of prematurity is significantly increased in this group due to brainstem immaturity and to greater compliance of the upper airway and chest wall that leads them to collapse more easily on inspiration. As a result, maldistribution of ventilation and perfusion are common. Hypoglycemia and jaundice are more common than in larger neonates.

Very and extremely premature infants (micropremies)

Infants of 28–31 weeks' gestation are very preterm, and those less than 28 weeks' gestation are extremely premature infants. Infants of 24–31 weeks' gestation make up about 1.6% of all liveborn infants [1]. However, they account for more than 70% of neonatal mortality. They also account for a major portion of neurologically damaged children later in life. The causes of death include birth asphyxia, acidosis, and respiratory failure (congestive heart failure, PDA, RDS, infections, especially β-streptococcus and listeria), NEC, and intracranial hemorrhage. All the problems of prematurity are exaggerated in these very immature infants who really are fetuses living outside the womb. Studies are underway to develop an artificial womb that may reduce some of these problems.

About one of 200 term infants, one of 20 moderately premature infants, and one of two infants weighing less than 1 kg at birth suffers birth asphyxia. Preterm fetuses are more prone to asphyxia than term fetuses because the preterm infant's blood oxygen content is lower (due to lower hemoglobin concentrations) than that of term infants. Slight degrees of stress lead to anaerobic metabolism and metabolic acidosis, which in turn reduce cardiac output and increase cerebral blood flow. The latter may damage the central nervous system (CNS) if it causes the fragile vessels of the periventricular areas of the brain to bleed [6,7]. Causes of asphyxia include antepartum hemorrhage, intrauterine infections, breech delivery, and RDS. Treatment of birth asphyxia has been described elsewhere [8].

Most extremely premature infants are asphyxiated at birth and often require tracheal intubation and assisted ventilation or nasal continuous positive pressure breathing (nCPAP) as part of delivery room resuscitation. It has been hoped that early application of nCPAP will avoid some of the complications of tracheal intubation and mechanical ventilation, although this is unproven [9]. However, early nCPAP does reduce the number of infants who require mechanical ventilation by approximately 50% [10] and does reduce bronchopulmonary dysplasia and death on meta-analysis [11]. Because these infants frequently have both metabolic and respiratory acidosis, they often require mechanical ventilation, blood volume expansion, and, if necessary, a slow, cautious infusion of enough sodium bicarbonate or tris(hydroxymethyl)aminomethane (THAM) to correct their pH to 7.3.

Ventilation should be controlled during sodium bicarbonate infusion, which should never be infused more rapidly than 1 mEq/kg/min. Rapid infusion of bicarbonate may quickly expand the intravascular volume, raise the arterial blood pressure, and increase the $PaCO_2$, all of which can cause intracranial hemorrhage in premature neonates. Fifty mL of sodium bicarbonate (50 meq) produces 1250 mL of CO_2 when the bicarbonate is fully reacted with hydrogen ions. This is of little consequence if the lungs are normal and can easily excrete the additional CO_2. If the lungs are abnormal, the $PaCO_2$ may rise rapidly and cause IVH or cardiac arrest. Artificial ventilation to increase CO_2 removal can prevent these complications. What is considered an "adequate" $PaCO_2$ has changed over the years. Many preterm neonates now undergo "permissive hypercapnia" with $PaCO_2$ as high as 70 mmHg if the pH is 7.2 or above [12]. However, data supporting the use of hypercapnia are lacking. Allowing hypercapnia has not reduced the incidence of chronic lung disease [13]. Compensation for the hypercapnia includes bicarbonate retention and a positive base excess. In this situation, if the $PaCO_2$ is reduced to normal, the attendant alkalosis decreases cerebral blood flow and may also decrease the ionized calcium concentration, myocardial function, and arterial blood pressure.

In the past, hypoglycemia was partly responsible for the increased incidence of CNS damage in small preterm infants [14]. Fortunately, hypoglycemia is less common today because blood glucose concentrations are maintained between 50 and 90 mg/dL, not 20–40 mg/dL as in the past. Hyperglycemia is also to be avoided because fewer hyperglycemic patients can be resuscitated from a cardiac arrest, and those who are resuscitated have more CNS damage [15]. Hyperglycemia also causes an osmotic diuresis and can cause hypovolemia. Unlike older patients, premature infants spill glucose in their urine with blood sugar concentrations as low as 125 mg/dL.

KEY POINTS: INTRODUCTION AND BACKGROUND: THE PREMATURE INFANT

- Ten percent of infants are born prematurely, i.e. before 37 completed weeks of gestation
- Seven percent of infants are late preterm, born at 34–36 weeks' gestational age
- Some 1.2% of infants are moderately preterm, born at 32–33 weeks' gestational age
- Very preterm (28–31 weeks' gestation) and extremely preterm (less than 28 weeks) comprise about 1.6% of livebirths, but more than 70% of neonatal mortality

Common problems associated with prematurity

The following are some problems associated with prematurity. While they are covered more fully in other chapters, they are presented here to give an overview of the problems and to provide a means of organizing one's thoughts when planning anesthesia for a preterm infant.

In general, anesthesia for premature infants is fraught with problems because they often have multisystem disease and respond poorly to anesthesia. To reduce the risk, it is important to garner as much information preoperatively as possible. A common mistake, especially among novice anesthetists, is to ignore the fact that those caring for the infant in the NICU have considered the patient's problems over an extended period of time and have come to a plan of therapy based on an understanding of these problems. It is neither appropriate nor sensible to alter this plan, unless there is an urgent reason to do so, without thorough discussions with the neonatologists.

Temperature regulation

Hypothermia, or even a short exposure to a cold environment, increases the metabolic rate and oxygen consumption of preterm infants, which can cause hypoxemia, acidosis, apnea, or respiratory distress and is a risk factor for infant mortality [16]. The minimal oxygen consumption of preterm infants is 4.3–5.4 mL/kg/min on day 1 and 8–9 mL/kg/min by 2 weeks of age [17]. As the oxygen consumption increases, so do the ventilation and caloric requirements. Body heat is dissipated by conduction, convection, radiation, and evaporation. During mechanical ventilation, heat and liquid are lost from the lungs, especially when dry gases are used in the operating room. This heat loss can be avoided by using warmed, humidified gases. The surface/volume ratio of preterm infants is high, and their flaccid, open posture tends to increase heat loss rather than conserve it. The preterm neonate's lack of insulating fat allows more heat loss from the core to the surface.

Evaporative heat loss accounts for approximately 25% of the heat lost in term neonates and adults. Brück [18] showed that preterm neonates can vasoconstrict and increase heat production when exposed to cold, but they still lose heat because they lack insulation and their overall heat production is lower. The rise in metabolic rate in preterm neonates is approximately linear between 28° and 36°C [17]. Extremely low birthweight neonates do not have subcutaneous fat nor do they peripherally vasoconstrict appropriately, which is a problem in cold operating rooms [19].

Young infants become agitated and move more in response to cold. Serum norepinephrine concentrations increase, which stimulates brown fat metabolism and heat production. The increased heat produced warms the CNS and vital organs [20]. Primitive brown fat cells begin to differentiate from reticular cells at 26–30 weeks' gestation [21] and increase in size and number for 3–6 weeks after birth. Infants born before the cells fully develop have more difficulty maintaining their body temperature when exposed to cold environments, as do hypoglycemic infants and those with CNS damage.

Because small premature infants lose heat and water through their thin, transparent skin, they easily become dehydrated, especially when cared for under a radiant warmer and are fluid restricted. Covering the premature infant's body with clear plastic film, and the head with a cap, significantly reduces both heat and water loss, as does warming and fully humidifying the inspired gases to 34–37°C [22,23]. The addition of forced air warming systems, circulating water blankets, and room temperature of 30°C provides maximal efficiency in reducing dry heat loss [24].

The clinical consequences of chilling include periodic breathing or apnea, bradycardia, metabolic acidosis, hyperglycemia, and aspiration of gastric contents. Fewer infants nursed in non-neutral thermal environments survive [25]. Those who survive gain weight more slowly. Maternal anesthesia (general) and neonatal fentanyl analgesia cause hypothermia in some infants, while morphine or conduction anesthesia do not [26].

Respiratory manifestations

Respiratory distress

Respiratory distress is common in preterm infants. It occurs three times more often after cesarean section than after a vaginal birth. The less mature the infant, the more severe the disease tends to be, although some very immature infants escape this affliction, especially if given surfactant shortly after birth or if there was chorioamnionitis [27]. Survival of preterm infants depends on their size and gestational age. Moderately premature babies (1500–2500 g) with RDS require more support of ventilation and fewer of them survive than their larger counterparts. Despite their small size, more than 95% of the former should survive. Eighty-five percent of those weighing less than 1000 g and about 80% of those weighing less than 750 g now survive. Administration of exogenous pulmonary surfactant at birth has increased survival and decreased serious complications [28,29]. This rapidly improves lung function, which can lead to pulmonary gas leaks and lung injury if ventilation pressures are not decreased appropriately. The increased lung compliance improves oxygenation, which increases the likelihood of both ROP (see section "Retinopathy of prematurity") and inflammatory lung damage. Thus the FiO_2 must also be rapidly reduced to acceptable levels (SaO_2 of 87–94%).

In addition to surfactant administration, in recent years ventilation strategies have changed in premature infants with RDS in an attempt to reduce the incidence and severity of bronchopulmonary dysplasia (BPD – see section "Bronchopulmonary dysplasia"). Targeting lower SpO_2 of 87–94% instead of 95–98%, employing nCPAP instead of endotracheal intubation, and limiting positive pressure ventilation by allowing permissive hypercapnia have all been shown to reduce the severity of RDS and the incidence of BPD. In contrast, high-frequency oscillatory ventilation does not improve RDS or reduce incidence of BPD. Routine treatment with dexamethasone resulted in a lower severity of lung disease and less BPD; however, it is associated with increased risk of intestinal perforation, cerebral palsy, and neurodevelopmental impairment so its use has greatly diminished in recent years [30]. Finally, inhaled nitric oxide in infants less than 1250 g, when administered for 14 days, resulted in significantly greater BPD-free survival in one large multicenter study, and did not adversely affect long-term neurodevelopmental outcomes [31].

Bronchopulmonary dysplasia

Many preterm infants develop chronic lung disease (BPD) as a result of mechanical ventilation, oxygen administration, infection, inflammation, or a combination of these factors [32]. The number of infants with BPD is increasing because more 500–750 g infants now survive [33,34]. Today's BPD differs from that described by Northway et al [35]. Many of today's preterm infants have no oxygen requirement above that of room air and normal lung function for a few days after birth, probably because of prenatal steroids and/or the administration of surface-active material after birth. Lung function then deteriorates, often in association with pulmonary infections [36], the oxygen requirements increase, and respiratory failure develops. The deterioration is made worse if the child has a PDA [36]. Furthermore, the chronic lung disease (CLD) of today's smaller infants has changed [37]. Today's CLD consists of simplified lungs, increased alveolar size, decreased alveolar number, and dysplastic pulmonary vasculature [38,39]. The end-result of these lung abnormalities is maldistribution of ventilation and perfusion, hypercarbia, hypoxemia, and occasionally the need for prolonged mechanical ventilation. Later in life, if these infants require surgery, their lung function [40] and gas transfer will be reduced [41]. Positive end-expiratory pressure (PEEP) and furosemide 0.5–1 mg/kg every 6–12 h are frequently used to treat pulmonary edema and improve gas exchange. However, furosemide often causes metabolic alkalosis, especially if these babies are not given sufficient potassium and chloride. CO_2 is retained to compensate for the alkalosis. Reducing the $PaCO_2$ may cause severe alkalosis, reduced arterial blood pressure, and reduced cerebral blood flow (Fig. 22.1). Some preterm infants require higher ventilator pressures (tidal volumes) and oxygen concentrations during surgery, but many have improved ventilation and reduced oxygen requirements. During surgery, many infants can be ventilated with room air to maintain appropriate oxygen saturations. Although an oxygen saturation of 87–94% is considered (hoped) to be safe, the infant's PaO_2 would be 30–40 mmHg were they still *in utero*.

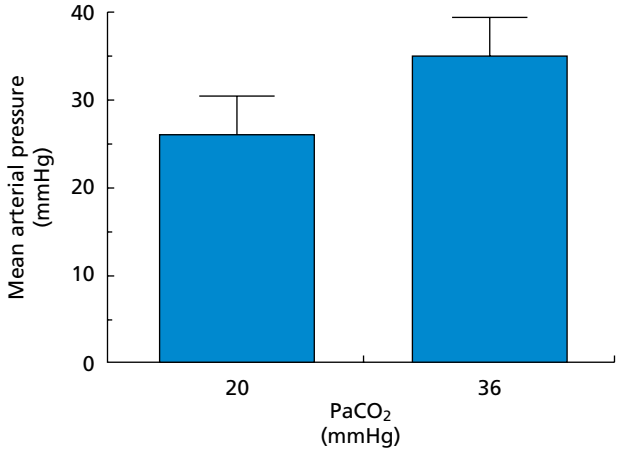

Figure 22.1 The effects of alkalosis on mean arterial pressure in premature infants. Ventilation was maintained constant and CO_2 was added to raise the $PaCO_2$ to normal.

Apnea

Periodic breathing (cessation of breathing for <15 s) and apnea (cessation of breathing for >20 s or <20 s with a decrease in SaO_2 plus bradycardia) are common in preterm infants, especially after the first week of life [42]. The incidence of apnea is inversely related to postconceptual age [43]. Apnea occurs in <2% of preterm infants after they reach 40 weeks of gestation [44]. The causes of apnea are multiple and include anemia (hematocrit <30%), hypo- and hyperthermia, hypo- and hyperglycemia, hypo- and hypercalcemia, hypo- and hypervolemia, decreased functional residual capacity, PDA, constipation, hypothyroidism, poorly developed control of respiration, excessive handling and stimulation, birth trauma, maternal drugs (narcotics), seizures, infections, and congenital heart disease. However, the primary cause of apnea of prematurity is immaturity of the CNS. Repeated apnea increases the likelihood of CNS damage due to repeated episodes of hypoxemia [45]. Infants who had apneic spells in the ICN usually must be ventilated from the time anesthesia is induced. Giving caffeine 5 or 10 mg/kg IV before surgery reduces or prevents postoperative apnea and oxygen desaturation, especially in patients who have had previous apneic spells, a hemoglobin concentration below 10 g/dL, or pre-existing CNS injury [46].

Moderately premature infants, especially those recovering from RDS and those requiring mechanical ventilation, may have chronic lung disease. If they do, the $PaCO_2$ is frequently elevated and the PaO_2 or SaO_2 decreased during room air breathing. (Alveolar oxygen decreases 1 mmHg for each 1 mmHg increase in CO_2.) Overexpansion of the lungs of premature infants should be avoided, as this may injure their lungs [47,48].

Patent ductus arteriosus

Fifty percent of full-term infants close their ductus arteriosus by 24 h of age and almost all of them do so after 72 h [49]. Most preterm infants of 30 weeks' gestation or more close their ductus arteriosus by 96 h of age. However, the ductus arteriosus of 70–80% of smaller preterm infants frequently remains open [50,51] and symptoms of a PDA often appear between the third and fifth day after birth [52]. Infants treated with surfactant at or near birth may have a significant PDA within a few hours of birth as the lungs expand and pulmonary vascular resistance decreases. A PDA murmur is usually heard at the left upper sternal border and is often continuous. It is loudest during exhalation or apnea, and its intensity is increased by hyperventilation. Patients with a PDA have bounding pulses and a widened pulse pressure (Fig. 22.2).

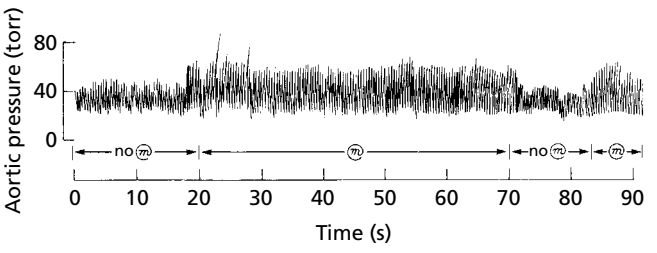

Figure 22.2 Aortic blood pressure of a preterm infant during periods when a patent ductus arteriosus was present and was absent. Note the widening of the pulse pressure and elevated arterial pressure when the murmur was present. *Source*: Courtesy of Dr Joseph A. Kitterman.

A gallop rhythm may be present. Up to 70% of extremely low birthweight infants receive some therapy (drugs, surgery) for their PDA.

As the left-to-right shunt increases, so does the pulmonary blood flow. If the heart cannot keep up with the increased demand for cardiac output, congestive heart failure (CHF), manifested by increased respiratory failure (intercostal retractions, diminished breath sounds, poor air entry, rales), tachycardia, and a gallop rhythm develop. The PaO_2 decreases and the $PaCO_2$ rises. Apnea, increasing requirements for oxygen and mechanical ventilation, and a widened pulse pressure are often the earliest signs of a PDA. Signs of heart failure often appear before a murmur is heard [53] and if the ductus arteriosus is very large, no murmur is heard. In this case, a PDA is usually detected by changes in oxygenation, increased need for mechanical ventilation, and an echocardiogram.

The initial treatment of a PDA is medical, which includes fluid restriction [54,55] (occasionally to the point of dehydration) and administration of cyclo-oxygenase inhibitors, indomethacin and ibuprofen [56,57], and diuretics. Indomethacin has greatly reduced the number of patients requiring surgical closure of a ductus arteriosus, but it has not reduced the incidence of CLD or CNS injury [58].

If fluid restriction prevents adequate calorie intake, surgical ligation of the ductus arteriosus is usually undertaken. Early closure of the ductus arteriosus (either with indomethacin or surgically) allows earlier weaning from mechanical ventilation and initiation of feeding within a few days after surgery. Several studies have demonstrated increased incidence of death and CNS injury in preterm infants who have undergone ligation of a PDA [59–61]. However, these studies failed to account for confounding problems present before surgery. After accounting for these factors, Weisz et al found no evidence of increased morbidity, CNS injury, CLD, or ROP in children who underwent ductus ligation [62].

A second reason to close a patent PDA early is to reduce the incidence of NEC [63]. With large PDA shunts, as much as 80% of the cardiac output is shunted away from the systemic circulation and into the lungs, leaving little blood for the remaining body. Because the gut of neonates is one of the first organs to be deprived of blood during periods of low systemic blood flow, it is the shock organ in neonates. The use of prostaglandin synthetase inhibitors has not decreased the incidence of NEC, but early ligation of the PDA may do so. Early detection and treatment of a PDA was associated with reduced in-hospital mortality and pulmonary hemorrhage. There were no differences in NEC, BPD, or CNS lesions [64].

Central nervous system injury

Premature infants have two predominant forms of CNS injury. The most common in very premature infants is periventricular white matter injury, which is a leading cause of later cerebral palsy. The pathophysiology is incompletely understood, but the immature oligodendrocyte precursors are exquisitely sensitive to a number of common insults, including hypoxemia, hypotension, and inflammation [30]. The arterial supply to these areas is not fully developed, leading to vulnerability to ischemia. In addition, because of the fragile state of the developing vascular supply in the germinal matrix, these vessels are prone to rupture, causing the common complication of IVH. Grade I IVH is confined to the germinal matrix, grade II IVH occurs when bleeding extends to the cerebral ventricles, grade III IVH involves ventricular dilation, and grade IV IVH includes parenchymal extension of the bleed. Grades III and IV IVH may lead to hydrocephalus requiring ventriculoperitoneal shunting, a common procedure in premature neonates. Chapters 8 and 25 discuss pathogenesis and treatment of these disorders in more detail. Recent data suggest that the type of injury has changed from cystic lesions to impaired cerebral growth of neurons and glia, not cell death [65].

Infection

Infections (e.g. pneumonia, sepsis, and meningitis) are common in preterm infants, especially those who are moderately or severely preterm, because both their cellular and tissue immunity are reduced. Although the signs of sepsis are often subtle, sepsis is suspected if the infant is hypo- or hyperthermic (despite a neutral thermal environment), lethargic, mottled, gray, or apneic. If, despite a constant infusion of glucose, the serum glucose concentration increases, sepsis should be suspected. Laboratory examinations may be helpful but preterm infants are often septic without positive blood cultures, elevated white blood cell (WBC) counts, or fevers. In fact, this is more often true than not. The presence of an abnormal WBC count, whether increased or decreased, is diagnostically helpful (Table 22.1). A shift to the left toward neutrophil predominance is also helpful, but this is not always present. Band counts in excess of 15% are abnormal and are a good indicator of infection in preterm infants [66]. Cerebrospinal fluid (CSF) should contain fewer than one WBC per 200 red blood cells (RBCs), although an absolute count of 70 WBC/mm^3 may be normal [67]. The concentration of glucose in the CSF should be at least 50–60% of that in the blood. Urine should contain fewer than five WBCs per high-power field. A bladder tap urine specimen should be devoid of WBCs.

Preterm infants respond appropriately to antibiotics, although the dosage and interval between doses often must be altered (see Appendix A). Aminoglycosides may cause muscle weakness or paralysis and act synergistically with non-depolarizing muscle relaxants to increase their effect. The hearing loss may be worse if the baby is simultaneously exposed to loud noise (as occurs in a busy ICN) [68].

Necrotizing enterocolitis

NEC is a common surgical emergency, especially in tiny preterm infants [63,69]; 20–50% of patients with this problem die [70–72]. The onset of NEC is usually between 27 and 34 weeks' gestation [73], but it can occur in term infants. The most common associations with NEC are prematurity, feeding per os, excessive feeding, and overgrowth of the bowel with non-normal bacterial flora [74,75]. There may also be genetic factors at work [76]. An infant who suddenly develops abdominal distension, vomiting, bloody stools, reducing substances in the stool, and shock should be suspected of having NEC. Shock occurs because large amounts of fluid are translocated into the peritoneal cavity, gut, and other tissues and because of bacterial toxins. Radiographs of the abdomen demonstrate distended loops of bowel, air in the bowel wall and, if the

Table 22.1 White blood cell count and differential count during the first 2 weeks of life

Age	Leukocytes	Neutrophils					Lymphocytes	Monocytes
		Total	Segs	Bands	Eosinophils	Basophils		
Birth								
Mean	18,100	11,000	9400	1600	400	100	5500	1050
Range	9.0–30.0	6.0–26	–	–	20–850	0–640	2.0–11.0	0.4–3.1
Mean %	–	61	52	9	2.2	0.6	31	5.8
7 days								
Mean	12,200	5500	4700	830	500	50	5000	1100
Range	5.0–21.0	1.5–10.0	–	–	70–1,100	0–250	2.0–17.0	0.3–2.7
Mean %	–	45	39	6	4.1	0.4	41	9.1
14 days								
Mean	11,400	4500	3900	630	350	50	5500	1000
Range	5.0–20.0	1.0–9.5	–	–	70–1,000	0–230	2.0–17.0	0.2–2.4
Mean %	–	40	34	5.5	3.1	0.4	48	8.8

Segs, segmented cells.
Source: Reproduced from Avery's Diseases of the Newborn, 6th ed. Philadelphia: Elsevier-Saunders, 2000, with permission of Elsevier.

bowel has perforated (which occurs about one-third of the time), free air in the peritoneal cavity. Such infants are extremely ill (often moribund), hypovolemic, and require fluid resuscitation with blood, colloid, fresh-frozen plasma, platelets, and large volumes of saline or lactated Ringer's solution prior to surgery if they are to survive (sepsis and bleeding are common problems). The volume of fluid required for resuscitation is often enormous. Administering the quantity of fluid needed to accomplish volume resuscitation often worsens any respiratory failure present and increases the need for mechanical ventilation. Infants with NEC should be started on IV broad-spectrum antibiotics preoperatively. Most survive, although about 10% of those who survive have short gut syndrome [77]. Many infants with NEC have cerebral palsy, severe neurological delay, and mental retardation, which may complicate anesthesia later in life [78]. Their treatment with aminoglycosides may cause hearing defects [68].

Hematological manifestations

Preterm infants are frequently anemic because their ability to produce RBCs is reduced and because their caregivers frequently take blood for tests. Compensatory responses include tachycardia, increased cardiac output, and increased extraction of oxygen from blood. If the oxygen demand is unmet, lactic acidosis occurs. Low iron stores and inadequate iron intake worsen the anemia. The amount of transfusion can be reduced by delayed cord clamping at birth, milking (stripping the cord), and drawing all NICU baseline blood studies from the placenta [79]. This may be important because NEC occurs more commonly in very low birthweight infants if they are transfused, as does IVH when they are transfused early [80]. As long as preterm infants have respiratory or cardiovascular problems, their hemoglobin levels should probably be maintained at or above 10 g/dL by blood transfusions from a limited number of units of packed RBCs and by the administration of epoetin alfa. A hemoglobin concentration of 14–15 g/dL is more likely to reduce the number of apneic spells and the CHF associated with a PDA than a hemoglobin of 8–10 g/dL. One study found that limiting transfusion was associated with higher rates of CNS hemorrhage, periventricular leukomalacia, and apnea [81] but another study failed to find these problems [82]. It is probably unwise to begin surgery for preterm infants if their hemoglobin concentration is <10 g/dL unless forced to do so by an absolute emergency. Transfusion of blood with adult hemoglobin, besides raising the hematocrit, shifts the oxygen dissociation curve to the right, which improves oxygen delivery to the tissues.

The WBC count of normal preterm infants is shown in Table 22.1. At birth, the WBC is higher than at later ages; it decreases over the first week of life. Stress can elevate the WBC count to 40,000–50,000/mm^3. Septic neonates either increase or decrease their WBC.

Erythropoietin (EPO) is produced in the kidney and regulates erythropoiesis. Growing fetuses have high levels of erythropoiesis, a relatively high hematocrit, and predominant synthesis of hemoglobin F (fetal hemoglobin). The high concentrations of EPO present at birth decline relatively rapidly. The concentration of hemoglobin decreases over time and causes many preterm infants to be anemic. Phibbs et al [83] showed that giving 100 μg/kg of recombinant human erythropoietin intravenously to anemic preterm infants twice weekly for 6 weeks increased the reticulocyte counts (and RBCs) faster than a placebo and did not suppress subsequent release of endogenous EPO. The need for blood transfusions was reduced.

On rare occasions, premature infants are polycythemic. If the hematocrit exceeds 65%, an exchange transfusion may be required before surgery to prevent occlusion of their renal, portal, or cerebral veins, especially if the patient becomes hypovolemic and/or hypotensive during surgery. If it is necessary to operate on a polycythemic child, sufficient fluid must be administered during surgery to maintain a normal or slightly increased intravascular volume. Hypotension must be treated immediately.

Nutrition and growth

Premature infants frequently have difficulty sucking effectively for some time after birth and require intermittent or continuous gavage feedings. While their gastric capacity and gastrointestinal motility are adequate to accept the

instilled food, they often have difficulty absorbing their feeds. As a result, intravenous fluids and nutrition are commonly required. Infants who will not be fed orally for 3 or 4 days after birth usually receive intravenous feedings with glucose 12.5%, protein (amino acids) 2–3 g/kg/day, and lipids 3 g/kg/day within the first few hours of life [84]. From this diet they derive 80–100 kcal/kg/day, depending on the volume of fluid infused, which is usually sufficient to maintain positive nitrogen balance, prevent tissue breakdown, and allow some growth (albeit inadequate). Attempts to feed asphyxiated infants early are often associated with NEC or abdominal distension and regurgitation of gastric contents. When this occurs, oral feedings are usually discontinued for 5–6 days. While enough free water is required to maintain normal intra- and extravascular fluid volumes, administering more than 130–150 mL/kg/day increases the likelihood of a PDA, congestive heart failure, and the risk for NEC. Electrolytes (3 mEq/kg sodium, 2 mEq/kg potassium, 200–500 mg/kg calcium gluconate) and vitamins (including vitamin E) should be administered in the maintenance fluids. Because antibiotics kill gut flora, vitamin K 0.2 mg is administered twice weekly as long as the patient is receiving antibiotics [85]. Failure to do this increases the risk of bleeding during surgery.

Serum chemistry determinations

Calcium

During the last trimester of pregnancy, fetal concentrations of calcium exceed those of the mother [86]. At birth, the maternal supply of calcium is withdrawn and the baby's serum calcium concentration decreases, often to 7.5–8.5 mg/dL. If the baby takes in sufficient calcium, the levels increase after several days. Despite the low concentrations of total calcium, ionized calcium concentrations are normal (because serum protein concentrations are lower, at 3–4.5 g/dL). Consequently, total serum calcium concentrations above 7 mg/dL are adequate if ionized calcium concentrations are normal [87]. Phosphate and magnesium concentrations are similar to those of term infants.

If the patient has symptoms of hypocalcemia (e.g. twitching, seizures, hypotension), calcium gluconate 10–30 mg/kg is administered slowly intravenously. Hyperventilation (alkalosis) decreases the unbound fraction of calcium, which can lower the seizure threshold. Despite the presence of hypocalcemia, the electrocardiogram (ECG) is usually normal.

Sodium

The serum sodium concentrations of tiny preterm infants are labile. They rise quickly with dehydration and decrease just as quickly with overhydration. Hypernatremia can damage the CNS, and hyponatremia (<120 mEq/L) can cause seizures. Water intoxication is usually associated with persistent hyponatremia. Hypertonic saline is seldom required to correct hyponatremia; fluid restriction usually suffices.

Glucose

Most neonatologists attempt to maintain the postnatal nutrition of preterm infants at or above their requirements during fetal life in the hope of maintaining normal growth. This goal is seldom met for many reasons [88]. Glucose provides most of the energy for many organs, including the brain. Most non-anesthetized larger preterm infants tolerate an infusion of 5–7 mg/kg/min of glucose without developing hyperglycemia, glucosuria, polyuria or dehydration, but many extremely low birthweight infants (23–25 weeks' gestation) require at least 10 mg/kg/min to maintain normoglycemia and growth. The only way to know the serum glucose concentrations is to measure them frequently, especially in the operating room. Excessively high serum glucose concentrations (>200 mg/dL) can cause an osmotic diuresis, hypovolemia, and possibly CNS injury [89,90]. With adequate nutrition, preterm infants gain 25–30 g/day and increase their head circumference by 0.8–1 cm/wk. It may, however, be difficult to provide sufficient nutrition to achieve this growth for myriad reasons. The level of nutrition and weight gain should be determined carefully before surgery because infants with poor preoperative nutritional states often tolerate anesthesia and surgery less well.

The blood glucose concentrations of many preterm infants are below 40 mg/dL, which constitutes hypoglycemia. If present, hypoglycemia should be corrected with 10–20% dextrose 2–5 mL/kg over 5 min and with a continuous infusion of sufficient dextrose to maintain the glucose concentration between 50 and 90 mg/dL. Many preterm infants have an SaO_2 of 80–90%. However, if they are hypoglycemic and anemic in addition to having their SaO_2 at these low levels, their growth rates are often reduced [91]. Care should be taken to avoid inducing hyperglycemia because it may lead to dehydration, reduced ability to resuscitate from cardiac arrest, and increased CNS injury.

Bilirubin

Because they conjugate substances less well, preterm infants often have higher serum bilirubin concentrations, especially infants who are bruised, polycythemic, or have intracranial, gastrointestinal, or pulmonary hemorrhage. The relative hypoproteinemia, the decreased effectiveness of the blood–brain barrier, and the often-present acidemia increase their susceptibility to kernicterus – brain injury secondary to the direct neurotoxic effects of prolonged high serum unconjugated bilirubin concentrations. Even low concentrations of bilirubin (10–15 mg/dL) are sufficient to produce kernicterus in acidotic infants [92–94]. It may be necessary to do a two-volume exchange transfusion before surgery if the patient's indirect bilirubin concentration is elevated and if time permits, because intraoperative hypoxemia and acidosis may prove disastrous (Table 22.2). It is important to determine the neurological status of preterm infants preoperatively because many of them have CNS injury that may later be attributed to anesthesia.

Retinopathy of prematurity

Fifty percent of infants weighing 1000–1500 g at birth have some degree of ROP [95]. Seventy-eight percent of those weighing 750–999 g have ROP, and more than 90% of those weighing less than 750 g have some degree of ROP. ROP is rare in term infants. Of extremely low birthweight infants weighing 500 g or less, 80–85% have some degree of ROP and 40% of them have severe ROP [96]. ROP is divided into five stages [97].

Table 22.2 Serum bilirubin concentrations for exchange transfusion

Birthweight (g)	Serum bilirubin concentrations for exchange transfusion (mg/dL)	
	Normal infants†	Abnormal infants‡
<1000	10.0	10.0§
1001–1250	13.0	10.0§
1251–1500	15.0	13.0
1501–2000	17.0	15.0
2001–2500	18.0	17.0
>2500	20.0	18.0

These guidelines have not been validated.
† There have been case reports of basal ganglion staining at concentrations considerably lower than 10 mg.
‡ Normal infants are defined for this purpose as having none of the problem listed below.
§ Abnormal infants have one or more of the following problems: perinatal asphyxia, prolonged hypoxemia, acidemia, persistent hypothermia, hypoalbuminemia, hemolysis, sepsis, hyperglycemia, elevated free fatty acids or presence of drugs that compete for bilirubin binding, and signs of clinical or central nervous system deterioration.
Source: Data from American Academy of Pediatrics, Committee on Fetus and Newborns Standards and Recommendations for Hospital Care of Newborn Infants, 6th ed. Evanston, IL: American Academy of Pediatrics, 1977.

- Stage 1: a thin white line separates the posterior vascularized portion of the retina from the anterior avascular retina.
- Stage 2: the demarcation line increases in volume and elevates. At this point it is known as the "ridge." The changes found in stage 1 and 2 regress in 80% of patients. Between 5% and 10% of premature infants with stage 1 and 2 disease progress to stage 3 [98].
- Stage 3: tissue proliferation develops from the ridge, usually posteriorly. Stage 3 can be mild, moderate, or severe, depending on the volume of the extraretinal tissue [97].
- Stage 4: partial retinal detachment occurs with the macula still attached (stage 4a). The macula is detached in stage 4b.
- Stage 5: total retinal detachment occurs in stage 5.

ROP begins with retinal blood vessel constriction, reduced vascular endothelial growth factor (VEGF), and retinal hypoxia [99]. The retinal hypoxia stimulates VEGF production and vascular proliferation, hemorrhage, and (in the worst cases) retinal detachment. While oxygen is a major contributing factor to the development of ROP, it is not the only factor. It is unknown what levels of oxygenation cause ROP, but a PaO_2 of 150 mmHg for as little as 1–2 h (the length of many surgical procedures) has done so. It is also possible that ROP might develop at considerably lower PaO_2s because the retinas of preterm infants, were they still *in utero*, would be exposed to a PaO_2 of 25–40 mmHg, not 50 mmHg or more, as often occurs after birth. Preterm infants whose SaO_2 was maintained between 80% and 96% for the first several postnatal weeks had less ROP than those with higher SaO_2 [99]. Interestingly, after 31 weeks' gestation, an SaO_2 of 94–99% was required to reduce the risk of further retinal damage. At this age the lower oxygen concentrations and mild hypoxia were adding to the retinal hypoxia. After discussion with the neonatologist, it may be appropriate to maintain higher oxygen saturations in *this specific group* of patients during surgery.

Hypoxia inducible factor-α (HIF-1α) is important in normal retinal development and is suppressed by increased oxygenation. This allows a decrease in the VEGF concentration and initiates retinal hypoxia and ROP. Increasing HIF-1α prevents ROP in animals [100]. The left-shifted oxygen dissociation curve of fetal hemoglobin (HbF) releases less oxygen to the tissues, which may protect the retina. Transfusion with adult blood may increase the risk of developing ROP because the relatively right-shifted oxygen dissociation curve releases more oxygen. Chorioamnionitis and neonatal systemic inflammatory disease also increase ROP [101].

Vitamin E and omega-3 fish oils may protect against ROP by their membrane-stabilizing and antioxidant actions [102,103]. While vitamin E concentrations normally decrease rapidly after birth, due to inadequate intake and storage of vitamin E, administering more than physiological amounts of vitamin E to premature infants has little beneficial effect and may increase the incidence of NEC and infection [104,105].

Approximately 85% of acute ROP undergoes spontaneous regression [106]. Grades 1 and 2 regress in 2–3 months, while grade 3 regresses in 6 months or more. Grade 4 and 5 ROP results in blindness or limited vision in approximately 25% in infants who were at high risk for retinal detachment [107].

Patients with ROP come to the anesthetist's attention because they require an eye examination, photocoagulation, or scleral buckling under anesthesia. It is unknown if exposure to increased oxygen concentrations during anesthesia worsens pre-existing ROP. Because we do not know, it is better to keep the SaO_2 during anesthesia at the same levels present in the ICN, usually between 87% and 94% [108]. Because many of these patients also have CLD and maldistribution of ventilation and perfusion, their SaO_2 can rapidly decrease with the induction of anesthesia. Adding a small amount of PEEP (2–5 cmH_2O) often improves both the match of ventilation-perfusion and oxygenation. Excessive PEEP may overdistend the ventilated portions of the lung and decrease oxygenation. Aoyama et al and Jiang et al have published sensible plans for anesthetizing patients with ROP [109,110]. They point out that many patients require postoperative mechanical ventilation and ICU care after surgery, even if they did not require them preoperatively. Ulgey et al demonstrated a significant reduction in the need for mechanical ventilation following retinal surgery by using an infusion of propofol plus ketamine [111]. Because the surgeons often inject air into the eye during surgery, it is best to use air as the carrier gas for inhaled anesthetics and avoid using nitrous oxide.

KEY POINTS: COMMON PROBLEMS ASSOCIATED WITH PREMATURITY

- Respiratory distress syndrome and bronchopulmonary dysplasia severity has decreased in recent years with routine surfactant administration, permissive hypercapnia, and non-invasive ventilation strategies
- Patent ductus arteriosus may be seen in up to 70–80% of small preterm infants, but medical therapy (fluid restriction, diuretics, cyclo-oxygenase inhibitors) has significantly reduced the incidence of surgical closure

- Periventricular white matter injury and intraventricular hemorrhage are common causes of CNS injury and long-term neurodevelopment problems in premature infants
- Necrotizing enterocolitis is a significant problem, usually between 27 and 34 weeks' gestation, and carries a 20–50% mortality
- Retinopathy of prematurity is a significant cause of loss of visual acuity; its incidence can be lessened with lower SpO_2 management, i.e. 87–94% in small premature infants

Preoperative preparation

History

During the preoperative visit, the patient's chart must be read, understood, and thoroughly discussed with the physicians and nurses caring for the patient. It is the nurses who stand at the bedside 24 h a day and provide the patient's minute-to-minute care. They know the idiosyncrasies of each patient. For example, the nurses may know that very brief periods of apnea cause severe hypoxemia and cyanosis or that the patient's perfusion decreases when his blood glucose concentration is <40 mg/dL or when the ionized calcium concentration is below 0.9 mmol/L.

Both the fetal and birth histories are important when planning an anesthetic for preterm infants. If the infant was asphyxiated before or at birth, the effects of asphyxia (right ventricular dysfunction, coagulation abnormalities, intracranial hemorrhage, etc.) may still be present. Autoregulation of the cerebral circulation may be absent [7,112,113]; if so, sudden increases in arterial pressure may rupture fragile cerebral vessels and cause intracranial hemorrhage [114].

Myocardial function may still be depressed, and the heart may show signs of hypoxic strain, including insufficiency of the tricuspid valve. Blood flow to the gut may be reduced. Both the blood volume and the hemoglobin concentration may be low if they were not corrected. These abnormalities can persist for several days after birth.

A maternal medication history should be sought in every case because many pregnant women take prescription or nonprescription drugs. A few use illicit drugs, and the baby may be undergoing drug withdrawal at the time of surgery. The symptoms of narcotic withdrawal include agitation, tremors, poor feeding, vomiting, and occasionally seizures. Infants withdrawing from barbiturates, diazepam, or methadone may only do so at 5–10 days of age. Fetuses who are repeatedly exposed to cocaine, which causes premature delivery, may also have pulmonary hypertension and bowel perforation. Infants born after maternal ingestion of large doses of aspirin or acetaminophen may have pulmonary hypertension and persistent fetal circulation (PFC) during the first few days of life [115,116]. PFC must be considered in any severely hypoxemic infant.

Systems review and examination

Head, eyes, ears, nose, and throat

Congenital anomalies of the face and mouth are common, either as part of a syndrome or as a lone entity. A cleft palate may be missed when infants are mechanically ventilated from birth. If the anesthetist must reintubate the patient's trachea, a cleft palate may make this more difficult because the tongue cannot be fixed against the palate and flops over the laryngoscope blade, obstructing the anesthetist's view of the glottis. The small mouth and the relatively large tongue of preterm infants frequently obstruct breathing, especially when pressure is applied to the submental triangle while holding an anesthesia mask on the patient's face. Even slight pressure in this area can completely obstruct the airway. Anesthesia masks with large air-filled cuffs are dangerous if they slip off the bridge of the nose and compress the nares while the mouth is being held closed. Most babies are obligatory nasal breathers for several months after birth [117]. A nasogastric tube (NGT) obstructs half of the unintubated infant's upper airway when the mouth is closed. This often increases respiratory work and leads to apnea during the induction of anesthesia. NGTs should be removed and reinserted orally if necessary. Atropine, if administered to patients with some types of cataracts or with glaucoma, may increase the intraocular pressure and further damage the eye (see Chapter 35).

Pulmonary system

As stated above, pulmonary dysfunction is common in preterm infants. Therefore, the pulmonary system must be evaluated carefully before anesthesia and surgery. Answers should be sought to the following questions.

- Does the patient now have or is he/she recovering from RDS? If so, how much support of breathing is required? What are the ventilator rates, pressures (peak-inspired and end-expiratory), inspired oxygen concentrations, and inspiratory times? Is the patient breathing spontaneously during mechanical ventilation? Is he/she triggering inspiration by the ventilator? What SaO_2, blood gas, and pH values do spontaneous breathing or the ventilator settings occasion? How labile are the blood gases? Do the blood gases and pH change when the patient is moved from side to side or onto the back or abdomen [118], when the trachea is suctioned, or when the chest is percussed [119]? It may be a problem if the patient must be turned into the lateral position for surgery and this position causes deterioration of the blood gases and pH.
- Has the patient had a pulmonary hemorrhage? If so, has the bleeding stopped and are there residual effects of the bleeding?
- Is pneumonia present? Pneumonia may be difficult to differentiate from RDS, pulmonary edema, or CLD on radiograph. A WBC count, a differential WBC count, and a smear of the tracheal secretions may be helpful in making this differentiation. If the infant has pneumonia, the tracheal smear will show both WBCs and bacteria. Either finding alone is seldom significant.
- Is the endotracheal tube (ETT) fixed securely in place? Accidental extubation of the trachea on the way to the operating room is disconcerting. Tape used to hold the ETT in place should not completely encircle the infant's head to avoid causing brainstem hemorrhage [120].
- Does the infant have intercostal retractions? Most preterm infants have grade 1-of-4 to 2-of-4 retractions because their chest walls are not fully developed. Those with pulmonary disease have grade 3-of-4 to 4-of-4 retractions. Retractions indicate increased work of breathing, decreased lung compliance, increased airway resistance or all three.

- Can rales be heard? Most preterm infants have occasional rales. Moist rales indicate intra-alveolar fluid, usually associated with pulmonary edema or infection. Dry rales are usually associated with atelectasis. Rhonchi are also common, especially after several days of tracheal intubation.
- Are there secretions? White or clear secretions seldom contain significant amounts of bacteria. Yellow, green, or brown secretions, on the other hand, often indicate infection. Frothy, pink, or blood-tinged secretions are usually indicative of pulmonary edema or pulmonary hemorrhage.

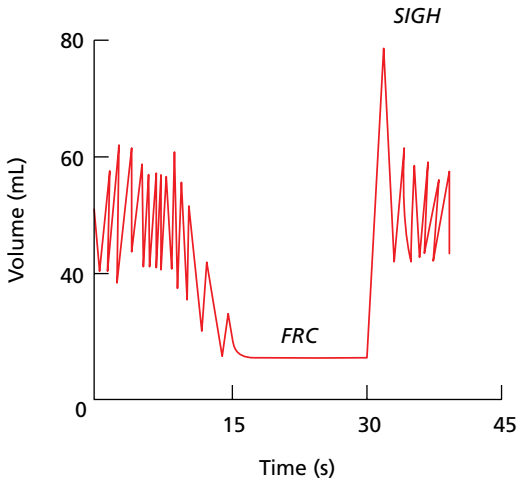

Figure 22.3 Changes in functional residual capacity (FRC) with bradypnea and apnea. *Source*: Reproduced from Gregory [121] with permission from Wolters Kluwer.

Preterm infants normally breathe 30–60 times per minute. However, those with lung disease can have respiratory rates of 150 breaths/min or more, especially when lung compliance is reduced. Babies "choose" to breathe rapidly and shallowly rather than slowly and deeply, probably because the metabolic cost of breathing rapidly and shallowly is less. Rapid respirations help maintain the functional residual capacity by not allowing sufficient time for complete exhalation. Unless PEEP is applied, slow respiratory rates decrease functional residual capacity (Fig. 22.3) [121].

Evaluating blood gas and oxygen saturation data gives important clues to the patient's responses to ventilatory maneuvers. Preterm infants normally have lower PaO_2 than term babies (Tables 22.3 and 22.4). Therefore, small changes in PaO_2 cause large changes in oxygen saturation and in oxygen content [122]. Brief periods of apnea lead to hypoxemia. Is the patient having apneic spells (see section "Retinopathy of prematurity")? Apneic spells are often indicative of other problems. If the infant is having or has had apnea, he/she may have postoperative apnea and require mechanical ventilation for a variable amount of time (see Chapter 23). Figure 22.4 shows the chest radiographs of a normal infant and one with hyaline membrane disease.

Cardiovascular system

Many preterm infants have problems with their cardiovascular systems (including PDA, hypotension, and shock) [123,124] but congenital heart disease is less common. Because the bulk of muscle is laid down in the pulmonary arteries during the third trimester of pregnancy, infants born earlier have less muscle and are prone to develop a PDA and increased

Table 22.3 Normal arterial blood gases

Parameter	Birth	1 hour	5 hours	1 day	5 days	7 days
PaO_2 (mmHg)						
$\overline{X}$	46.6	63.3	73.7	72.7	72.1	73.1
SD	9.9	11.3	12.0	9.5	10.5	9.7
$PaCO_2$ (mmHg)						
$\overline{X}$	46.1	36.1	35.2	33.4	34.8	35.9
SD	7.0	4.2	3.6	3.1	3.5	3.1
pH						
$\overline{X}$	7.207	7.332	7.339	7.369	7.371	7.37
SD	0.051	0.031	0.028	0.032	0.031	0.02

$\overline{X}$, mean; SD, standard deviation.
Source: Reproduced from Koch and Wendel [172] with permission of Karger.

Table 22.4 Arterial blood gases in normal preterm infants

Parameter	Birth	3–5 hours	13–24 hours	5–10 days
PaO_2				
$\overline{X}$	–	59.5	67.0	80.3
SD	–	7.7	15.2	12.0
$PaCO_2$				
$\overline{X}$	–	47.0	27.2	36.4
SD	–	8.5	8.4	4.2
pH				
$\overline{X}$	7.32	7.329	7.464	7.378
SD		0.38	0.064	0.043

$\overline{X}$, mean; SD, standard deviation.
Source: Reproduced from Orzalesi et al [173] with permission of BMJ.

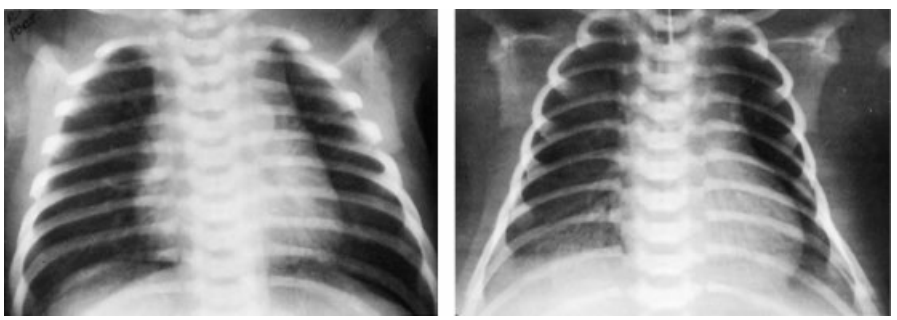

Figure 22.4 Chest x-rays of a normal preterm infant (*left*) and one with respiratory distress syndrome (*right*). Note the air bronchograms, the loss of lung volume and the heart border in the latter. *Source*: Courtesy of Dr Robert C. Brasch.

left-to-right shunting of blood through the ductus arteriosus earlier in life (3–5 days of age) than term infants (7–14 days of age). The net result is increased pulmonary blood flow, pulmonary edema, congestive heart failure (CHF), reduced lung compliance, hypoxemia, and CO_2 retention. Surfactant administration establishes the functional residual capacity (FRC) more quickly, which is associated with a PDA and left-to-right shunting of blood within a few hours after birth.

CHF may not be heralded by tachycardia in preterm infants, as it is in older patients. In fact, the heart rate is often monotonously regular and usually within normal limits (120–160 beats/min) (Table 22.5). A third heart sound (gallop) may be present but may be difficult to hear because of the rapid heart rate and environmental noise (e.g. mechanical ventilators, alarms, monitors, people). Murmurs can be difficult to hear for the same reason. Two murmurs are commonly present in preterm infants, that of a PDA and that of tricuspid insufficiency. The PDA murmur is a systolic ejection murmur that is best heard along the upper left sternal border when the ductal flow is small. When it is large, the murmur extends into diastole, is continuous, and is heard throughout the chest. The "machinery murmur" described in older patients is seldom heard. The murmur of tricuspid insufficiency is systolic in nature and is best heard along the right sternal border. It seldom radiates far, and it disappears after several days of life as ventricular function improves.

CHF reduces peripheral perfusion and slows capillary filling. The pulses are decreased, except in patients with a PDA. Peripheral edema is common, in part because serum protein concentrations are low. Edema usually appears first in the eyelids. Pitting edema of the feet and shins is uncommon in other than the sickest babies. Puffiness of the feet, however, is common.

The chest radiographs of preterm infants with CHF are frequently difficult to differentiate from those of infants with RDS. The former usually show central fluffiness and slightly larger markings than those of RDS (Fig. 22.5).

Table 22.5 Heart rate in preterm infants with patent ductus arteriosus

Condition	Heart rate (bpm)
Normal cardiac function	150 ± 18
Congestive heart failure	148 ± 22
Postligation ductus arteriosus	146 ± 18

The liver size is a good indicator of right-sided heart failure and of CHF in preterm infants because their livers are very distensible. The inferior margin is normally sharp and located 1–2 cm below the right costal margin; with CHF, the liver can quickly distend into the pelvis. Just as quickly, it returns to its normal position with appropriate therapy. Applying excessive pressure when examining the abdomen may push the liver up into the thoracic cavity and make the liver appear smaller than it really is. The position of the liver edge can usually be determined by gently running one's fingertips over the right upper abdomen or by percussing the abdomen. Percussion is especially useful when the abdomen is distended. Enlarged livers often extend across the midline, which may make it difficult to differentiate from the spleen, which also is often enlarged during CHF.

Abdomen

The abdomen of preterm infants is normally protuberant and soft. The venous pattern of the abdominal wall is prominent and is exaggerated with liver disease. Intra-abdominal organs are generally easy to palpate. The spleen is usually palpable below the left costal margin in patients who have erythroblastosis fetalis, systemic infections, liver disease, or fluid overload. The ascites of erythroblastotic infants may interfere with ventilation of the lungs and make it necessary to remove some of the fluid by paracentesis to allow adequate ventilation of the infant's lungs. In some cases paracentesis may be required before the induction of anesthesia.

The preterm infant's kidneys are easily palpable as small globular masses in the retroperitoneum. They may be enlarged by renal vein thromboses or by renal, ureteral, or bladder anomalies. The urinary bladder is usually felt as a round mass extending above the pelvic rim. Obstruction of the urethra can cause the bladder to distend above the umbilicus. The ureters are occasionally palpable as cords running longitudinally in the retroperitoneum.

It is often possible to see loops of distended bowel through the abdominal wall. Abdominal distension is seldom a cause of abdominal tenderness unless peritonitis is present. Then the abdomen is tender, rigid, and edematous enough to leave one's fingerprints on the skin. Intraperitoneal fluid often passes through the inguinal canals and distends the scrota. As a consequence, inguinal hernias occur in about 30% of premature male infants. Redness around the umbilicus is often a sign of systemic or intra-abdominal infections.

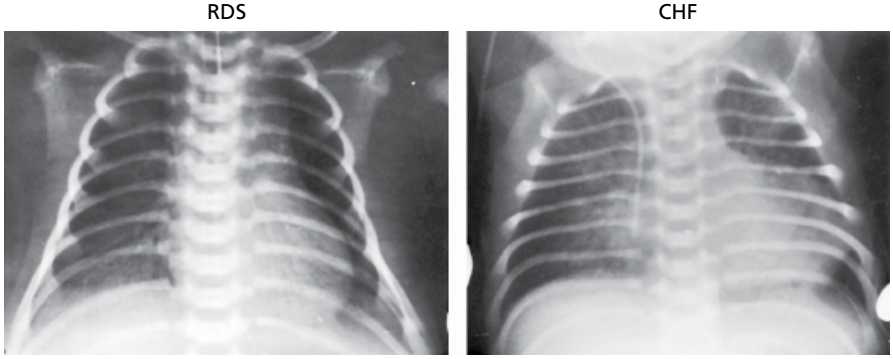

Figure 22.5 Chest x-rays of a normal preterm infant with respiratory distress syndrome (*left*) and one with a patent ductus arteriosus and congestive heart failure (*right*). Note the enlarged heart, the central fluffiness, and the loss of clear vascular shadows in the latter. *Source*: Courtesy of Dr Robert C. Brasch.

One should ascertain patency of the anus before the infant undergoes surgery. Occasionally an imperforate anus is missed in very sick infants. Nothing (including thermometers) should be inserted more than 0.5 cm into the rectum to avoid perforating the bowel.

Central nervous system

The incidence of CNS injury increases with increasing degrees of prematurity and asphyxia (see Chapter 25). CNS injury is usually manifested as flaccidity, hypertonia, hypotonia, or a difference in tone between the upper and lower or between the right and left sides of the body. Deep tendon reflexes and the grasp reflex are often absent. Healthy preterm infants normally have a positive Babinski sign. The back, neck, and sacral area should be examined for evidence of a meningomyelocele. Again, these lesions can be missed preoperatively when very ill infants are placed on their backs and left there for days because of the extent of their illness.

State of hydration

The hydration state of preterm infants should be carefully assessed during the preoperative visit. Their large surface/volume ratio, thin skin, rapid respiratory rates, relatively large minute volumes, and infrared warmers increase water losses [125,126]. Failure to replace these losses adequately leads to dehydration. Covering the baby with clear plastic film significantly reduces water and heat losses. Reducing fluid intake to less than 130 mL/kg/day decreases the incidence of PDA in preterm infants but can also lead to severe fluid and calorie restriction [55]. Restricting fluid and caloric intake may cause infants to be dehydrated and undernourished when they present for surgery. Administration of potent diuretics, such as furosemide, can cause further dehydration. Preterm infants third-space fluids more easily than older patients because the preterm infant's capillaries leak easily, serum protein levels are lower, and the oncotic pressure is reduced [127,128]. As a consequence, infants with sepsis or shock lose large amounts of fluid into the peritoneal cavity. These patients commonly gain 20–50% of their bodyweight, despite being intravascular volume depleted.

Laboratory findings

Most sick preterm infants undergo a multitude of laboratory tests, the results of which must be reviewed and understood before anesthesia is induced.

Hematology

In well infants, a hemoglobin concentration above 7 g/dL is usually adequate. In infants with cardiorespiratory disease, the concentration of hemoglobin should exceed 9 g/dL to ensure adequate oxygen-carrying capacity. As discussed previously, the hemoglobin (Hb) concentration decreases rapidly after birth, frequently because caregivers extract large volumes of blood for tests.

Besides knowing the PaO_2 and SaO_2, it is important to determine the oxygen content of the patient's blood:

$$\left(\left[\left\{1.36\,\text{mL oxygen/g Hgb}\times\text{Hgb g/dL}\right\}\times SaO_2\right]+0.003\times PaO_2\right)$$

0.003 is the solubility coefficient of oxygen in plasma. If the hemoglobin concentration were 10 g, the oxygen content would be about 13.1 mL oxygen/100 mL of blood. The entire body extracts about 5 volumes percent of oxygen from the blood. However, the heart extracts 12 volumes percent from blood passing through it. There is barely enough oxygen present to meet cardiac demands. If the Hb concentration were 5 g, the oxygen content of the arterial blood would be about 6.5 mL/100 mL of blood, which is insufficient to meet cardiac demands, unless coronary blood flow increases and cardiac oxygen requirements remain constant or decrease while the oxygen extraction from blood increases. This is a precarious position in which to begin surgery. Infants with low Hb concentrations should be transfused before surgery if possible to normalize their blood oxygen content.

Electrolytes

The concentrations of the serum electrolytes vary more in preterm infants than in older patients because premature infants are affected more severely by small changes in fluid and electrolyte intake, by fluid and electrolyte losses, and by the infant's environment. A single electrolyte value can be misleading; serial values are much more helpful. A rise in serum sodium is usually a result of either dehydration or excessive sodium administration. The latter is associated with peripheral edema. Although hyperkalemia is common, it seldom affects the ECG. Hypokalemia (<3 mEq/L) is also common, especially when preterm infants are given potent diuretics. Inadvertent hyperventilation and alkalosis further reduce the serum potassium concentration when potassium moves into the cells in exchange for hydrogen ions. The serum concentration of chloride is normally higher in preterm infants (105–115 mEq/L) than in older children, which in part accounts for the commonly present metabolic acidosis.

The total calcium concentration is usually lower than that of term infants (see section "Calcium"), but the ionized calcium concentrations of the two groups are similar. Hyperventilation may reduce the ionized calcium concentration to unacceptable levels. The tendency of most neonatologists is to maintain the total serum calcium concentration above 7 mg/dL if the ionized calcium concentrations are normal for age [86]. Failure to provide sufficient phosphorus in the diet may lead to hypercalcemia [129].

Coagulation status

At birth, the levels of coagulation factors are approximately 50% of adult values (see Chapter 12), although babies seldom bleed because of this [130–132]. Their platelet counts are similar to those of normal adults, but their platelets probably function less well. Does the infant have a bleeding diathesis? Infants who are asphyxiated at birth have depression of factors V, VII, and VIII, which return to normal within 3–4 days if the infant is resuscitated quickly [133]. These levels may not return to normal for a week or more if the hypoxia is prolonged. The latter infants are frequently thrombocytopenic, often below 10,000/mm^3. Even at these levels, bleeding seldom occurs in the absence of surgery or injury. Therefore, it is seldom necessary to transfuse platelets to premature infants unless they require surgery or their platelet count is below 5000/mm^3, especially when their other clotting parameters are normal and there is no evidence of bleeding. When

surgery is required, platelets should be transfused to raise their concentration to 50,000/mm^3 or greater. If the surgical procedure lasts for several hours, another platelet transfusion may be required. If the patient has not received vitamin K after birth, has been nil per os (NPO), and has received IV antibiotics, vitamin K 0.2 mg/kg should be administered preoperatively to preterm infants [132–134].

Bleeding disorders such as disseminated intravascular coagulation (DIC) must be corrected preoperatively with fresh frozen plasma, cryoprecipitate, or factor VIIa. If both the clotting factors and the platelets are decreased, the patient will benefit from fresh whole blood because it contains all of the clotting factors, platelets, proteins, and RBCs required.

Preoperative plan

For very ill preterm infants, it is advisable to have the help of a second anesthetist during surgery. It is difficult for one person to ventilate the patient's lungs, give fluids and blood, watch the surgical field and monitors, and keep the anesthesia record at the same time (although automatic record keeping has made this easier – see Chapter 49). In an attempt to prevent hypothermia, the operating room should be warmed to 35–37°C or above before the patient arrives and a servo-controlled infrared heater should be placed over the operating table. An air-circulated heating pad should be placed under the child and maintained at 35–37°C. Pressure transducers used to monitor arterial and central venous pressure should be set up and calibrated if needed. Intravenous solutions are made up if they differ from those being infused in the nursery. Patients often receive 5% dextrose in 0.2 normal saline in the ICN. *This solution should not be used to replace fluid losses during surgery*. Ringer's lactate or normal saline is used for this purpose; large volumes of normal saline may cause metabolic acidosis. Fluid should be warmed and delivered through an infusion pump when possible. If a drip chamber is used, it should never contain more fluid than is safe to give in 1 h. This avoids accidental overhydration if the IV infusion runs wide open.

Before transport to the operating room, an exchange of information between the ICN physician and nurse and the anesthesiologist should occur, summarizing the patient's current status and any special concerns the team has. Transporting preterm infants to and from the operating room can be dangerous. During transport, the anesthetist should always accompany sick infants to reduce this risk. The patient is connected to battery-operated arterial blood pressure, ECG, and oxygen saturation monitor during transport. Infusion pumps should continue to infuse fluids and drugs, especially vasoactive drugs. Ventilation is supported during transport, usually with a Jackson Rees device, and a portable air–oxygen blender. Sufficient oxygen should be administered to keep the oxygen saturation between 87% and 94% [122].

The inspired oxygen concentration should not be 100% during transport or in the operating room unless that concentration of oxygen is needed to maintain the desired oxygen saturation. Otherwise, the FiO_2 should be kept as low as possible while providing appropriate oxygen saturations. Use of an air–oxygen blender is required during transport to the operating room so the FiO_2 can be properly adjusted.

Table 22.6 Body temperature of preterm infants during transport to and from the operating room

Time	Body temperature (°C)
Preoperative: nursery	36.4 ± 0.5
Preoperative: operating room	35.7 ± 0.7
End of surgery	36.4 ± 1.0
Postoperative: nursery	35.9 ± 1.7

Keeping the patient warm is a major problem during transport. Table 22.6 shows the changes in body temperature of preterm infants being transported 11 floors to and from the operating room for surgery. Note the loss of nearly a degree of body temperature during this short period. Their body temperature increased to normal in the operating room and decreased again during the trip back to the nursery. These heat losses can usually be prevented by covering the baby's body with clear plastic film and warm blankets, covering the infant's head with a cap, and placing a chemical heating pad under the patient (Porta-Warm, Allegiance Health Care Corp.). Elevators should be waiting for the patient, not vice versa. The operating room should be warm, and the infant should go directly into the operating room and be immediately placed under a servo-controlled radiant warmer.

KEY POINTS: PREOPERATIVE PREPARATION

- Preoperative history must be thoroughly understood, not only from review of the medical record, but from discussion with the bedside physicians and nurses
- Review of systems and examination are crucially important; particular attention to respiratory, cardiovascular, CNS, infection, and congenital anomalies is warranted
- Preoperative discussion and planning of location of surgery (bedside versus operating room) and recovery (extubation of trachea, PACU versus direct transfer to nursery) should occur for every case

In most instances, it is better to ligate a PDA, insert a Broviac catheter, or treat NEC in the NICU rather than transport the child to the operating room. This allows the patient's mechanical ventilator and monitors to be used during surgery. The infection rates of patients undergoing surgery in the ICN are the same as those of patients undergoing surgery in an operating room [135].

Induction of anesthesia

Although preterm infants require anesthesia [136,137], their requirements are lower than those of older patients [138,139]. Failure to provide adequate anesthesia predisposes them to hypertension and intracranial hemorrhage if their cerebral vascular autoregulation is absent, which it commonly is [140,141]. When this occurs, increases or decreases in arterial blood pressure increase or decrease cerebral blood flow. Adequate anesthesia prevents or attenuates these changes in pressure. Because deep anesthesia reduces the arterial blood pressure of infants and children more than it does that of adults [140], arterial blood pressure must be supported with

fluid and vasopressors when necessary. Increases in heart rate and arterial blood pressure are usually signs of light anesthesia. However, the heart rate often does not change during hypotension because the baroreceptors of preterm infants are obtunded by even light levels of anesthesia [142–144]. Seventy percent nitrous oxide reduces the baroresponse to the same extent as halothane [143]. Fentanyl 10 μg/kg also depresses the baroreceptor reflex significantly [144] though this does not cause hypotension. Anand and associates showed that inadequate anesthesia induces a stress response in preterm infants [136] and that underanesthetized infants have a 10-fold greater complication rate.

Inserting an ETT without anesthesia or analgesia increases arterial and intracranial pressures [145]. Obviously, some patients are too ill to anesthetize before inserting an ETT, but this is uncommon after the immediate neonatal period.

Anesthesia is often induced with inhaled anesthetics (usually sevoflurane) and sufficient oxygen to maintain the desired SaO_2. If controlled ventilation is required during the induction of anesthesia, the anesthetic concentration must be reduced to prevent sudden, severe hypotension [146]. An alternative anesthetic technique employs propofol 1–2 mg/kg or fentanyl 10–30 μg/kg IV given over 1–2 min [138]. Once the eyelid reflexes are lost, an ETT can be inserted. If an assistant places a finger in the patient's suprasternal notch, the tip of the ETT can be felt as it encounters the finger. At this point the tube tip is in the mid-trachea and advancement of the tube can be stopped and the tube fixed in place. This reduces inadvertent endobronchial intubation. If necessary, the patient can be paralyzed with rocuronium 0.3–1.0 mg/kg. Muscle relaxants that increase the heart rate are preferred for preterm infants because this better maintains cardiac output.

Maintenance of anesthesia

There are few data on the anesthetic requirements of preterm infants, especially extremely premature infants [139]. However, experience suggests that premature infants require less anesthesia than their healthy full-term counterparts. The sevoflurane requirement for infants undergoing ligation of a PDA is approximately 50–80% of that of term infants. At that dosage, no change occurs in either heart rate or arterial blood pressure with skin incision [139].

Preterm infants anesthetized with inhaled anesthetics are more often hypotensive than older patients [147], probably because there is less response of peripheral vessels to catecholamines [142], myocardial depression, and loss of baroresponse [148]. Because preterm infants depend heavily on heart rate for cardiac output, loss of baroresponses makes it difficult for them to respond appropriately to hypotension. Table 22.7 shows the heart rate and arterial blood pressures of preterm infants anesthetized with halothane for ligation of a PDA. Note the heart rate did not increase when the blood pressure decreased or increased, so baroreceptor function was reduced. Similar data are unavailable for sevoflurane, but the changes are almost certainly similar because sevoflurane depresses the baroreceptor responses of adults [149].

Table 22.7 Relation between heart rate and systolic blood pressure in preterm infants anesthetized with halothane for ligation of a patent ductus arteriosus

Condition	Heart rate (bpm)	Systolic pressure (mmHg)
Preinduction	146 ± 20	62 ± 16
Before ductal ligation	143 ± 17	48 ± 16
After ductal ligation	145 ± 16	66 ± 15

To avoid anesthesia-induced hypotension, fentanyl is commonly used to anesthetize preterm infants [138,150]. Administering 10–30 μg/kg of fentanyl prevents changes in both heart rate and arterial blood pressure with a skin incision. When the blood volume is adequate, administration of fentanyl seldom causes hypotension. Patients who are regularly receiving fentanyl in the NICU may require much higher doses of fentanyl for surgery, often more than 50 μg/kg. As with all drugs, fentanyl should be titrated to the desired clinical effect. Muscle relaxants are often used to prevent movement and to reduce anesthetic requirements. Premature infants receiving muscle relaxants must, however, be anesthetized! Nitrous oxide, like other anesthetics, can cause hypotension and cardiac arrest in hypovolemic patients.

The lungs of preterm infants should be mechanically ventilated during anesthesia and surgery. Operating room mechanical ventilators are poor substitutes for those used in the ICN, but ICN ventilators cannot deliver inhaled anesthetics. If an ICN ventilator is used, a narcotic-based anesthetic will provide adequate anesthesia. No ventilator adequately compensates for changes in compliance and resistance of the lungs induced by retractors, surgical packs, and the surgeon's hands. Consequently, the lungs of small preterm infants are often ventilated by hand while observing the surgical field and chest expansion. The lowest pressures and tidal volumes possible should be used to *normally* expand the chest and lungs. If the neonate required PEEP in the NICU, he/she will require it during anesthesia and surgery. The initial ventilator settings used during anesthesia should mimic those used by the physicians, nurses, and respiratory therapists in the NICU to produce the best blood gases and oxygen saturations. These variables can be adjusted as needed. To avoid administering a high oxygen concentration, it must be possible to adjust the FiO_2 between 0.21 and 1.0 during surgery. Administering high oxygen concentrations to preterm infants who do not need them unnecessarily exposes the infants to the risk of ROP (see section "Retinopathy of prematurity").

Actively determining and replacing the premature infant's blood losses with blood and fluid is crucial because the blood volumes of premature infants are small, about 100 mL/kg. Consequently, in a 1 kg infant a loss of 10 mL of blood is equivalent to a 10% loss of blood volume. It is often difficult to accurately determine such small blood losses during surgery. Weighing the used sponges is a more accurate method of doing so than merely looking at them and guessing how much blood is in them. A 1 g increase in sponge weight equals 1 mL of blood. Suctioned blood should be collected in small bottles to more accurately determine blood losses. Volumes of flush solutions must be accurately recorded so they can be subtracted from the amount of fluid in the blood collection bottle. The most difficult part of estimating blood loss is determining how much blood is lost into the surgical drapes and into the tissues. Because of these inadequacies in blood loss determinations, it is often necessary to increase the estimated blood loss by 25–50% and to administer that amount of blood or an

appropriate volume of crystalloid while monitoring intravascular pressures and heart rate and determining serial hematocrits. Low hematocrits are corrected with packed RBCs.

The volume of fluid administered depends in great part on the amount of surgical trauma occurring. Abdominal or thoracic procedures are more traumatic than peripheral procedures and therefore require 8–12 mL/kg/h or more of lactated Ringer's solution. Replacing fluid losses with 0.2 or 0.3 normal saline is dangerous because it leads to hyponatremia, water overload, and occasionally death. Infusing approximately 5–7 mg/kg/min of glucose is a good starting dose under anesthesia, unless the patient was receiving higher concentrations of glucose in the ICN. The blood glucose concentration should be measured frequently and maintained between 50 and 90 mg/dL. Giving more glucose may cause hyperglycemia (Tables 22.8–22.10).

Additional fluid should consist of lactated Ringer's solution (without glucose), 5% albumin, blood, or a combination of these. Blood products and plasma contain dextrose and may increase blood glucose concentrations. Intravenous alimentation fluid is *never* used to replace fluid losses during surgery because doing so causes severe hyperglycemia and possibly CNS damage. Instead, the anesthetist should infuse hyperalimentation fluids at their preoperative rate and provide additional fluid needs with plain lactated Ringer's solution. The blood glucose concentration should be determined during surgery with a glucometer and the infusion rates of dextrose altered as needed.

Adequate replacement of colloid and crystalloid is aided by measuring central venous pressure (CVP), mean arterial pressure (MAP), and urine output. MAP is a good indicator of intravascular volume. An arterial blood pressure that is two standard deviations below normal for that age group [151] indicates hypotension and suggests hypovolemia (Fig. 22.6).

Table 22.8 Serum and urine glucose values and urine volume in a 1 kg infant

Assay	Time (h)			
	Baseline	1	2	Recovery
Serum glucose (mg/dL)	45–90	90	175	130
Urine glucose	1+	2+	4+	4+
Fluid intake (mL/kg/h)	4	7	15	12
Glucose infused (mg/h)	400	700	1500	1200

Table 22.9 Blood and urine glucose concentrations in term and preterm infants during surgery (% of patients)

Age	% of Patients by urine* results				% of Patients by blood† results (mg/dL)		
	Negative	2+	3+	4+	45–90	130–175	≥250
Preterm	50	20	15	15	40	50	10
Term	70	14	10	6	66	20	25

* Labstix.
† Dextrostix.

Table 22.10 Effects of adding glucose to intravenous fluid of infants and children during surgery

Age	Glucose concentration (mg/dL)			
	Ringer's lactate		D-5 Ringer's lactate	
	Infants	Children	Infants	Children
Preoperative	78 ± 12	95 ± 13	76 ± 9	87 ± 13
Anesthesia				
20 min	88 ± 20	122 ± 17	143 ± 18	147 ± 38
60 min	78 ± 12	93 ± 18	201 ± 39	186 ± 37
120 min	81 ± 15	93 ± 12	213 ± 41	158 ± 32

* Glucose was added when the intravenous infusion was started in those receiving glucose. Infants were 1 week to I year of age. Children were 1–7 years of age.

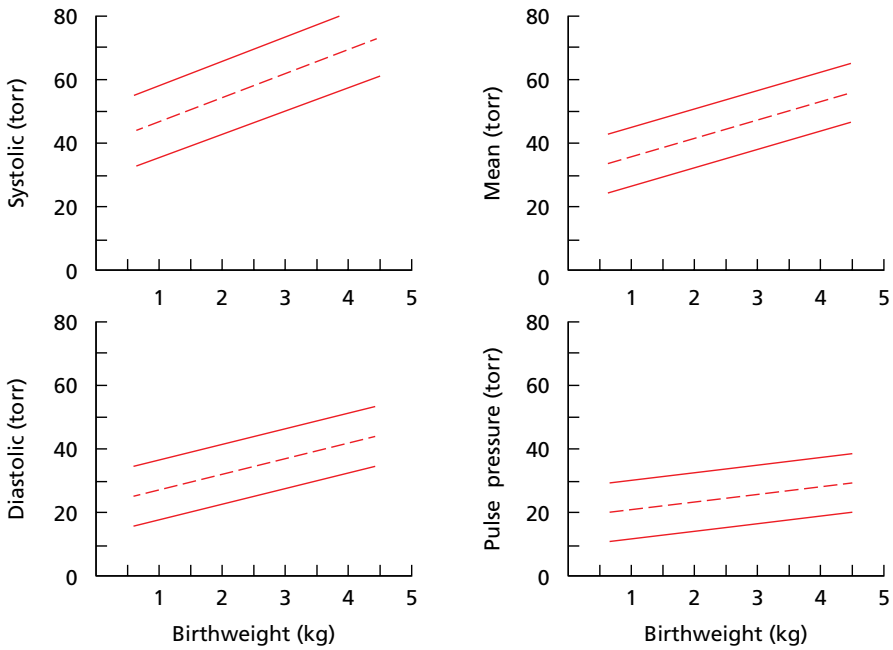

Figure 22.6 Systolic, diastolic, and mean arterial blood pressures and pulse pressures of infants between 610 and 4200 g. *Source*: Reproduced with permission of Gregory, Versmold.

Infusing adequate fluid usually returns the blood pressure to normal. CVP is also a useful measurement of intravascular volume status. A CVP below 3 cmH_2O suggests hypovolemia.

Urine output is also a good indicator of intravascular volume. It should exceed 0.75 mL/kg/h. The urine specific gravity of normal neonates is usually less than 1.005 [152]. A urine specific gravity in excess of 1.009 usually indicates that the patient is conserving fluid. If the skin over the fontanelle is below the inner table of the skull, and the baby is not crying, he is probably hypovolemic.

Body temperature is maintained between 36°C and 37°C to avoid postoperative hypoventilation, delayed awakening from anesthesia, atelectasis, respiratory and metabolic acidosis, infection, poor feeding, and aspiration of gastric contents. The body temperature is maintained in the normal range by warming the operating room and the inspired gases. Intravenous fluids and blood can be warmed using a conventional fluid warmer set to 38–41°C and leaving only a short length of tubing to the patient's IV catheter, so that the fluid will not cool in a long length of tubing. The short segment of tubing must be visible so air bubbles can be detected and removed. Even small air bubbles (0.1 mL) can be lethal if they lodge in a coronary or cerebral artery, which is possible because the foramen ovale is patent in most of these neonates.

Recovery from anesthesia

Emergence from anesthesia can be as dangerous as induction of anesthesia. There is often pressure to quickly remove the patient from the operating room so that the next case can start. This pressure must be resisted while careful preparations are made to transport the patient to the recovery area, usually the ICN. Before the patient leaves the operating room, it must be known that the ICN nurses are available and ready to receive and care for the patient. The ICN should be informed of the FiO_2, ventilator settings, body temperature, and planned postoperative pain therapy before the patient leaves the operating room. After transport to the ICN, a complete verbal exchange of information from the anesthesia team and surgeons to the ICN nursing and physician team is important, to inform them of intraoperative events.

In most instances the lungs of preterm infants should be ventilated on the way to and in the ICN. It can then be decided whether mechanical ventilation is required postoperatively or not. Muscle relaxants must be reversed and adequate spontaneous ventilation established before an ETT is removed.

Many preterm infants who are less than 44 weeks' gestation develop postoperative apnea [153,154]. The incidence of apnea is related inversely to the gestational age at birth [155]. Although the cause of apnea is unknown, it may be due to persistence of small amounts of anesthetic in the CNS that affect the autonomic nervous system [156] or it might be related to an incompletely developed CNS [157]. Most postoperative apnea occurs during the first 4 h after surgery, but apnea may occur 12 or more hours after surgery [158]. Patients who are <46 weeks' gestation are usually monitored for apnea and SaO_2 in hospital for 12–24 h after surgery due to their high risk for apnea. Those with gestational ages of 47–60 weeks are evaluated carefully for 6 h postoperatively. If there is no evidence of apnea, bradycardia, or oxygen desaturation, they can be discharged home, all else being normal. Those older than 60 weeks' gestation can be treated as normal term infants and can be discharged home after surgery if there are no other problems. Infants who develop postoperative apnea may require mechanical ventilation for several hours to several days. This possibility usually precludes outpatient surgery for infants who are less than 50 weeks' postconceptual age, although one study disputes this conclusion [159].

Welborn and associates found that ex-premature infants whose hematocrit was below 30% had an increased incidence of apnea [160]. Eighty-nine percent of the infants with low hematocrits were apneic after surgery while only 21% of those with a hematocrit of greater than 30% were apneic.

The same authors found less apnea in infants treated with spinal anesthesia than in those anesthetized with general anesthesia [161]. No instances of apnea occurred with spinal anesthesia unless the patients were also sedated. Eight of nine infants premedicated with ketamine had significant apnea while five of 16 had postoperative apnea if not given the drug. Although spinal anesthesia caused fewer instances of postoperative apnea [162], apnea and total spinal anesthesia have occurred [163,164]. Kunst et al found no difference in the rate of apnea in patients who received either form of anesthesia [165]. This was also true of recent data [166]. Patients undergoing general anesthesia were more likely to have oxygen desaturation and bradycardia than those undergoing spinal anesthetic. Tashiro and associates [167] found that gestational age, birthweight, postconceptual age, and use of aminophylline preoperatively were associated with a need for postoperative ventilation. Approximately one-third of the infants undergoing hernia repairs had postoperative apnea [168]. Welborn et al found that IV caffeine 5 mg/kg prevented life-threatening postoperative apnea and eliminated the need for mechanical ventilation [169]. It had no effect on lesser degrees of apnea. By delaying surgery until the patient is more than 44 weeks' postconceptual age, most postoperative apnea can be avoided. Patients who require surgery before 44 weeks' gestation should receive IV caffeine.

KEY POINTS: INDUCTION, MAINTENANCE, AND RECOVERY FROM ANESTHESIA

- Failure to provide adequate depth of anesthesia in premature infants predisposes to hypertension and intracranial hemorrhage
- Anesthetic requirements are lower in premature infants than for full-term neonates
- Hypotension is common in premature infants, especially with volatile anesthetics; treatment with fluids or vasopressors is frequently required
- Because the blood volume of premature infants is small, i.e. 100 mL/kg, replacing moderate or significant blood loss is crucial
- Strict attention to body temperature, glucose, and FiO_2 is an important component of anesthesia for premature infants
- Postanesthetic apnea in premature infants less than 46 weeks' gestation is common and monitoring should be used

Anesthesia for micropremies

The marked improvement in the survival of very premature infants ("micropremies," i.e. 400–1000 g at birth) over the past few years has resulted in many surgeries before discharge from hospital. Some of these patients have poor neurological and developmental outcomes. Evidence suggests that only 67–71% of 24–25-week gestation infants are neurologically normal compared to 89% of those born at 26 weeks' gestation (Table 22.11). An additional 22% of 24-week gestation infants have neurological examinations that are suspicious for injury [170,171].

Only 28% of neonates born at 24 weeks' gestation have normal cognitive development at 4.5–7 years of age. Eleven percent of 24–27-week gestation infants had cerebral palsy. The outcome of small infants was significantly improved by delaying their birth until 26 weeks' gestation. Infants with CNS injuries are more likely to have hypotension and bradycardia with anesthesia.

The problems of micropremies are similar to those of larger premature infants, but worse. Because they are so immature, micropremies do not have true alveoli and the distance between their capillaries and their gas exchange units is greater, making oxygenation more difficult. The high surface/volume ratio and the thin fragile skin increase fluid loss and make it more difficult to maintain their body temperature. Removing tape or monitor pads often removes their skin and leaves large weeping abrasions.

To maintain hydration and prevent/treat hypotension, it is often necessary to administer very large volumes of fluid (often >200 mL/kg/day) and vasopressors. Failure to do so results in dehydration and hypotension. However, administering these volumes of fluid may cause a PDA, heart failure, and pulmonary edema.

Table 22.11 Neurological and developmental outcome of micropremies

	24 Weeks	25 Weeks	26 Weeks
No. of infants followed	18	30	38
Neurologically normal	12 (67%)	22 (73%)	34 (89%)
Neurologically suspicious	4 (22%)	2 (7%)	0
Cerebral palsy	2 (11%)	6 (20%)	4 (11%)
Normal cognitive development	5 (28%)	14 (47%)	27 (71%)
Borderline cognitive development	6 (33%)	7 (23%)	7 (18%)
Deficient cognitive development	7 (39%)	9 (30%)	4 (11%)

* Data are presented as n (%).
† Kruskal-Wallis χ^2 = 10.6542, p = 0.005 for cognitive outcome and gestational age.
Source: Reproduced from Piecuch et al [171] with permission of Elsevier.

The normal MAP for infants of 24–26 weeks' gestation is debatable but is grossly the same as the gestational age. Blood pressures measured by non-invasive means are often higher than those measured intravascularly (Table 22.12). Consequently, micropremies may be hypotensive despite having non-invasive MAPs that would be considered normal for gestational age. Determining the state of hydration is more difficult in these patients because they have little or no subcutaneous tissue, their skin is paper thin, and their pulses are frequently difficult to feel. The skin over their fontanelles is level with the outer table of the skull. Their urine output is usually more than 1 mL/kg/h and the specific gravity <1.005.

The anesthesia requirement of micropremies is unknown. However, from previous data it appears that the MAC for halothane is less than 0.55. The dose of sevoflurane is about 60% of that of term infants. Opioids in adequate doses provide anesthesia for these infants; their arterial pressures are more stable than during inhaled anesthesia (Table 22.13). Since these children are often mechanically ventilated after surgery, muscle paralysis with rocuronium 0.3–1.0 mg/kg and anesthesia with fentanyl 10–50 μg/kg provides adequate conditions for any surgery. Although small premature infants have cerebrovascular autoregulation, it is very fragile and easily disrupted. This increases the likelihood of intracranial hemorrhage and CNS injury if the anesthesia is inadequate.

Micropremies have high fluid requirements during surgery. Failure to provide the required amount of fluid results in hypotension and/or shock. All fluid should be administered via calibrated pumps when possible to avoid excess fluid administration.

Where should the surgery for micropremies be performed? Many institutions do it in the NICU because it is easier to take nurses, doctors, and technicians to the NICU than it is to take the patients to the operating room. The infection rate is no different whether the patient undergoes surgery in the ICN or the operating room.

Common surgical problems of micropremies are described elsewhere in this book. PDA is covered in Chapter 27, thoracotomy for pulmonary resection in Chapter 26, hydrocephalus in Chapter 25, and NEC and inguinal hernia in Chapter 31. The following case study illustrates and integrates many of the points discussed above.

Table 22.12 Arterial blood pressures determined non-invasively and from an indwelling arterial catheter: comparison of cuff and intra-arterial pressures

Method	n	MAP	Systolic/diastolic
Cuff	15	32 ± 5	46 ± 5/22 ± 3
Line	15	26 ± 6	38 ± 4/15 ± 3

MAP, mean arterial pressure.

Table 22.13 Vital signs during fentanyl and halothane anesthesia (23–26 weeks' gestation)

	Halothane				Fentanyl		
	HR	MAP	CVP		HR	MAP	CVP
Awake	148 ± 17	31 ± 3	4 ± 1	Awake	152 ± 17	31 ± 3	4 ± 1
0.5 MAC	138 ± 26	28 ± 4	5 ± 1	10 μg/kg	148 ± 26	30 ± 4	4 ± 1
1.0	130 ± 28	27 ± 3	5 ± 2	30 μg/kg	147 ± 13	30 ± 3	3 ± 1

CVP, central venous pressure; HR, heart rate; MAC, minimum alveolar concentration; MAP, mean arterial pressure.

CASE STUDY

The infant was 5 days old at the time we were asked to evaluate him for anesthesia and surgery for NEC. He was born after 29 weeks' gestation and weighed 980 g at birth. On the day of surgery his weight was 840 g, a 15% weight loss from birth. He was severely asphyxiated at birth and required immediate tracheal intubation and assisted ventilation.

His initial blood gas values were pH 7.00, $PaCO_2$ 63 mmHg, and PaO_2 43 mmHg (SaO_2 91%) despite ventilation with 100% oxygen. His mean arterial blood pressure was 16 mmHg at 5 min of age. Ventilation was continued, and 10 mL of whole blood were administered over 5 min, which brought his mean arterial blood pressure to 28 mmHg. His blood gases improved following the transfusion. By 25 min of age the PaO_2 was 165 mmHg (SaO_2 100%), the $PaCO_2$ 33 mmHg, and the pH 7.34. He was transferred to the NICU after the PaO_2 had been reduced to 50 mmHg (SaO_2 97%) by progressively decreasing the FiO_2 to 0.67. A chest radiograph demonstrated classic RDS.

During the next 4 days, the RDS improved and the NICU staff reduced the level of assisted ventilation. On day 1 he received 5% dextrose in water, equal to 50 mL/kg/day, plus electrolytes. This rate was increased to 70 mL/kg/day thereafter. He was covered with clear plastic film to reduce evaporative heat loss and placed under a servo-controlled radiant warmer. He was started on ampicillin and gentamicin shortly after birth because it was uncertain if sepsis was present. When the blood, urine, and CSF cultures failed to demonstrate bacteria on day 3, the antibiotics were discontinued. The initial hemoglobin value was 12.5 g/dL. Because of blood sampling, the hemoglobin concentration decreased to 9.5 g/dL. He was transfused to increase it to 11.2 g/dL on the third day of extrauterine life and started on erythropoietin.

On day 5, he developed abdominal distension, vomiting, and bloody stools following attempts to feed him with breast milk. His RDS, which had been improving, now worsened. He required higher ventilator rates and pressures and a higher FiO_2. An abdominal radiograph showed free air in the peritoneal cavity and a diagnosis of necrotizing enterocolitis was made. At this point, he was scheduled for surgery.

A review of the records and his physical examination demonstrated the following.

Hydration

His skin was pale and mottled and failed to return to its resting position for 8 s after being tented up. The fontanelle was sunken below the inner table of his skull. It took more than 6 s for the skin of his fingers and toes to fill with blood after they were blanched. His extremities were cold from the groins and axillae outward. There were no pulses in his feet or wrists and his groin pulses were markedly diminished. The pulse rate was 150 beats per minute (bpm) and the arterial pressure 40/15 mmHg, with a mean pressure of 23 mmHg. There had been no urine output for 6 h and only 2 mL of urine during the 4 h previous to that. The urine specific gravity of his last sample was 1.028.

Chest findings

He had bilateral rales that did not clear when the ETT was suctioned. Air entry into the upper lobes of the lungs was appropriate but was decreased in the bases. An ETT was in place in the mid-trachea and was fixed securely. The PaO_2 was 72 mmHg (SaO_2 98%), $PaCO_2$ 30 mmHg, and pH 7.21. His base deficit was −15 mEq/L. He was ventilated 20 times per minute with peak pressures of 30 cmH_2O, and PEEP of 5 cmH_2O.

Cardiovascular findings

His heart rate was normal (150 bpm) and there was no murmur or gallop. However, one would expect it to be higher to compensate for the hypotension present. The point of maximal cardiac impulse was in the fourth interspace anteriorly. His pulses were as listed previously.

Abdominal findings

His abdomen was grossly distended. Loops of bowel were visible through the anterior abdominal wall, which was edematous, warm, and tender. Bowel sounds were absent. The liver was not palpable, but it could be percussed 1 cm below the right costal margin.

Laboratory data

His WBC count was 29,300/mm^3 with a shift to the left. Fifteen percent of these cells were bands. His hemoglobin was 14.5 g/dL. His electrolytes showed a sodium concentration of 147 mEq/L, potassium 5.3 mEq/L, chloride 120 mEq/L, and bicarbonate 17 mEq/L. His serum total calcium concentration was 6.3 mg/dL and his ionized calcium was 1.0 mmol/L. The total protein concentration was 4.5 mg/dL.

Discussions with the nurses indicated that the infant would become severely cyanotic and his SaO_2 would abruptly decline to 80–88% when the ETT was disconnected for tracheal suctioning. They also pointed out that his body temperature was labile and that, over the past few hours, he required increasing amounts of exogenous heat to maintain his body temperature in the normal range.

Preoperative preparation

On the basis of this information, it was clear that the infant was severely intravascular volume depleted, although his bodyweight had not changed over the past 12 h, probably because volume had been translocated to the peritoneal cavity and bowel. His peripheral perfusion and arterial blood pressure were decreased. The lack of urine output for 6 h indicated not only that the intravascular volume was decreased but also that he had more than a 70% chance of becoming hypotensive with the induction of anesthesia. The rise in his hemoglobin concentration also indicated intravascular volume depletion. A central venous line was inserted with local anesthesia and was connected to a pressure transducer. The CVP was 0 cmH_2O. Lactated Ringer's solution 10 mL/kg was infused over 15 min which increased his CVP to 2 cmH_2O. Additional lactated Ringer's solution 10 mL/kg raised the CVP to 5 cmH_2O. With this increase, the peripheral perfusion improved and the

mean arterial pressure rose to 32 mmHg. His urine output increased to 2 mL/kg/h, and the urine specific gravity decreased to 1.006. He needed less mechanical ventilation because the PaO_2 rose to 123 mmHg (SaO_2 100%) and the $PaCO_2$ decreased to 18 mmHg. His base deficit rose to −5 meq/L without infusing sodium bicarbonate. His blood glucose concentration was now 128 mg/dL. Calcium gluconate 30 mg/kg was administered to treat the hypocalcemia. Repeat electrolyte determinations showed a calcium concentration of 8.1 mg/dL and ionized calcium of 1.02 mmol/L, a sodium concentration of 140 mEq/L, a potassium concentration of 4.5 mEq/L, and a chloride concentration of 115 mEq/L. His hemoglobin concentration had decreased to 11.0 g/dL after rehydration.

After 90 min of preparation, the patient was transported to the operating room while being manually ventilated at the same pressures, rates, and inspired oxygen concentration used in the nursery.

Surgery

The patient was anesthetized and operated on in his intensive care bed. Anesthesia was induced with fentany 20 μg/kg, and he was paralyzed with pancuronium 0.1 mg/kg. Surgery began within 5 min of his arrival in the operating room. The inspired oxygen was maintained at a level that kept the PaO_2 between 50 and 70 mmHg (SaO_2 91–96%) by using air as the carrier gas and adding oxygen as needed. Oxygen saturation was measured continuously with a pulse oximeter, and the blood gases and pH were measured intermittently, as was the serum glucose. The total calcium concentration was determined once during the 2-h procedure and was found to be 6.9 mg/dL. The concentration of ionized calcium was 1.01 mmol/L. Calcium gluconate 20 mg was given slowly through the central venous line. A blood loss of 15 mL was replaced with packed RBCs, bringing the hemoglobin to 15 g/dL. His IV fluids included 5% dextrose in lactated Ringer's solution 4 mL/h and lactated Ringer's solution without glucose 6 mL/h, which maintained the blood glucose concentration and the arterial and central venous pressures within normal limits. The bowel was resected and an end-to-end anastomosis performed in addition to a diverting colostomy.

His body temperature was maintained within normal limits by wrapping the extremities with sheet wadding, covering his head with a cap, placing a warming pad under him, warming and humidifying the inspired gases to 37°C, warming the infused fluids, and placing him on a forced air warming blanket. At the end of the procedure he was covered with warm blankets and clear plastic film. His ventilation was controlled during transport to the NICU. Mechanical ventilation and paralysis were continued in the postoperative period. Once we were sure that the vital signs and ventilation were adequate, his care was transferred to the NICU staff after a complete report of intraoperative events.

His condition continued to improve over the next week, and he was weaned from mechanical ventilation and fed intravenously through the central venous line. He was discharged from the hospital at 2 months of age neurologically intact and eating well. At 4 months of age, his colostomy was closed, and he has done well since.

Conclusion

This case illustrates how severely dehydrated such premature patients can be and how well they respond to fluid replacement. It also shows how stable they can become once the deficits are replaced.

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A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 23

Anesthesia for the Full-term and Ex-premature Infant

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Introduction

More premature babies are surviving and presenting for surgery in early life with residual effects of prematurity, complications of prematurity and neonatal intensive care, and co-morbidities. The risk of perioperative apnea has been elucidated and anesthetic techniques with modern volatile agents or using awake regional anesthesia have been developed and compared, particularly for inguinal hernia repair. For more major congenital abnormalities such as tracheo-esophageal fistula, abdominal wall defects, and congenital diaphragmatic hernia, the principles of neonatal anesthesia are described in general with particular refinements of technique for each of these major lesions described in detail. The dilemma for the anesthesiologist of having to provide anesthesia for a muscle biopsy in an infant is also discussed. The current neonatal resuscitation algorithm is discussed with information from recent trials of techniques aimed at trying to improve outcomes.

Residua and complications of prematurity

With advances in obstetric and neonatal care, a higher proportion of premature babies are surviving and presenting for anesthesia and surgery in early life [1–3]. Often the survivors have one or more residua of prematurity (Box 23.1) or complications of prematurity or neonatal intensive care unit (NICU) management. The incidence and severity of disabilities tend to be in proportion to the degree of prematurity and length of NICU stay [3,4].

Chronic lung disease

Significant chronic lung disease, or bronchopulmonary dysplasia (BPD), persists in up to 10% of ex-premature infants. The severity and incidence have been ameliorated by antenatal maternal steroid therapy, exogenous surfactant treatment, new ventilatory support strategies to minimize barotrauma and volutrauma, and improved monitoring to prevent oxygen toxicity (see Chapter 22). However, because a higher proportion of premature babies are surviving, the number of babies presenting for surgery and anesthesia with some degree of lung disease has tended to increase. The mechanisms leading to chronic lung disease are detailed in Chapter 7, but a useful clinical classification of severity of BPD [5] highlights for the anesthesiologist those at particular risk of perioperative pulmonary complications such as pneumothorax, interstitial emphysema, bronchospasm, hypoxemia, and pulmonary hypertension. For babies born at less than 32 weeks' gestational age who are assessed at hospital discharge or 36 weeks' postconceptional age (PCA) as having needed supplemental oxygen for at least 28 days, the severity of BPD is *mild* if the baby is now breathing room air, *moderate* if the baby is now needing less than 30% oxygen, and *severe* if the baby now needs 30% oxygen or more and/or positive pressure

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

Box 23.1: Residua or complications of prematurity in the young infant of importance to the pediatric anesthesiologist

- Chronic lung disease
- Airway problems: laryngotracheomalacia, subglottic stenosis
- Apnea: spontaneous and post anesthetic
- Cerebral damage: intraventricular hemorrhage, white matter injury
- Eye problems: retinopathy of prematurity
- Anemia
- Patent ductus arteriosus (PDA)
- Difficult vascular access
- Altered pain threshold

ventilation or nasal continuous positive airway pressure (CPAP) [5]. To minimize perioperative deterioration in lung function, strategies for the anesthesiologist include use of awake regional anesthesia techniques where feasible or, for patients who need general anesthesia, tracheal intubation with controlled ventilation is usually recommended with administration of the minimum effective inspired oxygen concentration to maintain arterial oxyhemoglobin saturation between 92% and 96%, use of minimum effective peak inspiratory pressures, application of low levels of positive end-expiratory pressure (PEEP) to minimize airway collapse, permissive hypercapnia, and relatively slow ventilatory frequency with shorter inspiratory:expiratory (I:E) ratio to minimize gas trapping and overinflation of lung segments. Bronchodilator medication should be continued on the day of surgery and postoperatively. For severe BPD cases, elective postoperative ventilatory support may well be required, although with good regional analgesia, early extubation may be possible for certain operative procedures.

Airway problems

Subglottic stenosis, tracheal stenosis, tracheomalacia, and bronchomalacia may occur in up to 10% of ex-premature babies.

Subglottic stenosis at the level of the cricoid ring is most often due to repeated tracheal intubation, use of too large a tracheal tube, or prolonged tracheal intubation. It may also be associated with gastro-esophageal reflux with repeated spillover of acid or bile into the airway. It may well be that in an infant presenting for elective surgery, consideration should be given to therapy for the subglottic stenosis as a higher priority, depending on its severity, but this decision requires careful discussion. Where anesthesia has to be given, a much smaller tracheal tube diameter than expected may be required and elective steroid therapy given prior to extubation to minimize mucosal edema.

Tracheomalacia may be primary or secondary to extrinsic compression (e.g. vascular ring) or prolonged positive pressure ventilation. The tracheal cartilages may be underdeveloped and the membranous part of the trachea posteriorly may be widened. Tracheal collapse typically occurs on expiration giving expiratory stridor, a seal-like cough, and expiratory wheeze. A similar pattern may be seen with *bronchomalacia* which may be primary or secondary to extrinsic compression, for example from a large pulmonary artery or left atrium. Bronchomalacia may lead to unilateral lung collapse or hyperinflation. Care must be exercised on starting positive pressure ventilation to ensure sufficient end-expiratory pressure to splint the collapsible large airways open on expiration to avoid stacking of breaths and gross hyperinflation of the lung. On extubation of the trachea, babies with tracheobronchomalacia benefit from postextubation CPAP or bilevel positive airway pressure (BiPAP) to minimize postoperative lung collapse and respiratory failure.

Apnea

The mechanisms of apnea in the premature and ex-premature infant are described in detail in Chapter 22. Apnea has long been recognized as an issue for such babies [6]; soon after it was reported, the use of xanthine derivatives such as aminophylline [7] or theophylline [8,9] and their active metabolite caffeine [8–14] as therapy was elucidated. Anesthesiologists became aware of this work when the problem of postoperative apnea was highlighted by landmark reports during the 1980s [15–20] and key dose-finding studies of caffeine as prophylaxis [21,22]. Around this time there was also interest in the use of "awake" regional anesthesia as an alternative to general anesthesia for such cases, particularly for inguinal surgery. Comparative trials of general with regional anesthesia were undertaken and risk factors for postoperative apnea were further elucidated [23–28] most notably in a combined analysis by Cote et al [29]. This made clear that the main risk factors are young PCA, anemia (hematocrit <30%), and nature of the surgery [29]. The importance of this analysis for clinical practice has been immeasurable in helping clarify risks for all ex-premature infants up to 60 weeks' PCA, allowing guidance for monitoring and postoperative care to be developed and helping decision making about day care and time of discharge [29]. Recently, a secondary analysis of apnea from the GAS study (a large randomized controlled trial comparing general anesthesia with awake regional anesthesia for hernia repair in 722 infants) reinforced these principles and risk factors, although it did not find an effect of anemia [30]. The incidence and severity of early apneas in the postanesthesia care unit (PACU) (0–30 min) were lower in the regional anesthesia group [30,31]. In summary, the risk to benefit ratio suggests a default position of considering admission for monitoring of all ex-premature infants who are younger than 60 weeks' PCA as the risk is around 1 in 200 for non-anemic infants who have not exhibited apnea in the PACU until around 55 weeks' PCA (Fig. 23.1).

For those with co-morbidities, those scheduled for more major surgery, those who are anemic with hematocrit <30%, or those who become apneic in the PACU, admission for at least 12 h after the last apneic episode is recommended. Caffeine 10 mg/kg intravenously is recommended [32,33]. These guidelines apply whatever anesthetic technique has been used, including awake regional anesthesia, although some authors have questioned this based on their own local expert practice [34,35]. There have been reports of postoperative apnea in full-term neonates [36–39] and it is prudent therefore to admit and monitor full-term infants of less than 44 weeks' PCA who show any respiratory abnormality during recovery from anesthesia for monitoring for at least 12 apnea-free hours.

Cerebral damage

Residual cerebral damage may be present from birth asphyxia, intraventricular hemorrhage, periventricular leukomalacia, hydrocephalus, and seizures. The mechanisms of cerebral

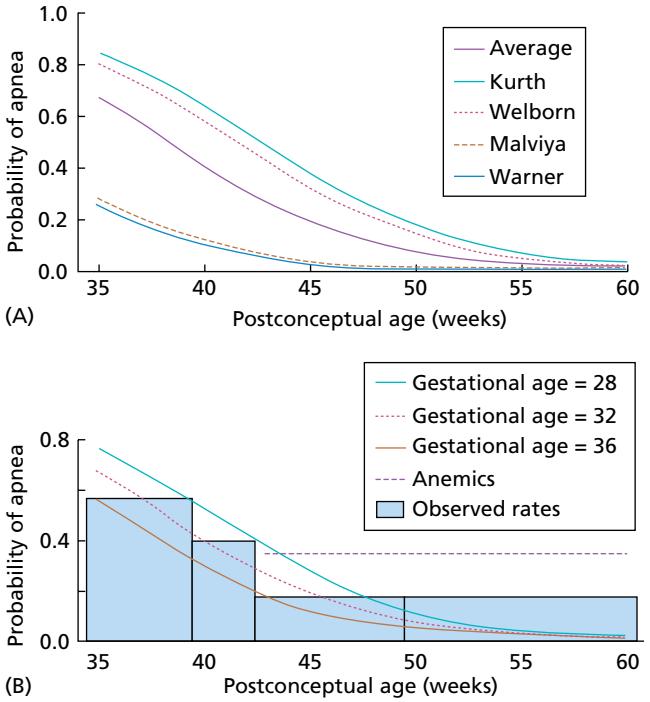


Figure 23.1 Postoperative apnea risk (A) showing variation among centers, (B) by gestational age and postconceptual age and influence of apnea.
Source: Reproduced from Coté et al [29] with permission from Wolters Kluwer.

damage are detailed in Chapter 22. The clinical effects are manifest as cerebral palsy, cognitive and behavioral deficits, hearing loss, and visual impairment. Published longer-term follow-up in 2005 showed that around one in five very premature babies had severe disabilities at age 5 years, and only one in four exhibited normal development [40]. More recent analyses [41] suggest that some centers are achieving much lower prevalence rates of cerebral palsy (as low as 1.9% in very preterm infants born at 20–27 weeks' gestation) and rates of hearing and vision loss as low as 1% [41]. The anesthesiologist should make a detailed preoperative assessment of residual neurological impairment and document this baseline carefully, noting the pathology underlying the deficit, presence of hydrocephalus and/or a ventriculoperitoneal shunt, seizures and their pattern and frequency, and antiseizure medication. These findings may affect choice of anesthetic agent and technique, use of central regional blockade, need for perioperative antibiotics, and decisions about early extubation or elective postoperative ventilatory support. The documentation is also important from a medico-legal perspective to minimize the risk of subsequently being accused of causing neurological damage by anesthetic agents, techniques, or procedures. Anesthetic goals should be to maintain a normal range of blood pressure, carbon dioxide levels, and arterial oxyhemoglobin saturation in the range 92–96%, and in particular to minimize episodes of fluctuation above and below these norms for age.

Eye problems

The mechanisms of retinopathy of prematurity (ROP) are described in Chapter 22. Residual eye problems occur in up to 50% of ex-premature babies [42] and the anesthesiologist needs to be aware of the importance of avoiding hypoxia and hyperoxia and thereby potentially exacerbating the retinal damage. Thus titrating oxygen delivery to maintain stable arterial oxyhemoglobin saturation values of 92–96% and avoiding major fluctuations is recommended [43].

Anemia

The full-term neonate usually has a high hematocrit of 45–55%, depending on the degree of placental autotransfusion at delivery, and this level starts to fall within the first week of life. In response to increased oxygen saturation after birth, the levels of erythropoietin decrease and so replacement of short half-life red blood cells containing fetal hemoglobin with longer half-life cells containing adult hemoglobin is delayed. This results in a low point of hematocrit of 24–30% at around 2–3 months of age. In the premature baby, this low point of hematocrit often occurs earlier (1–2 months of age) and is more profound (21–27%) due to repeated blood sampling and nutritional deficiencies of iron, folic acid, and vitamin E. Many NICUs aim to maintain the hematocrit in the range 36–45%, especially in the sickest infants with severe lung disease, low arterial oxyhemoglobin saturations, and low cardiac output states. A study of preterm babies weighing between 500 and 1300 g showed that restricting blood transfusion resulted in more medical complications (brain hemorrhage, periventricular leukomalacia, and apnea) [44]. Use of exogenous erythropoietin as therapy to increase hematocrit levels in the NICU showed initial promise but resulted in an increased incidence of ROP [45]. For anesthesia, it is important to optimize oxygen delivery. Transfusion with blood containing adult hemoglobin, which releases oxygen to tissues more readily, may be required. There is an important association between the incidence and severity of perioperative apnea and anemia [24,29]. For individual cases transfusion triggers will depend on the starting hematocrit, the likelihood of blood losses, the risk of apnea, and the presence and severity of co-morbidities such as BPD and cardiac disease [46].

Patent ductus arteriosus

PDA is common amongst ex-premature babies and the prevalence has increased with improved survival rates and as a concurrent effect of exogenous surfactant therapy. PDA may still be present when an ex-premature baby presents for other surgery, especially emergency surgery. For elective surgery, consideration should be given to closure of the duct first, by medical therapy (e.g. with indomethacin or ibuprofen [47]), transcatheter device closure, thoracoscopic duct ligation/clipping, or open duct ligation/clipping as appropriate. The presence of a PDA adds risks because of left-to-right shunting with increased lung water, decreased lung compliance, pulmonary hypertension, congestive heart failure, potential for shunt reversal, and increased risk of hypotension, especially diastolic hypotension due to excessive run-off into the pulmonary circuit. Coronary arterial hypoperfusion with myocardial ischemia can occur. The low diastolic blood pressure can also result in splanchnic hypoperfusion. Cardiac output reserves are also diminished for the ill baby (e.g. with necrotizing enterocolitis – NEC) or should bleeding occur during surgery; severe hypotension may occur in such cases.

Difficult vascular access

Ex-premature infants may present serious difficulties with peripheral and central venous access and sometimes also arterial access, particularly if they have had a long and complicated NICU stay. Peripheral veins may have been used repeatedly for blood sampling or cannulated for intravenous fluid and drug administration or for central venous access using a peripherally inserted central catheter (PICC). Central veins may have become thrombosed; this often induces the expansion of collateral venous channels that can be very difficult to cannulate, catheterize, and sustain.

Altered pain perception and responses and tolerance to analgesics and sedatives

Most premature babies are exposed to multiple painful procedures in early life. These can alter sensory perception, including that for pain, and also induce long-term changes in sensory responses and behavior [48–56]. This can manifest clinically as increased sensitivity to pain [56] and increased analgesic requirements or alternatively reduced sensitivity to pain [48]. For the anesthesiologist, this emphasizes the importance of individualizing pain assessment and management [57]. In addition, premature babies may have had considerable exposure to sedative and analgesic drugs during their NICU stay and may have developed tolerance with important effects on their individual dose requirements [58–61].

KEY POINTS: RESIDUA AND COMPLICATIONS OF PREMATURITY

- Chronic lung disease persists in up to 10% of ex-premature infants; incidence and severity have decreased due to modern ventilatory strategies
- Postanesthetic apnea is a risk until approximately 60 weeks' postconceptional age, with young postconceptional age, anemia, and type of surgery as major risk factors
- Cerebral damage, mainly from white matter injury and intraventricular hemorrhage, may manifest as cerebral palsy, cognitive and behavioral deficits, hearing loss, and visual impairment
- Residual eye problems, from retinopathy of prematurity, can occur in up to 50% of ex-premature infants, and avoiding hyperoxia and hypoxia is crucial for those patients at risk

Operating room environment for the neonate

The operating room (OR) environment for the neonate must carry a range of appropriate equipment drugs and fluids and must have appropriate means of maintaining the baby's temperature to minimize heat losses to the environment. The ambient room temperature should be increased to around 23–25°C (80–85°F), anesthetic inspired gases should be warmed and humidified, IV fluids should be delivered via a warming device, and a forced warm air delivery device and/or warming blanket used. Exposure of the baby to the ambient environment should be minimized to avoid heat losses. For awake regional anesthesia, the ambient light level should be lowered and monitor alarm volumes reduced to a minimum. Monitoring equipment should comply with current standards and include electrocardiogram (ECG), precordial/esophageal stethoscope, pulse oximetry, and monitors for blood pressure (BP), temperature, and both inspired and expired anesthetic agent and gas composition. Appropriate sizes of pulse oximeter probes and provision to monitor pre- and postductal saturations should be available. The anesthetic machine should be able to deliver air and oxygen to allow titration of inspired oxygen to avoid hypoxia or hyperoxia and should have a ventilator capable of supporting small infants, including delivery of PEEP if needed. Many pediatric anesthesiologists prefer non-rebreathing circuits but circle systems are now being used more widely. Technological advances allow improved gas monitoring, including accurate tidal volume and pressure measurement, which can be very helpful. Invasive pressure monitoring should be readily available. A full range of airway equipment appropriate for small infants must be immediately available including facemasks, oral airways, laryngeal mask airways (LMAs), suction catheters, stylets, tracheal tubes, and laryngoscope blades. A full range of anesthetic, analgesic, muscle relaxant and resuscitation drugs, and IV fluids (including dextrose 10%) should be immediately available. Peripheral and central venous cannulae of appropriate size and length should be immediately to hand, as should small size intraosseous needles. Many ORs construct a neonatal cart which is checked regularly to ensure all equipment is present in case of an emergency. When difficult intubation is anticipated, an appropriate sized fiberoptic bronchoscope, videolaryngoscope, and intubation aids such as guidewires and airway exchange catheters should be available.

There is a growing acceptance that it may be advantageous for some groups of neonates to undergo surgery outside the OR in the NICU [62,63]. This is not a new concept: for many years surgical ligation of a PDA has been performed in the NICU and found to be safe and cost effective. Repair of congenital diaphragmatic hernias and laparotomies for NEC have also been extensively reported. Ex-premature or low birthweight neonates who are ventilated and/or critically unstable may not tolerate handling and transport to the OR. They may be stable on neonatal ventilators or high-frequency oscillators delivering respiratory parameters that are not possible to achieve on ventilators in the OR. Surgery in the NICU has the advantages of avoiding disruption to ongoing critical care management by maintaining the presence of specialist neonatology input, physiological stability, and a thermoneutral environment, and avoiding the potential risks of inter- or intrahospital transportation such as dislodgement of intravenous or arterial lines or endotracheal tubes.

There are anesthetic and surgical challenges to overcome in facilitating surgery in the NICU. It is an unfamiliar, often hot and poorly lit environment, with minimal space and scavenging for anesthetic machines. Anesthesia is usually delivered intravenously and opioid-based as a result. Access to the neonate in the incubator can be difficult and the lack of space can lead to disruption for the other neonates and their families, and staff on the unit.

The NICU environment must provide the same range of anesthetic equipment, adequate monitoring, and drugs found in the OR. These are often transported from the OR in a prestocked neonatal trolley to minimize delay and avoid the need to retrieve equipment from the OR intraoperatively.

Postoperative extubation versus postoperative ventilation

For the neonate undergoing surgery under endotracheal general anesthesia the question of whether to extubate or not at the end of surgery is a common dilemma. For some infants with major co-morbidity undergoing major surgery the decision may be clear, but for others it may be more difficult. Because of their size and their relative physiological immaturity, neonates and ex-premature infants require careful consideration for postoperative extubation. They are sensitive to many environmental, physiological, and pharmacological factors; before the decision to extubate is taken, the anesthesiologist must take all of these factors into account.

Newborn and ex-premature infants differ physiologically from older children with regard to certain aspects of their respiratory physiology, and this has some bearing on the decision (see Chapters 7 and 22). Minute ventilation and therefore the relative work of breathing in the neonate is three to four times greater than in adults because of much higher oxygen consumption [64]. During normal tidal ventilation, neonatal lungs are close to closing volume [65]. This means more rapid desaturation during apneic episodes. Furthermore respiratory control mechanisms are not fully mature and hypoxia can result in short periods of hyperventilation followed by apnea [66]. An immature respiratory center is also sensitive to the effects of volatile anesthetics and sedative and opioid drugs. These factors mean that, for all but the shortest and non-stimulating procedures, tracheal intubation and controlled ventilation are appropriate.

In general, the attainment of normal physiological parameters is a prerequisite prior to extubation of the ex-premature or term neonate following general anesthesia. The infant should be awake and able to flex the hips and lift the arms. Muscle relaxation should be fully reversed and there should be a regular respiratory pattern with adequate minute ventilation and a satisfactory $PaCO_2$. The infant should also be normothermic as the consequences of hypothermia include delayed drug metabolism, hypoxia, and apnea [6]. Apnea risk is a particularly important factor in those under 44 weeks' PCA) [28] with a lesser but not insignificant risk in those infants born at less than 37 weeks, in whom the risk persists until 60 weeks' PCA [29]. Prophylactic respiratory stimulants such as caffeine or theophylline are highly recommended in these groups, particularly if early extubation is being considered [32,33,67]. Anemia in the immediate postoperative period should be corrected because a hemoglobin level of <10 g/dL has also been shown to significantly increase the risk of postoperative apneic episodes [24], although this was not confirmed in the GAS study [30]. Opioid administration is also a factor that must be considered. The less well developed neonatal blood–brain barrier allows greater penetration of opioids into the cerebrospinal fluid in the newborn [68]. Moreover, an immature respiratory center is more sensitive to the respiratory depressant effects of opioid drugs [69]. The use of shorter acting opioids such as alfentanil or remifentanil may facilitate extubation more easily but transition to ongoing analgesia can be difficult to manage. Care must be exercised with the use of morphine, which has a much longer half-life. Also, its active metabolite morphine-6-glucuronide is excreted renally. Immature renal tubular function in the term and ex-premature infant therefore means there is reduced clearance of morphine and its main metabolites, thus prolonging their effects. For the neonate undergoing surgery, intubation and postoperative ventilation may be mandatory, for example in the case of repair of congenital diaphragmatic hernia or in long-gap esophageal atresia. Significant hypothermia, hypoglycemia, hypocalcemia, or other uncorrected biochemical abnormalities are also indications for postoperative ventilation. Similarly, there is rarely reason to consider extubation in the syndromic infant or in the case of major thoracic, abdominal, or airway surgery. However early extubation, either in the OR or within 3 h, has been found feasible in some neonates undergoing cardiac surgery [70]. The advantages are thought to be reduced postoperative complications, a shorter hospital stay, and reduced costs. This is only achievable in some centers and with a dedicated and highly involved multidisciplinary team approach.

For infants undergoing some abdominal or thoracic procedures, the choice of anesthetic technique can influence the decision to extubate post procedure. Desflurane, with its low blood/gas and tissues/gas solubility coefficients has a very rapid offset and while it may be irritant and unsuitable for spontaneous ventilation it is a very useful agent in the ventilated neonate and is the volatile agent of choice for maintenance of anesthesia when extubation is required. The addition of local anesthetic techniques to supplement general anesthesia may reduce or eliminate the need for opioids. Inguinal hernia repair, for example, can be achieved easily without opioids by either supplemental ilioinguinal nerve blockade or caudal epidural anesthesia. Epidural techniques are appropriate in many scenarios and often allow a reduction in opioid administration. Caudally sited epidural anesthesia is a straightforward procedure and is useful for both abdominal and thoracic surgery depending on level. In esophageal atresia repair it has been shown to reduce the need for postoperative ventilatory support [71].

KEY POINTS: OPERATING ROOM ENVIRONMENT AND POSTOPERATIVE EXTUBATION VERSUS VENTILATION

- The OR environment must be fully prepared with equipment and drugs for small neonates
- Temperature maintenance with a warm OR, forced air warming, and warmed IV fluids is essential
- Careful attention to stability during transport to and from the OR is crucial
- Bedside surgery in the NICU is safe and cost effective for many conditions
- Early tracheal extubation is desirable for many full-term neonates; full reversal of neuromuscular blockade, adequate respiratory effort, and emergence need to be ensured

Inguinal hernia

Inguinal hernias are found in up to one-third of ex-premature neonates [72] and it is recommended that they are repaired surgically in early life because of the risks of incarceration of bowel in the hernia sac (bowel obstruction, bowel infarction) and testicular infarction. The need for early surgery has to be balanced against the risks of anesthesia, perioperative apnea, and medical co-morbidities, including the residual effects of prematurity. The optimal timing of surgery [73] has to be decided on an individual case basis but some hernias need urgent repair, particularly those that are irreducible, those associated with frank signs of bowel obstruction, or those that are very large where the testicular blood supply may be compressed or compromised. The decision-making process has been affected by recent concerns about developmental neurotoxicity of general anesthetic and sedative agents [74–76]. This has led to renewed interest in awake regional anesthesia techniques [77–92]. The GAS study [76] reported no difference in neurodevelopmental outcome at 2 years of age (a secondary outcome milestone) when comparing sevoflurane anesthesia with awake regional anesthesia [93]. Some units now favor delaying repair but the risks of leaving hernias unrepaired are significant in an already vulnerable population [73]. Surgical techniques and attitudes to prophylactic repair of the contralateral side are evolving with the advent of laparoscopy [94,95]. Many centers now undertake these procedures entirely laparoscopically, while others use the technology to inspect the contralateral side. Open repair is still widely practiced and gives good results [96]. All surgical repair techniques have complications (infection, bleeding, testicular infarction, bowel perforation, hernia recurrence) and opinion is still divided as to whether open surgery or laparoscopy has a lower incidence of these various problems [94]. Often the hernia repair is scheduled toward the end of the baby's hospital stay prior to discharge home from NICU or the specialist children's center, although some babies go home first and are then readmitted at a slightly later stage if the hernias are deemed to be low risk.

The baby should be assessed for residual effects or complications of prematurity or NICU care as noted previously and in particular for the known risk factors related to PCA, anemia, co-morbidities [29] and nature of the hernia (elective, emergency, unilateral, bilateral, very large, incarcerated, or complex) and surgical technique (open, laparoscopic, open with contralateral inspection) [94]. Whichever anesthetic technique is used, general anesthesia or awake regional anesthesia, the earlier guidance about monitoring and aftercare should be used. Consider the use of caffeine 10 mg/kg IV if the baby is not already receiving it. The choice of anesthetic technique should be discussed in detail with the surgical team and with the parents and informed consent obtained.

Anesthetic and analgesic techniques

There are two main groups of techniques, both with a considerable evidence base behind them, namely awake regional anesthesia and general endotracheal anesthesia (usually with a regional analgesic component).

Awake regional anesthesia

This may be provided by a single-shot spinal (subarachnoid) injection of local anesthetic [35,78–80,83,84,87,88,90,97–108], a single-shot caudal (epidural) injection of local anesthetic [20,79,85,87,88,109,110], a combination of these (see Case study at the end of this chapter), or a catheter-based caudal anesthetic (single or multiple shots and/or continuous infusion of local anesthetic) [77, 91]. Plain local anesthetic solutions are preferred for ex-premature and term neonates because additives such as clonidine can produce an increased apnea risk [111–115]. However, epinephrine has been shown to prolong spinal anesthesia with tetracaine by about one-third. The local anesthetic agents used include tetracaine [100], bupivacaine [78,80,116], ropivacaine [108,116], and levobupivacaine [116] (see Table 23.1).

Spinal anesthesia has the advantage of quicker onset than a caudal but duration may be shorter and the institution of the block can be technically challenging with a failure rate of up to 15%. In the GAS study, the only predictor of failure was a bloody tap on first attempt at lumbar puncture [117]. The doses in Table 23.1 typically give a block adequate for inguinal surgery lasting around 1 h but a tetracaine spinal may extend this by a further hour [79]. Additionally, even with a successful block, the conversion rate to general anesthesia because of inadequate surgical conditions is as high as 20% [117]. Supplementation of the spinal block with any sedative or anesthetic agent results in loss of the benefits in terms of reduced apnea. Sucrose analgesia is a useful adjunct and often helps settle a restless baby [118]. Some authors feel that a caudal is more likely to succeed, and more anesthesiologists are familiar with caudal blocks so the disadvantage of slow onset is countered by improved reliability and longer duration of action [79].

Table 23.1 Recommended doses of local anesthetic agents for awake regional anesthesia for inguinal hernia repair in neonates

Local anesthetic	Concentration	Dose (mg/kg)	Reference
Spinal anesthesia			
Tetracaine	10 mg/mL hyperbaric	1	[100]
Bupivacaine	5 mg/mL hyperbaric	0.3	[78]
Bupivacaine	5 mg/mL isobaric	1	[116]
Levobupivacaine	5 mg/mL isobaric	1.2	[116]
Ropivacaine	5 mg/mL	1	[108,116]
Caudal anesthesia			
Bupivacaine	2.5 mg/mL	2	[79]
Levobupivacaine	2.5 mg/mL	2	[214]
Ropivacaine	2 mg/mL	2	[214]

General anesthesia

General endotracheal anesthesia could be regarded as the standard technique but early study results were confounded by use of older volatile agents such as halothane [100]. With newer volatile agents such as sevoflurane and desflurane showing promise for infant anesthesia in terms of speed of recovery and low incidence of postoperative respiratory complications [119–121], a head-to-head study of spinal versus sevoflurane anesthesia for hernia repair in ex-premature infants [104] favored spinal anesthesia in terms of reduced early respiratory adverse events but there were a number of failures to secure a spinal block which gave cause for concern. The GAS study results confirmed these findings [30,31,93]. General anesthesia with modern volatile agents, supplemented by local anesthetic infiltration, peripheral nerve block, or a caudal is therefore a more reliable and flexible technique and may be essential in certain cases, in particular incarcerated, complex, or very large bilateral hernias. With an increasing trend toward laparoscopic repair, it may well be that general anesthesia for such cases will be needed more often in the future. A number of initiatives to improve the quality and safety of general anesthesia in infants are recommended, such as Safetots (www.safetots.org), which focuses on maintaining physiological norms for age throughout the perioperative period and ensuring appropriate facilities and trained staff [122]. The importance of this approach is emphasized by the GAS study secondary results showing significantly more hypotension and interventions to treat hypotension in the general anesthesia group compared with the regional anesthesia group [123].

KEY POINTS: INGUINAL HERNIA

- Each baby should be assessed for residual effects or complications of prematurity or NICU care and for the known risk factors related to postconceptual age, anemia, co-morbidities and nature of the hernia (elective, emergency, unilateral, bilateral, very large, incarcerated, or complex) and surgical technique (open, laparoscopic, open with contralateral inspection)
- Awake regional anesthesia has advantages in some cases but should only be used by experts with adequate training and ongoing experience in the technique
- If awake regional anesthesia is used, there should be a clear plan in case of failure of the technique and should surgery become more complex or extensive
- For cases under general anesthesia, an appropriate regional block should be used as part of the technique unless specifically contraindicated

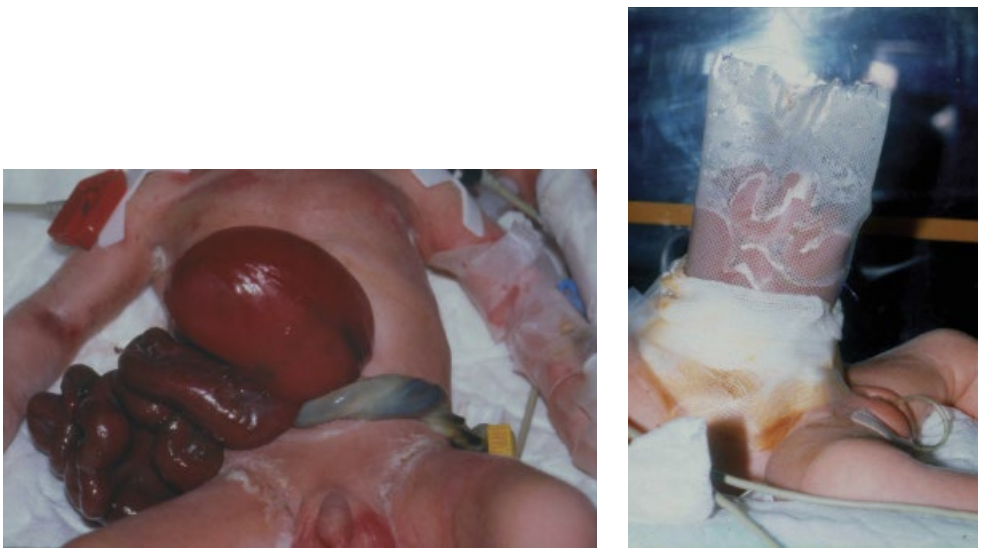
Abdominal wall defects

Abdominal wall defects are congenital abnormalities that are usually detected antenatally by fetal ultrasonography. Gastroschisis and omphalocele are the most common defects, resulting in herniation of viscera through a defect in the upper or lower abdominal wall [124,125]. Although the anesthetic management of these conditions is essentially the same, the two conditions have significant embryological and clinical differences [126].

Gastroschisis

The incidence of gastroschisis is approximately 1 in 3000–8000 livebirths. It is more common in mothers aged <20 years, the infant tends to be born prematurely with a low birthweight, and in recent years the incidence has been rising for reasons unknown [127–129]. Specialist antenatal and postnatal care results in a survival rate of over 90%. Gastroschisis is a congenital defect of the abdominal wall resulting in herniation of the abdominal contents, most commonly the small and large intestine (Fig. 23.2).

The defect is usually on the right side of a normally developed and positioned umbilical cord, and the viscera are not enclosed in a peritoneal sac. The vertical opening is approximately 2–5 cm in length making herniation of other organs,



(A) (B)

Figure 23.2 (A) Gastroschisis. (B) Silo for gastroschisis.

such as the liver, unusual. The herniated intestine often appears dilated, foreshortened, and edematous, and is covered in a thick inflammatory fibrin peel, likely due to exposure to amniotic fluid *in utero*. The intestine is often functionally abnormal and this may be complicated by the presence of intestinal atresia, stenosis, or malrotation [130]. Associated congenital anomalies are uncommon in gastroschisis, however initial routine investigations should aim to exclude potential cardiac abnormalities. The etiology of gastroschisis is not certain but is thought to involve vascular disruption of either the right umbilical vein or right omphalomesenteric artery. The result is paraumbilical ischemia and atrophy of the layers that form the anterior abdominal wall at the base of the umbilicus [131].

Following delivery the initial priorities for gastroschisis must focus on ensuring the newborn has a safe and patent airway, ventilation and oxygenation are not compromised by the defect, the exposed bowel is protected, and fluid and heat loss are minimized and adequately managed. Reduction of the abdominal contents should take place urgently within hours of delivery to minimize the risk of volvulus, ischemia, and infection. A nasogastric tube should be inserted to decompress the bowel, minimizing any splinting of the diaphragm, and reducing the risk of regurgitation and aspiration. If signs of respiratory distress are evident or the newborn requires large volumes of fluid resuscitation then endotracheal intubation and ventilation are necessary.

The exposed bowel should be covered and supported using a sterile plastic wrap or a clear polythene bag to cover the lower limbs and abdomen to minimize fluid and heat loss.

The newborn should be dried and then placed under a radiant heater or in a heated incubator. Patients with gastroschisis should be nursed on their right side in a lateral decubitus position to enhance venous return from the gut and avoid vascular compromise. Intravenous access is required early to allow fluid resuscitation, administration of broad-spectrum antibiotics, blood sampling, and cross-match if going to surgery. Umbilical vessel catheterization is contraindicated. Third space losses in gastroschisis can be substantial and require fluid resuscitation with isotonic solutions: 0.9% normal saline, Hartmann's solution, PlasmaLyte®, 5% albumin, blood, or blood products. Boluses of 20 mL/kg should be given and the adequacy of resuscitation regularly monitored. Regular assessment of capillary refill, core–peripheral temperature gradients, heart rate, urine output, and evidence of correction of acid–base disturbance will help guide the resuscitation efforts. Insertion of a peripheral arterial line is invaluable for repeated sampling to detect acid–base or electrolyte changes during the resuscitation and perioperative period.

Surgical management of the newborn depends on the size of the defect. Small defects can be closed by primary closure in the OR under general anesthesia or in the NICU without an anesthetic. If the defect is large, concerns arise about the effects of returning the abdominal viscera into a relatively small abdominal cavity, resulting in raised intra-abdominal pressure and abdominal compartment syndrome (ACS). Raised intra-abdominal pressure reduces venous return from compression of the inferior vena cava, decreasing cardiac output. Perfusion of the renal and splanchnic circulation is impaired, potentially leading to renal failure and bowel ischemia causing intestinal perforation, NEC, and a metabolic acidosis. Raised intra-abdominal pressure increases tension on the wound, causing dehiscence, and also results in splinting of the diaphragm, causing respiratory failure. The safety of primary closure can be assessed intraoperatively by measurement of intragastric, bladder, and central venous pressures or changes in ventilatory pressures as an indirect way of measuring intra-abdominal pressure. Intragastric or intravesical pressures less than 20 mmHg were found to result in successful primary closure and no ACS in neonates with gastroschisis [132,133]. Peak plateau respiratory pressures should be kept below 25 cmH_2O [134]. Gastric tonometry and pulse oximetry have also been used to help predict the onset of ACS [135,136]. If the surgeon is unable to perform a primary closure then a staged reduction is undertaken. The neonate may initially be taken to the OR and fitted with a protective Silastic® silo, or in some cases the silo may be applied in the NICU without general anesthesia. The silo is suspended above the incubator, allowing gravity to ease the viscera back into the abdominal cavity over the next 5–7 days. Each day the silo is gradually reduced in size, minimizing the risk of ACS. Once reduced, the neonate is returned to the OR for surgical closure of the abdominal wall defect.

Important anesthetic considerations include the following.

1. Ensure the baby is adequately resuscitated and preoperative tests are performed before coming to the OR.
2. Actively warm the neonate during transfer to the OR in their incubator and on arrival in the OR with overhead radiant heaters, warm air blankets on the OR table, intravenous fluid warmers, and humidified and warmed anesthetic gases. Monitor core and peripheral temperature perioperatively.
3. Aspirate the nasogastric tube before induction in left lateral, right lateral, prone, and supine positions.
4. Induction may be a rapid-sequence induction (RSI) or modified RSI. Sevoflurane induction may be performed and atracurium, vecuronium or rocuronium used for muscle relaxation prior to intubation.
5. Nitrous oxide should be avoided to prevent further intestinal distension.
6. Provide analgesia using morphine or fentanyl; for smaller defects where early extubation is anticipated, a regional block technique may be used.
7. Maintenance fluids (containing 10% dextrose) supplemented with boluses of albumin 5% or other isotonic solutions should be titrated according to the cardiovascular status of the neonate.
8. In addition to routine monitoring of intragastric or intravesical pressures, urine output and lower limb oxygen saturations may be measured to assist in deciding whether a primary closure is possible.
9. An intra-arterial cannula is useful for regular blood sampling and acid–base monitoring. Central venous cannulation, either conventional via internal jugular or subclavian routes, or PICC lines, is necessary for large defects where repeat procedures or prolonged total parenteral nutrition (TPN) are required.
10. The majority of neonates are returned to NICU intubated, ventilated, paralyzed, and sedated for further monitoring and ongoing management. They are ventilated until the bowel has settled back into the abdomen. TPN feeds, antibiotics, and muscle relaxants are given.

In some centers reduction may take place in the NICU without general anesthesia. NICU reduction is carried out in newborns who are stable and uncomplicated, i.e. absence of perforations, volvulus, atresias, and obstruction [137,138]. The introduction of a spring-loaded silo that can be fitted at the bedside without any sutures or anesthesia has permitted staged closure in the NICU. When the reduction is complete the umbilicus is often used to plug the defect.

Spinal anesthesia has been described as a technique suitable for primary surgical closure of gastroschisis, however its short duration of action and unpredictable block level was less than ideal [139]. Similarly, a combined spinal–epidural technique has also been described but was found to be time-consuming and often technically difficult [140]. A recent small case series has advocated the use of caudal anesthesia as an alternative to general anesthesia [141]. The authors suggest it may be useful in high-risk cases to avoid general anesthesia and the subsequent requirement for postoperative mechanical ventilation. They also suggest it may be a useful technique in areas of limited resources.

Outcome in gastroschisis is generally good unless complicated by intestinal atresia, stenosis, perforation, NEC, volvulus, sepsis, rare associated cardiac abnormalities, or problems relating to prematurity (respiratory distress syndrome, intraventricular hemorrhages) [130].

Omphalocele

Omphalocele has an incidence of 1in 5000 livebirths. It is an abdominal wall defect where the abdominal viscera herniate into the base of the umbilical cord through the umbilical ring. It is thought to result from failure of the midgut to return to the abdominal cavity around week 10 of gestation causing incomplete closure of the anterior abdominal wall around the umbilicus. Unlike gastroschisis, the viscera are covered by a membrane and the bowel looks normal. Occasionally the peritoneal sac may rupture and can resemble gastroschisis although examination of the intestine helps differentiate these two conditions. The herniation may be a small defect 2–5cm in diameter (exomphalos minor) or may be large (greater than 10 cm) involving liver and spleen, with poorly developed abdominal and thoracic cavities and pulmonary hypoplasia (exomphalos major) (Fig. 23.3). In patients with a large omphalocele, the position of the viscera and liver may compress the inferior vena cava in the supine position and so preferentially these infants require to be nursed on their left side. A ruptured omphalocele can result in considerable third space fluid loss.

Associated congenital abnormalities are much more common than in gastroschisis with at least 60% of infants born with omphalocele having at least one associated anomaly. These may be cardiac in origin (30–40%), chromosomal abnormalities (trisomy 13, 18, or 21), cloacal or bladder extrophy, or Beckwith–Wiedemann syndrome (macroglossia, organomegaly, hypoglycemia, gigantism, and congenital heart disease) [142]. Rarely, omphalocele may be part of the thoraco-abdominal pentalogy of Cantrell with a cleft sternum, anterior diaphragmatic hernia, heart defects, and an absent pericardium [143]. Given that associated anomalies are more common in this condition, a thorough preoperative examination with appropriate investigations (chest x-ray, cardiac echo, renal ultrasound, and routine blood investigations) should be performed before surgical correction.

Anesthetic management of omphalocele is very similar to that for gastroschisis. Unless the membrane is ruptured, omphalocele repair is less urgent. Defects without rupture of the membranous sac may be allowed to epithelialize on the ward using topical agents (silver sulfadiazine or antibiotic preparations) and a silo, avoiding any surgical intervention in the initial stages. This may take several weeks to months, after which the infant will return to surgery for repair of the ventral hernia defect [144]. Care must be taken for cases that come to the OR for reduction or silo fitting if the liver is herniated. Damage to the liver parenchyma or compression of the hepatic veins can result in dramatic periods of cardiovascular instability. Outcome in omphalocele is mainly dependent on the severity of additional abnormalities and chromosomal defects. Infection, surgical complications, low birthweight, hernia rupture, and intestinal obstruction also contribute to mortality rates.

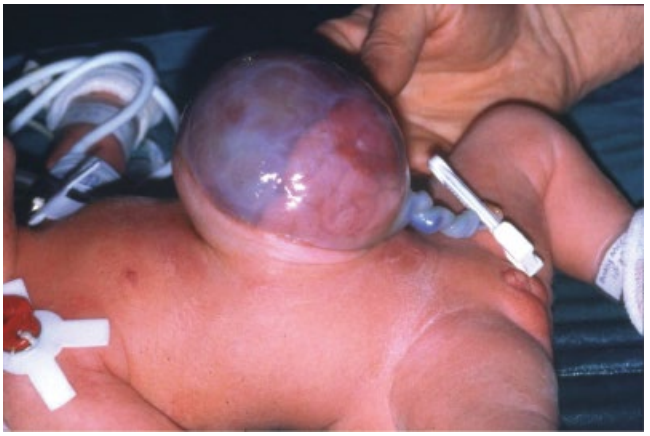


Figure 23.3 Omphalocele (exomphalos major).

Many centers are now utilizing non-operative delayed closure of giant omphaloceles, consisting of gradual intra-abdominal reduction followed by delayed epithelialization of the defect, facilitated by silver sulfadiazine or povidone–iodine ointment. A systematic review of this approach versus standard operative treatment revealed similar mortality rates with non-operative closure (21.8% versus 23.4% in the surgical group) and shorter time to full enteric feedings (14.6 versus 23.5 days). This approach has reduced the number of these infants undergoing primary surgical closure [145].

KEY POINTS: GASTROSCHISIS AND OMPHALOCELE

- Gastroschisis is usually right-sided, the umbilical cord is not involved, the intestines are not covered by peritoneum, and the patient usually has no other congenital anomalies except that prematurity is common
- Omphalocele herniates into the base of the umbilical cord, intestines are covered by a membrane, and 60% of patients have at least one associated anomaly, including cardiac in 30–40%
- Delayed closure and use of silo techniques are becoming the norm for management of abdominal wall defects
- In addition to routine monitoring of intragastric or intravesical pressures, urine output and lower limb oxygen saturations may be measured to assist in deciding whether a primary closure is possible

Esophageal atresia and tracheo-esophageal fistula

Esophageal atresia (EA) encompasses a group of congenital anomalies in which there is interruption of the continuity of the esophagus. In 86% of cases this coexists with a distal tracheo-esophageal fistula (TEF), while in 7% there is no fistulous connection. In 4% of cases there is a TEF but no EA. EA occurs in around 1 in 2500–3000 livebirths. In less than half of these the condition exists in isolation while more than 50% occur in the presence of other congenital anomalies, the commonest being one or more of those associated with the VACTERL group of anomalies (vertebral, anal, cardiac, tracheo-esophageal, renal and limb defects). The presence of a major cardiac anomaly reduces an almost complete survival rate to around 80%. Low birthweight is also associated with a survival rate of around 80%, while the presence of both of these risk factors together reduces survival to 30–50% [146]. Respiratory insufficiency, however, is the single most significant risk factor affecting outcome [147]. Together these factors provide a significant challenge to the anesthesiologist [148,149].

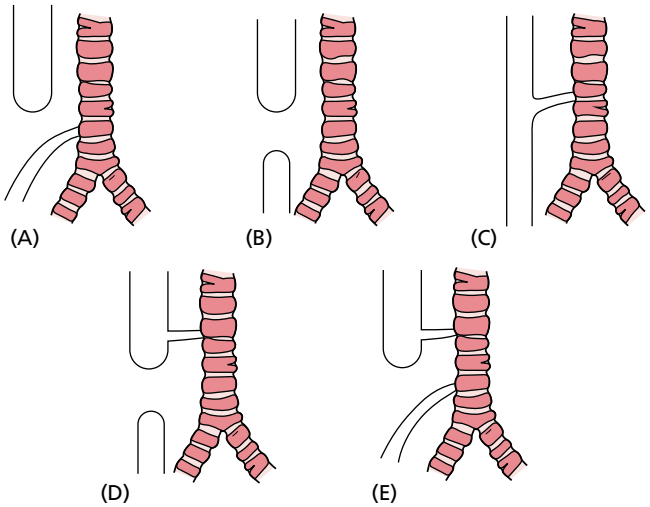


Figure 23.4 Esophageal atresia and tracheo-esophageal fistula variants. (A) The commonest arrangement with a blind upper esophageal pouch and a distal tracheo-esophageal fistula (Gross type C, Vogt type 3B). (B) Proximal and distal esophageal stumps with a missing segment and no TEF (Gross type A, Vogt type 2). (C) H-type fistula (Gross type E). (D) Proximal esophagus meets distal trachea with distal esophageal stump (Gross type B, Vogt type 3A). (E) Proximal esophagus terminates on lower trachea with distal esophagus arising from carina (Gross type D, Vogt type 3C).

Clinical features

Two classification systems are in use today, the first being that proposed by Vogt in 1929, later modified by Gross in 1953. These are summarized in Table 23.2.

The most commonly occurring defect is Gross type C (Vogt 3B), which accounts for 86% of EAs (Fig. 23.4). These classification systems are, however, not comprehensive, and variations other than those described can occur.

Diagnosis

Suspicion may be raised by antenatal ultrasound scan at around 18 weeks' gestation. This may show an absent or small gastric bubble. The incidence of EA is also increased in the presence of polyhydramnios. The diagnosis may be confirmed at birth in these babies by failure to pass a nasogastric tube beyond 9–10 cm from the mouth. This is usually confirmed by a plain abdominal and chest radiograph that may reveal other associated anomalies such as vertebral or rib abnormalities or the "double bubble" associated with duodenal atresia. However, if not suspected prenatally, EA may not manifest itself until feeding begins, whereupon the baby may cough, choke, and become cyanosed. Failure to recognize the condition swiftly can result in the development of aspiration pneumonitis, and dehydration can result due to accumulation of saliva and disturbed swallowing. Initial preoperative surgical management involves the passage of a suction catheter, often a radio-opaque double-lumen tube (Replogle tube) into the blind-ending pouch for continuous irrigation and suction.

Table 23.2 Classification of esophageal atresia and tracheo-esophageal fistula

Gross	Vogt	Description
	Type I	Esophageal agenesis (not included by Gross). No fistula present
Type A	Type 2	Proximal and distal esophageal stumps with a missing mid segment. No fistula present
Type B	Type 3A	Proximal esophagus meets lower trachea with distal esophageal stump
Type C	Type 3B	Proximal esophageal atresia. Esophagus ends in blind loop superior to sternal angle with the distal esophagus arising from the lower trachea or carina
Type D	Type 3C	Proximal esophagus terminates on lower trachea or carina with distal esophagus arising from carina
Type E (or Type H)	–	Type D variant where the esophagus is continuous but the presence of a fistula creates the appearance of the letter H
Type F	–	Esophageal stenosis

Preoperative evaluation

The baby presenting with EA/TEF presents many challenges for the anesthesiologist. First, due to the large variation in the anatomy of these lesions, correct placement of the endotracheal tube may be difficult. Furthermore, prematurity of 34 weeks' gestation or less is present in 12% of babies presenting with esophageal atresia [150] and may result in moderate to severe neonatal respiratory distress syndrome. Associated anomalies may also impact significantly on both the difficulty of the anesthetic and the outcome for the patient. Cardiovascular anomalies account for 29% [151] and have been shown to be the single most common mortality-related association in EA [152]. Of the other associated anomalies, anorectal defects comprise 14%, genitourinary 14%, gastrointestinal 13%, vertebral/skeletal 10%, respiratory 6%, genetic 4%, and others 11% [151]. Preoperative evaluation of infants with EA should include a detailed history of the neonatal course including delivery. A history of polyhydramnios may also indicate possible renal anomalies and is more common where there are associated chromosomal abnormalities such

as Down syndrome or Edwards syndrome. Major neurological anomalies may impair fetal swallowing, also resulting in polyhydramnios. If there is no antenatal suspicion and the infant presents later, a feeding history should be obtained with special attention being paid to episodes of cyanosis or choking that may indicate aspiration and the possible development of aspiration pneumonia. Preoperative preparation by this time will have established a blind-ending esophagus with continual suction and irrigation of the pouch being provided, preferably by a Replogle tube. A full anesthetic history should also be obtained from the parents regarding any significant family reactions to anesthesia. A plain radiograph of the chest and abdomen will confirm the tip of the suction catheter proceeding no further than the upper mediastinum while gas in the stomach is significant in that it confirms the presence of a TEF. Absence of gas suggests an isolated atresia. A clinical examination of the neonate should have established any dysmorphic features and indicated the presence of any major cardiac anomaly. However, cardiac echo is required routinely as a preoperative investigation in these cases. This will define any structural abnormality of the heart but may also reveal a right-sided aortic arch, which occurs in 2.5%. This has implications for patient positioning and surgical approach [153] and may also significantly affect ventilation. A congenital cardiac lesion producing high pulmonary blood flow is unlikely to pose significant physiological problems during the first few days after birth as pulmonary vascular resistance remains high initially. These patients can usually proceed safely for surgical correction. However, patients who have lesions with significant right- or left-sided obstructive components may have either a systemic or pulmonary circulation that is ductus arteriosus dependent. Babies with duct-dependent circulation have been shown to have a significantly increased risk of mortality [154]. In these cases the duct can be kept open with an infusion of prostaglandin E_1 and if the baby remains stable and in good condition, surgery may proceed. A small number of patients will present in poor condition with a closed or closing duct. In these cases resuscitation is often required and surgery needs to be delayed. Rarely, such babies will require a palliative shunting procedure or cardiac repair prior to surgery for EA [155]. A renal tract ultrasound scan is required due to the associated incidence of genitourinary anomalies. Blood biochemistry and hematology should be ascertained and blood should be cross-matched for surgery. Assessment of the respiratory system is paramount. The presence of respiratory distress is a significant prognostic indicator [147] and has an important bearing on the conduct of anesthesia in particular with regard to the principle of maintaining low airway pressures. Preoperative oxygen saturation should be measured and increased oxygen requirement noted.

Conduct of general anesthesia

Preparation of the operating environment is as for any other small baby. However, particular attention needs to be paid to the ambient temperature. This may need to be increased in the case of the premature infant. A heated warming mattress, heated and humidified breathing circuit, and warmed intravenous and irrigation fluids will help to prevent heat loss. Intravenous access would ordinarily have been established prior to surgery as these babies are unable to feed. This can be used for maintenance fluids with 5–10% glucose where required. A second IV line is required for replacement therapy, and this should be of sufficient caliber to allow for rapid replacement of blood loss if required. In addition to the application of standard monitoring, invasive arterial pressure monitoring is invaluable as it allows for real-time measurement. This is especially so in the case of aberrant cardiac or great vessel anatomy where surgical access may cause hemodynamic compromise. It also allows for easy blood sampling intraoperatively. This can be particularly useful where significant respiratory compromise exists and allows for rapid and accurate assessment of gas exchange and acid–base status. Central venous access is not usually required but may be necessary in the event of failure to establish adequate peripheral intravenous access.

The major consideration of both anesthetic and surgical management of the neonate with EA and TEF is ventilation of the lungs without ventilation of the fistula (Fig. 23.5). Endotracheal tube misplacement can result in undesirable consequences such as massive gastric distension and resulting respiratory and cardiovascular compromise. Even with a correctly placed endotracheal tube, poorly compliant lungs and a large distal fistula can result in selective passage of anesthetic gases into the gastrointestinal tract resulting in hypoventilation, hypercarbia, and a respiratory acidosis [156]. The interplay between the variable anatomy of the defect, pre-existing co-morbidity, and anesthetic technique may be unpredictable. As a result, techniques have focused on the avoidance of muscle relaxants and positive pressure ventilation until ligation of the fistula is achieved [157]. Traditionally, intubation may have been performed awake but in the preterm neonate this is associated with an increased risk of intraventricular hemorrhage [158].

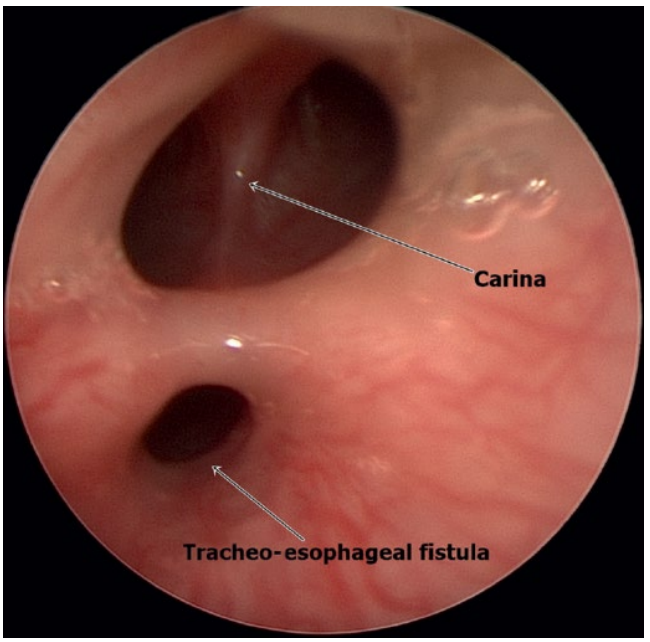


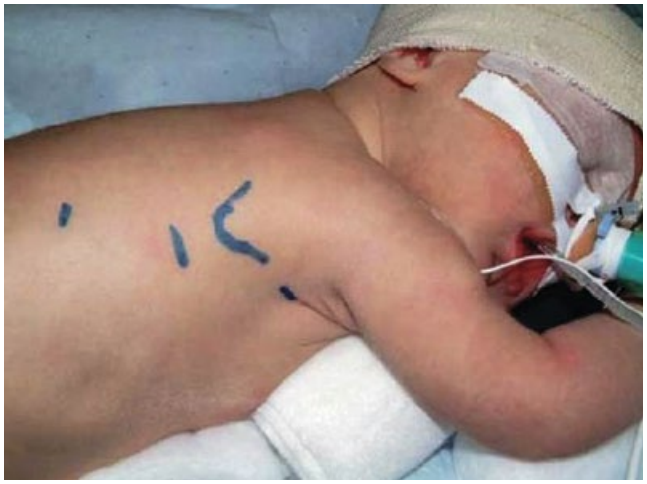
Figure 23.5 Bronchoscopic view of a large tracheo-esophageal fistula (TEF) at the level of the carina. This size and position of the TEF is associated with a higher incidence of ventilation difficulties. See text for further details. *Source*: Reproduced from Teague and Karpelowsky [167] with permission from Elsevier.

One recognized technique is induction of general anesthesia by inhalation with the patient in a semi-supine position. Once adequate depth of anesthesia is achieved, and with the patient spontaneously ventilating, laryngoscopy should be performed and the vocal cords sprayed with no more than 3 mg/kg of lidocaine. An appropriately sized endotracheal tube is then passed through the cords and beyond the carina, aiming for endobronchial intubation. This is then confirmed by auscultation and the tube is withdrawn until ventilation is just heard on both sides. At this point it is possible to confirm the position of the endotracheal tube by passage of a flexible bronchoscope through it. If all is well then a muscle relaxant may be administered and the patient positioned for surgical repair. This technique is limited, however, by the assumption that the fistula is proximal enough to allow passage of the endotracheal tube beyond it. It also may not be an adequate technique where there is a large fistula. In one series, 11% of fistulae were at or below the carina, with a further 22% being within 1 cm of it [159]. Even with such a lesion it may be possible to achieve adequate ventilation initially, with problems only being encountered on repositioning of the patient or during surgical manipulation, particularly compression of the right lung. Additionally the patient's condition may preclude spontaneous ventilation, requiring that muscle relaxation be instituted followed by gentle positive pressure ventilation. It is, however, in the preterm neonate with respiratory distress that this is most problematic. Poorly compliant lungs and a large distal fistula can mean an easy egress of ventilator gases into the stomach with resultant compromise in ventilation [156]. With progressively increasing gastric distension the stomach may rupture, resulting in a tension pneumoperitoneum which further impairs ventilation [160]. The traditional approach in this instance would be to perform an emergency gastrostomy. However this often worsens the situation as the sudden reduction in intragastric pressure further facilitates escape of ventilator gas through the fistula. Resuscitation in this instance is often ineffective until leakage of gas through the esophagus is controlled [161]. Placement of a 2 Fr or 3 Fr Fogarty embolectomy catheter (Baxter Healthcare Corporation, Irvin, CA, USA) through a rigid bronchoscope to occlude the fistula in a neonate with severe respiratory compromise was first described in 1982 [162]. Since then, routine rigid bronchoscopy has become standard practice for some institutions as part of the airway management in TEF, with 18% of patients in a retrospective review requiring the insertion of a Fogarty catheter [157]. In this same series, ventilation difficulty was only encountered with a fistula >3 mm in diameter at or near the carina. Smaller fistulae or those greater than 5 mm above the carina were not associated with ventilation problems. Routine preoperative rigid bronchoscopy has also been found to be useful in the diagnosis of abnormal variants and unsuspected findings [147,163]. However rigid bronchoscopy in the newborn can be technically difficult, often resulting in arterial desaturation; it may be impossible altogether in preterm neonates weighing less than 1500 g who have severe respiratory compromise. Tracheoscopy-assisted repair of TEF has also been reported [164]. The technique described involves passage of a narrow-diameter fiberoptic bronchoscope through the endotracheal tube in a neonate who is intubated with established muscle paralysis and low-pressure intermittent positive pressure ventilation (IPPV). The aim is for gentle ventilation with the tip of the endotracheal tube sitting above the fistula so that identification and repair of the fistula take place under direct visual control. In 47 cases over a 10-year period, no adverse events related to the tube being positioned above the fistula occurred. The authors suggest that mandatory positive pressure ventilation with their technique avoids hypercapnia, hypoxia, and respiratory acidosis that can result in a potentially disastrous return to fetal circulation. With this technique, unlike rigid bronchoscopy, visualization of the airway can take place at any point during the surgical repair.

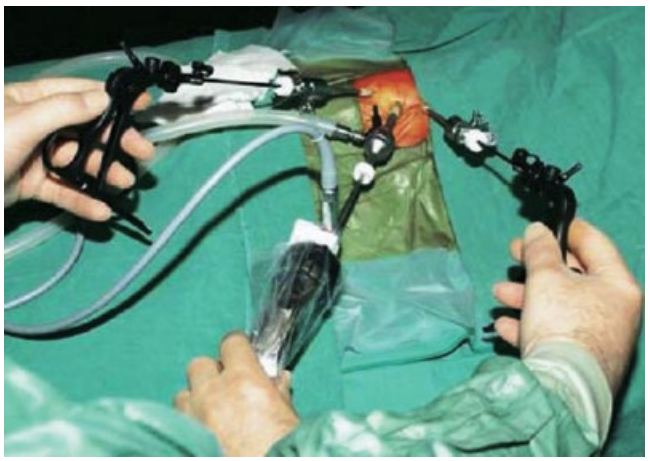
In the past, the infant with TEF/EA often underwent an initial surgical gastrostomy, sometimes under local anesthesia, with the thought that this would decompress the stomach and minimize ventilation problems. The thoracotomy was then performed several days later. However, as noted previously, a gastrostomy may allow egress of ventilator volume through the fistula and out the gastrostomy. In modern practice the gastrostomy is rarely performed primarily, and usually not at all except in cases of long-gap EA where prolonged healing is required.

An alternative surgical option to prevent the egress of gas through a large type C fistula just above the carina into the stomach has been described. A bulldog clamp is placed on the lower end of the oesophagus just above the stomach to prevent gastric dilatation while the fistula is identified and ligated [165].

Thoracoscopic repair of EA with or without TEF has also been accomplished. McKinlay described a series of 26 neonates, 20 with TEF/EA and six with isolated EA [166]. Anesthetic technique is described as standard tracheal intubation without bronchial blocker or other special technique. Three thoracoscopic ports are inserted in the right hemithorax with insufflation of CO_2 to a pressure of 6 mmHg, which is often accompanied by hypercarbia and arterial desaturation, requiring adjustment of ventilation, as the lung collapses to afford the surgeon a view of the field. The TEF is suture ligated and the esophageal pouches dissected, mobilized, and anastomosed with 5-0 vicryl sutures (Fig. 23.6). The anesthetic techniques were not described in detail, but no severe ventilation problems were apparently encountered. Patient weights were 1.4–3.9 kg and gestational ages 31–41 weeks. There were two early deaths (one patient with trisomy 18 and another with associated congenital diaphragmatic hernia), and one late death from congenital heart disease. There were seven minor esophageal anastomotic leaks managed conservatively, one recurrent TEF managed thoracoscopically, and nine anastomotic strictures. Further details on the anesthetic management of thoracoscopic surgery are discussed in Chapter 26. The advantages of a thoracoscopic technique over an open technique are said to be a lower incidence of musculocutaneous sequelae (winged scapula, chest wall asymmetry, thoracic scoliosis), a smaller scar, better visualization of the fistula and a reduction in postoperative pain [167] (Fig. 23.7). Both in open and thoracoscopic techniques the anesthesiologist must be vigilant to changes in airway pressures, tidal volumes, and end-tidal CO_2 that may occur as a result of surgical compression or kinking of the trachea or bronchi in order to improve surgical access. Accumulating evidence in the literature suggests that both short- and longer-term outcomes with thoracoscopic repairs are equivalent to open surgery [167].



(A)



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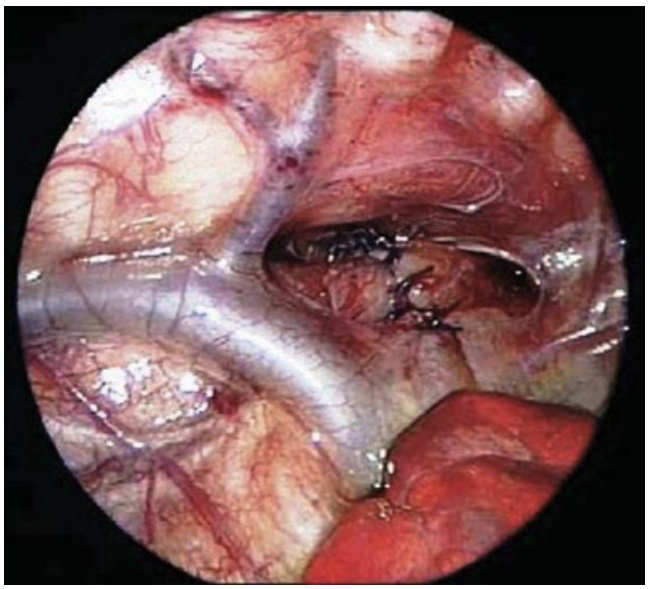


(C)

Figure 23.6 (A) Neonate in semiprone position, with tip of scapula and three port sites for thoracoscopic instruments marked. (B) Port sites and instrument position for surgeon and assistant. (C) Esophageal anastomosis completed with azygous vein intact; note collapsed right lung at lower right quadrant of picture. *Source*: Reproduced from McKinlay [166] with permission of Elsevier.

Because of the numerous different approaches to TEF/EA repair, and even variation within institutions, a thorough preoperative discussion with the surgeon, focusing on airway and ventilation management strategies and a contingency plan in case of severe ventilatory compromise, must be held when approaching these patients.

Postoperative anesthetic care

Postoperative ventilation is mandatory in neonates weighing less than 2000 g [64] and in those with respiratory distress or significant cardiac pathology. Repair of the esophageal anastomosis under tension is also an indication for postoperative ventilation, usually for a period of 5 days [146,168]. Furthermore, it has been proposed that safe awake extubation may affect every anastomosis to some degree, whether or not it is a long-gap anastomosis under tension, and that emergent reintubation may have catastrophic consequences for an anastomosis [169]. This latter problem leads some institutions to routinely leave the trachea intubated in all of these patients until it is clear that the threat of respiratory insufficiency has passed. Tension at the anastomotic site is recognized to be the most important factor contributing to anastomotic complications, however it is very difficult to assess and measure and should therefore be assumed [170]. Analgesia both intra- and postoperatively can be provided by a long-acting opioid such as morphine. This can be given by intravenous bolus at surgery and continued by infusion in the intensive care unit.

Although postoperative ventilation should be the norm where staffing and facilities exist to provide this, there may be occasions when extubation is planned at the end of surgery. Avoidance of opioids or minimizing their use is desirable although it may be necessary to use a short-acting opioid such as alfentanil or remifentanil. Regional anesthesia may be provided by a caudal catheter technique with insertion to T6/7 level or a thoracic epidural catheter; alternatively, supplementary local anesthetic can be injected by the surgeon. If morphine is required postoperatively, it must be used with extreme vigilance.

KEY POINTS: ESOPHAGEAL ATRESIA AND TRACHEO-ESOPHAGEAL FISTULA

- The major consideration of both anesthetic and surgical management of the neonate with esophageal atresia and tracheo-esophageal fistula is ventilation of the lungs without ventilation of the fistula
- Both in open and thoracoscopic techniques the anesthesiologist must be vigilant to changes in airway pressures, tidal volumes, and end-tidal CO_2 that may occur as a result of surgical compression or kinking of the trachea or bronchi in order to improve surgical access
- Preoperative and intraoperative bronchoscopy is now often used to evaluate and manage the fistula and its closure

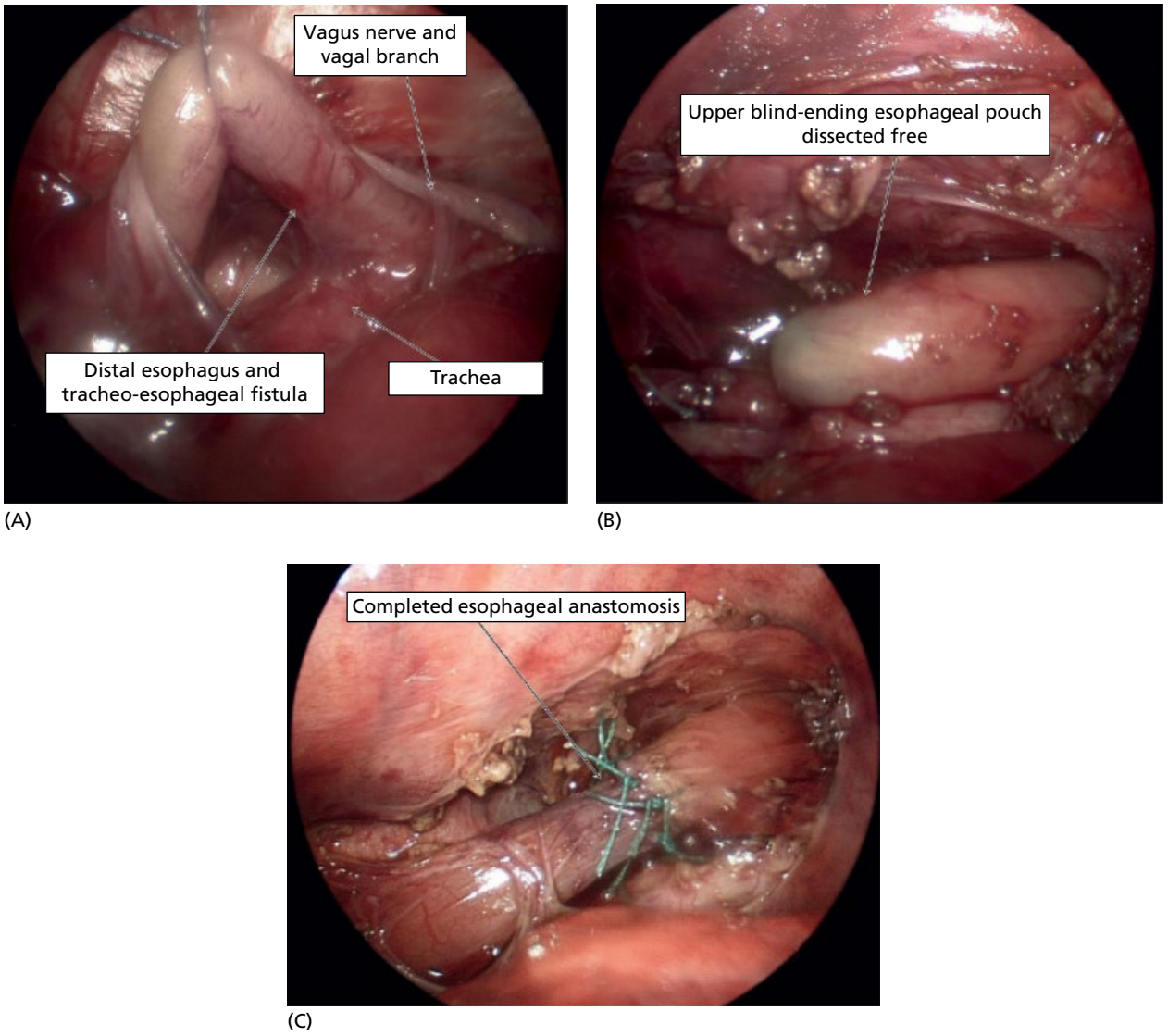


Figure 23.7 (A) Thoracoscopic view of tracheo-esophageal fistula (TEF) before ligation. (B) Upper esophageal pouch dissected free with bougie dilator distending the esophagus. (C) Completed esophageal anastomosis.

Congenital diaphragmatic hernia

Congenital diaphragmatic hernia (CDH) occurs with an incidence of approximately 1 in 3000 births and was described by Bochdalek in 1848. The commonest left-sided form bears his name and accounts for approximately 80% of CDH. The embryological development of CDH is incompletely understood but it is thought that the defect may result from failure of closure of the pleuroperitoneal canals. Animal studies using rats exposed to the teratogenic herbicide nitrofen showed that the defect is formed very early in the embryonic period with early ingrowth of the liver through the defect [171]. At a cellular level there may be abnormalities of epithelial and mesenchymal growth and differentiation that may also have implications for lung development [172]. Further rat studies have suggested that lung hypoplasia as a result of fibroblast growth factor deficiency may precede the development of CDH and lend support to the theory of a global mesenchymal embryopathy [173]. Infants presenting with the condition are often born at full term and weigh in excess of 3 kg [174]. Around half of infants with CDH will have other congenital anomalies, with the heart being commonly affected. Some 4–16% will have chromosomal abnormalities. Survival is often severely affected by the presence of associated anomalies. In the infant with CDH, abdominal viscera, most commonly bowel, herniate through the defect into the thoracic cavity, effectively acting as a space-occupying mass. This is accompanied by abnormal pulmonary development, particularly on the affected side, but mediastinal shift can prevent normal growth and development of the contralateral lung. Despite the apparent simplicity of the anatomical defect, the pathophysiology of the condition is complex. The lungs show a decreased number of bronchopulmonary segments, decreased alveolar surface area, and abnormal pulmonary vasculature [175]. There is also a thickening of arteriolar smooth muscle that extends to affect the alveolar capillaries. This impairs pulmonary function further by increasing pulmonary artery pressure that can lead to right-to-left shunting.

Diagnosis

In the majority of affected infants, CDH is discovered at prenatal maternal ultrasound scan. This provides both an opportunity to arrange for delivery of the infant in an appropriate center for management and to arrange prenatal counseling for the parents and family. It may also allow fetuses with poor outcome to be identified. Ultrasound is, however, dependent on equipment, expertise, and experience and may fail to detect the condition prenatally in up to 50% of cases [176]. Two parameters have been shown to be of some prognostic value. First, if there is herniation of the liver into the thoracic cavity, the likelihood of survival is halved [177]. Second, at 24–26 weeks' gestation it is possible to measure the cross-sectional area of the contralateral lung and to compare it with the head circumference. A lung to head ratio (LHR) of >1.4 is associated with no mortality, compared to a LHR of <0.8 which carries a 100% mortality rate [178]. With the advent of three-dimensional ultrasound some centres are now able to assess LHR usefully from 24 to 34 weeks' gestation. Furthermore, fetal MRI scanning has also been found to be a useful modality in the prenatal assessment of CDH [179] including measurements that can be predictive of CDH pulmonary morbidity such as observed versus expected total fetal lung volumes and the percentage of liver herniation [180]. For left-sided CDH with poor prognosis, prenatal intervention consisting of fetoscopic tracheal occlusion (FETO) with a detachable balloon has been reported [181]. This intervention can promote lung growth by preventing amniotic fluid egress and expanding the lungs. The balloon is placed at 27–29 weeks' gestation and removed at 34–35 weeks, and delivery is at term where possible. Belfort and colleagues reported lower extracorporeal membrane oxygenation (ECMO) rates (30% versus 78%, p = 0.05) and greater 6-month survival (80% versus 11%, p = 0.01) with FETO versus conventional treatment in a small series of 19 patients. See Chapter 21 for further details of fetal intervention and surgery.

Following prenatal diagnosis, a birth at or as close to term as possible is preferred because preterm delivery is associated with a poorer outcome [182]. The infant born with CDH usually presents with a scaphoid abdomen and an unusually prominent ipsilateral chest with an increased anteroposterior diameter. Breath sounds are diminished on the side of the lesion and heart sounds may be deviated towards the contralateral side. Diagnosis may be confirmed with a plain chest radiograph that demonstrates air-filled intestinal loops in the affected side of the thorax and a paucity of intestine in the abdominal cavity. There can also be mediastinal shift with a resultant deviation of heart sounds (Fig. 23.8).

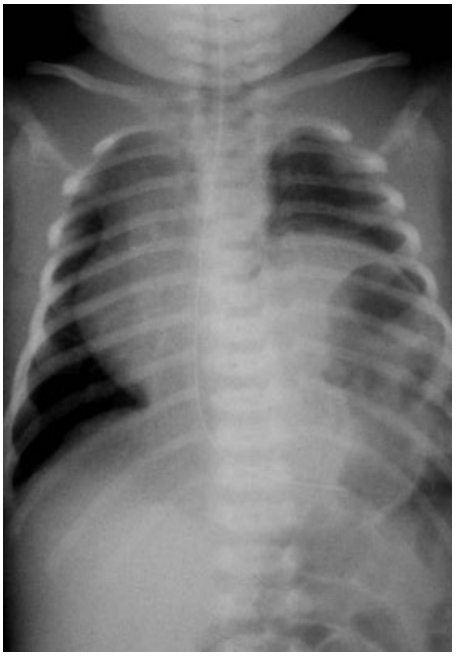


Figure 23.8 Chest radiograph of left congenital diaphragmatic hernia. Note liver and intestines in left hemithorax with heart displaced to right.

Postnatal management

At or shortly after birth, the majority of infants will develop signs of respiratory distress. If the defect is large then severe hypoxia and respiratory acidosis will be present and the infant will require immediate resuscitation including endotracheal intubation and mechanical ventilatory assistance. A naso- or orogastric tube is passed to decompress the gut. Pulmonary hypertension may worsen the situation and can result in a persistent fetal circulation with shunting of blood from right to left through the ductus arteriosus and foramen ovale. This further exacerbates hypoxia and hypercarbia, and a decrease in systemic oxygenation results in a metabolic acidosis. However, a small minority of infants are born asymptomatic and remain so for the first day of life. In these cases the defect is small and physiologically much less significant. This group usually has an uneventful course following surgical repair.

In the past CDH was considered a surgical emergency and infants were rushed to the operating room but the last decade has seen a change to preoperative stabilization of the infant prior to surgery [183,184]. In particular, stabilization strategies have been aimed at preserving extrapartum circulation and minimizing acidosis with avoidance of further damage to the lungs. Current practice involves transfer of the infant to an intensive care unit and institution of gentle ventilation aimed at minimizing barotrauma [185,186]. Strategies include permissive hypercapnia to a pCO_2 of no greater than 7.8 kPa (60 mmHg). However, with the frequent association of pulmonary hypertension, this level of hypercarbia is sometimes not tolerated. An oxygen saturation of no less than 80% on 60% inspired oxygen is considered an indication for alternative forms of ventilation or respiratory support [187]. Typically the stabilization period may range from 24 h to a number of days depending on the condition of the child. Current practice may allow for stabilization of the sick infant, thus allowing a potentially less fraught perioperative course. However in a large multistudy review, no difference in outcome was demonstrated when delayed repair after stabilization was compared to both repair within 24 h and repair immediately after birth [188]. The availability of ECMO has become widespread in line with the advent of delayed surgery in these infants. It has been shown that the overall survival rate for infants requiring ECMO is 52.9% versus 77.3% (p <0.001) for non-ECMO infants. However, in those who were deemed to have a mortality risk of 80% or more, ECMO is associated with improved outcome. Furthermore, in infants with additional risk factors, ECMO may worsen outcome [189,190]. High-frequency oscillatory ventilation (HFOV) and inhaled nitric

oxide (iNO) are also frequently used when failure of conventional ventilatory support occurs. HFOV and iNO are both aimed at improving oxygenation. HFOV achieves improved ventilation with a reduction in barotrauma [191] while iNO is used as a selective pulmonary vasodilator aimed at reducing pulmonary vascular resistance. Neither modality has been shown to have any conclusive effect on outcome in infants with CDH [188]. Recently, the detailed protocol for a long-term trial of the selective phosphodiesterase 5 (PDE5) inhibitor sildenafil has been agreed [219]. Sildenafil can be given orally or intravenously and inhibition of PDE5 results in an increase in cGMP and nitric oxide-mediated vasodilatation. There is some evidence of the efficacy of sildenafil in CDH cases and it is easier to administer than iNO, but improvement in outcome has not yet been proven. Surfactant and prenatal steroids have found vogue in recent years. Although steroids are a recognized and valuable treatment for immature lungs, they are of unproven benefit in CDH. Similarly, surfactant has been found to be of little value [188].

Overall conclusions of a recent systematic review of six management issues for CDH revealed very little high-quality evidence [192]. Using available lower quality of evidence, conclusions were that gentle ventilation with permissive hypercapnia provides the best outcomes, with initial HFOV of unproven benefit. Routine iNO or other medical treatment for pulmonary hypertension does not provide benefit. There was no evidence for routine corticosteroid administration. Mode of ECMO (veno-venous versus arteriovenous) does not appear to affect outcomes. Early repair on ECMO may have outcome benefits. Open repair has significantly fewer recurrences than laparoscopic repair.

Anesthetic care for congenital diaphragmatic hernia repair

Immediately after birth, the infant with CDH may be in acute respiratory distress and will require emergent tracheal intubation. Where possible, bag and mask ventilation should be avoided to prevent gaseous distension of the stomach. A naso- or orogastric tube should then be placed to provide intestinal decompression. The infant will need to be transferred to a neonatal intensive care unit for assessment and stabilization. When it is deemed appropriate to undertake repair, there are several anesthetic concerns. First, pulmonary hypoplasia and the resulting pulmonary hypertension can make the maintenance of adequate oxygenation challenging. Hypoxia, hypercarbia, and acidosis all act to increase the pulmonary vascular resistance further [193,194]. Instrumentation of the airway may also result in a dangerous increase in pulmonary vascular resistance [195] and so an opioid such as fentanyl should be given at the beginning of the procedure and can be repeated as necessary. A dose of 25 μg/kg has been shown to abolish the stress response to airway instrumentation [196]. The OR should be prepared as for any neonate requiring major surgery. Standard monitoring is applied. Good venous access is mandatory, and central venous access is highly desirable for both the measurement of central venous pressure and for the administration of inotropes such as dopamine. Invasive arterial blood pressure monitoring is also required as it provides real-time measurement of intra-arterial pressure. Umbilical artery and vein catheterization is achieved preoperatively in most CDH patients. This is particularly useful as surgical access (Fig. 23.9) may result in acute compression of the great vessels resulting in sudden acute hypotension. The surgical approach usually involves a left thoracoabdominal incision, reduction of the intrathoracic intestinal viscera and liver, and repair of the diaphragm, often with a patch made of synthetic material.

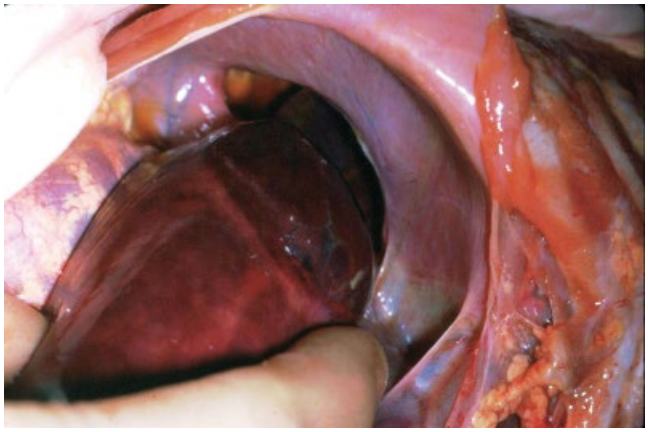


Figure 23.9 Operative appearance of congenital diaphragmatic hernia via left thoracoabdominal incision. Liver is being reduced through large diaphragmatic defect.

Furthermore, the changes in pressure that may be seen during the cycling of ventilation can indicate hypovolemia. A urinary catheter is useful to monitor urine output. The goals of anesthetic management are to provide adequate analgesia and depth of anesthesia with minimal impact on pulmonary vascular resistance and myocardial function. Therefore great care must be exercised with the maintenance of anesthesia. Volatile anesthetic agents are known to attenuate hypoxic pulmonary vasoconstriction [196]. However, they may cause systemic hypotension if not used carefully. For this reason a fentanyl-based anesthetic may be preferable. Nitrous oxide has been shown to have little effect on pulmonary vasculature in infants [197], however it should be avoided because of its effect on alveolar PaO_2 and its propensity to worsen bowel distension. Muscle relaxation may be provided by competitive neuromuscular blockade. Vecuronium and rocuronium are appropriate. Pancuronium is best avoided because of its intrinsic sympathomimetic activity. Mechanical ventilatory parameters should be set to allow for adequate oxygenation. A degree of hypercarbia is acceptable as high inflation pressures should be avoided, again being mindful of pulmonary hypertension. If the infant has been stabilized prior to surgery, preoperative PaO_2 and $PaCO_2$ levels serve as reasonable targets. Throughout the procedure the anesthesiologist must be prepared to treat a sudden pulmonary hypertensive crisis. In the event of this, moderate hyperventilation, often manual, may be required with 100% oxygen. The cardiac output may require support and adequate preload should be ensured. Selective pulmonary vasodilators such as inhaled nitric oxide should be available in addition to appropriate inotropic support that may include drugs such as phenylephrine, epinephrine, dopamine, and milrinone. On occasion it is necessary to repair CDH with the patient supported either by HFOV or ECMO. This makes patient transfer hazardous, and in this situation repair is usually undertaken in the neonatal intensive care unit.

KEY POINTS: CONGENITAL DIAPHRAGMATIC HERNIA

- Fetal MRI can be important in prenatal assessment and give an indication of morbidity and outcome
- About half of infants with CDH have other congenital anomalies including congenital heart disease
- Awareness of pulmonary hypertension and its modern management is vitally important
- Modern management of CDH includes preoperative stabilization with ECMO or HFOV; bedside repair may be necessary with these modalities

Meningomyelocele

Meningomyelocele is a form of neural tube defect that occurs in 0.5–1 per 1000 livebirths and is usually diagnosed antenatally. The spinal cord and meninges are exposed to the intrauterine environment and this results in a central sac filled with cerebrospinal fluid and damaged spinal cord and nerve roots. Invariably this defect is associated with the Arnold–Chiari malformation and hydrocephalus. The cerebellar vermis, fourth ventricle, and lower brainstem are herniated downwards below the level of the foramen magnum. Primary closure is usual within the first 2 days to minimize infection. Treatment of hydrocephalus is individualized but a concurrent ventriculoperitoneal shunt placement may be needed.

Fetal repair has been described with reduced need for ventriculoperitoneal shunting at age 1 year, but no improvement in neurological deficits was demonstrated [198]. A recent review has suggested that prenatal repair of fetal myelomeningocele may be preferable when compared to postnatal repair [199]. Specifically it has now been shown in a randomized trial of 183 patients that as well as reducing the need for ventriculoperitoneal shunting, fetal repair improves motor outcomes at age 30 months [200]. This will have an impact on future practice and the requirement for postnatal repair may decline over time as the prenatal repair technique becomes more widespread. See Chapter 21 for further details.

For postnatal repair, problems for the anesthesiologist are: positioning for induction solved by use of pads or a circular gel ring to protect the fragile sac; prone positioning for surgery; awareness of preventing latex allergy by use of a latex-free environment and equipment; the potential for large intraoperative blood losses due to dissection of skin flaps to gain coverage of the defect; and postoperative respiratory problems associated with Arnold–Chiari malformation. These babies may have reduced or absent response to hypoxia and hypercarbia and may have impaired swallowing and gag reflexes [201–203]. See Chapter 25 for further discussion of anesthetic care for patients with this lesion.

Muscle biopsy

Muscle biopsy in an infant usually requires a general anesthetic supplemented by local anesthetic infiltration at the biopsy site. This presents a dilemma for the pediatric anesthesiologist who is being asked to provide anesthesia in a child without a definitive diagnosis and therefore a degree of uncertainty about the individual's response to anesthetic and other drugs. A muscle biopsy is often required for definitive diagnosis of a wide range of disorders (Box 23.2) and supplements information from family history, symptoms and signs, biochemistry, genetic tests, and electromyography.

Box 23.2: Indications for muscle biopsy in infants

- Benign congenital hypotonia
- Perinatal asphyxia
- Hypotonic cerebral palsy
- Metabolic disorders
- Spinal cord injury
- Spinal muscular atrophy
- Peripheral nerve disorders
- Congenital myasthenia
- Neonatal myasthenia
- Infantile botulism
- Congenital myopathies
- Muscular dystrophies
- Mitochondrial myopathies
- Glycogen storage disorders

Clinically the infant will usually present with hypotonia or floppiness which may be associated with swallowing difficulties, gastroesophageal reflux, and failure to thrive. If reflux is significant, episodes of aspiration may have caused significant lung damage. Try to assess the degree and extent of muscle weakness and any evidence of respiratory compromise as these infants often have reduced respiratory reserve and may need postoperative respiratory support even for a short procedure such as muscle biopsy. Avoid sedative premedication and opioids if at all possible. A preoperative ECG and echocardiogram are recommended to check for cardiac involvement, for example in Duchenne muscular dystrophy or mitochondrial myopathy. Avoid prolonged fasting as infants with hypotonia often are prone to hypoglycemia, and consider giving IV dextrose from the start of the fluid fast period and continuing intra- and post-operatively. Inhalational anesthesia with sevoflurane with or without tracheal intubation and ventilatory support as appropriate to the individual child is indicated along with local anesthesia of the biopsy site by the surgeon and simple analgesia thereafter with acetaminophen and or non-steroidal anti-inflammatory drugs (NSAIDs). If possible, avoid muscle relaxants and certainly succinylcholine, which can cause dangerous hyperkalemia in some of these disorders. If a non-depolarizing neuromuscular blocking agent is needed, titrate carefully against neuromuscular monitoring and ensure complete reversal at the end of the procedure. Rocuronium would be an appropriate choice of muscle relaxant as reversal is predictable and complete with administration of sugammadex. The possibility of malignant hyperthermia is a concern, and for this reason some anesthesiologists avoid volatile agents. Dantrolene should be available but not administered prophylactically as it can itself exacerbate muscle weakness in some of these disorders. Even after a short procedure, postoperative monitoring should be extended and ventilatory support must be available as required. This may be best carried out in an intensive care setting. In a large series of 877 pediatric muscle biopsy patients, regional anesthesia was utilized in 15.6% of patients and consisted of spinal anesthesia in 80 patients, caudal in five, and

peripheral nerve block in 27. Volatile agents were utilized in only 16% of patients, non-depolarizing muscle relaxants in 46%, and succinylcholine in two cases. Interestingly, no incidences of malignant hyperthermia, hyperkalemia, rhabdomyolysis, cardiac dysfunction, or intensive care admission were observed [204]. See Chapter 33 for further discussion of neuromuscular diseases.

KEY POINTS: MENINGOMYELOCELE AND MUSCLE BIOPSY

- Postnatal myelomeningocele repair is a surgical emergency, and prone positioning to protect the sac from rupture, a latex-free environment, and postoperative prone positioning are principles of anesthetic care
- Prenatal myelomeningocele repair reduces the need for ventriculoperitoneal shunting and improves longer-term motor outcomes
- Muscle biopsy in infants presents the problem of a hypotonic infant without a diagnosis; a variety of techniques including general anesthetic with or without volatile agents, and spinal anesthesia have been safe and effective

Resuscitation of the newborn

During the transition from intrauterine to extrauterine life, the neonate will undergo a significant and complex physiological change from the fetal circulation to the adult circulation, with a period of time in a transitional circulation. At birth, the neonatal systemic blood pressure increases after the cord is clamped. The first breath of air needs to expand fluid-filled alveoli and for this may require negative intrapleural pressures of up to 70 cmH_2O. Oxygen causes the pulmonary vascular resistance to fall because of a reduction in hypoxic pulmonary vasoconstriction and also causes the ductus arteriosus to constrict, thus making the pulmonary artery the route of least resistance from the right ventricle. Flow through the foramen ovale ceases due to the rise in pressures in the left side of the heart. The left ventricle, which is of a similar size at birth, will gradually increase in its function of compliance and contractility.

The World Health Organization estimates that 19% of neonatal deaths worldwide are caused by birth asphyxia [4]. That equates to nearly 1 million deaths annually. The vast majority of newborn infants, however, do not require any form of resuscitation other than drying and being kept warm by being given to their mother, often skin to skin. Approximately 10% of newborns require some assistance to begin breathing at birth, with 1% needing extensive resuscitation [205]. Other studies have estimated that between 5% and 10% of neonates need resuscitation at birth, from simple stimulation to assisted ventilation [206]. Resuscitation of the newborn is commonly managed by the obstetrician or midwife; however, if there is an anticipated sick neonate, cesarean section, or preterm delivery, neonatologists and occasionally anesthesiologists are involved.

The following is based on current practice and evidence as well as guidelines produced by the Neonatal Resuscitation Program (NRP) in association with the American Heart Association (AHA) for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care (ECC) of Pediatric and Neonatal Patients [205]. Although neonatologists and pediatricians generally manage newborn resuscitation, the techniques that are set out in the neonatal resuscitation algorithm could be extrapolated to form competencies relevant for any neonatal resuscitation, especially for those patients in their first few weeks of life and those that are preterm. Important trials and studies looking at aspects of neonatal resuscitation caused significant changes in the therapeutic algorithm in the 2010 resuscitation guidelines. These studies include discussion on the use of supplemental oxygen as part of initial resuscitation and therapeutic cooling which aims to decrease the neurological damage caused by asphyxia at birth. The 2015 guidelines (updated in 2017 [220]) expand on and define these issues, as discussed in the following.

It is important to note that anticipating the need for resuscitation as well as the preparation of appropriate equipment, environment, and trained staff are all crucial to a successful outcome. Cardiac arrest at birth remains predominantly due to asphyxia so the resuscitation guidelines have a heavy focus on delivering good initial ventilation.

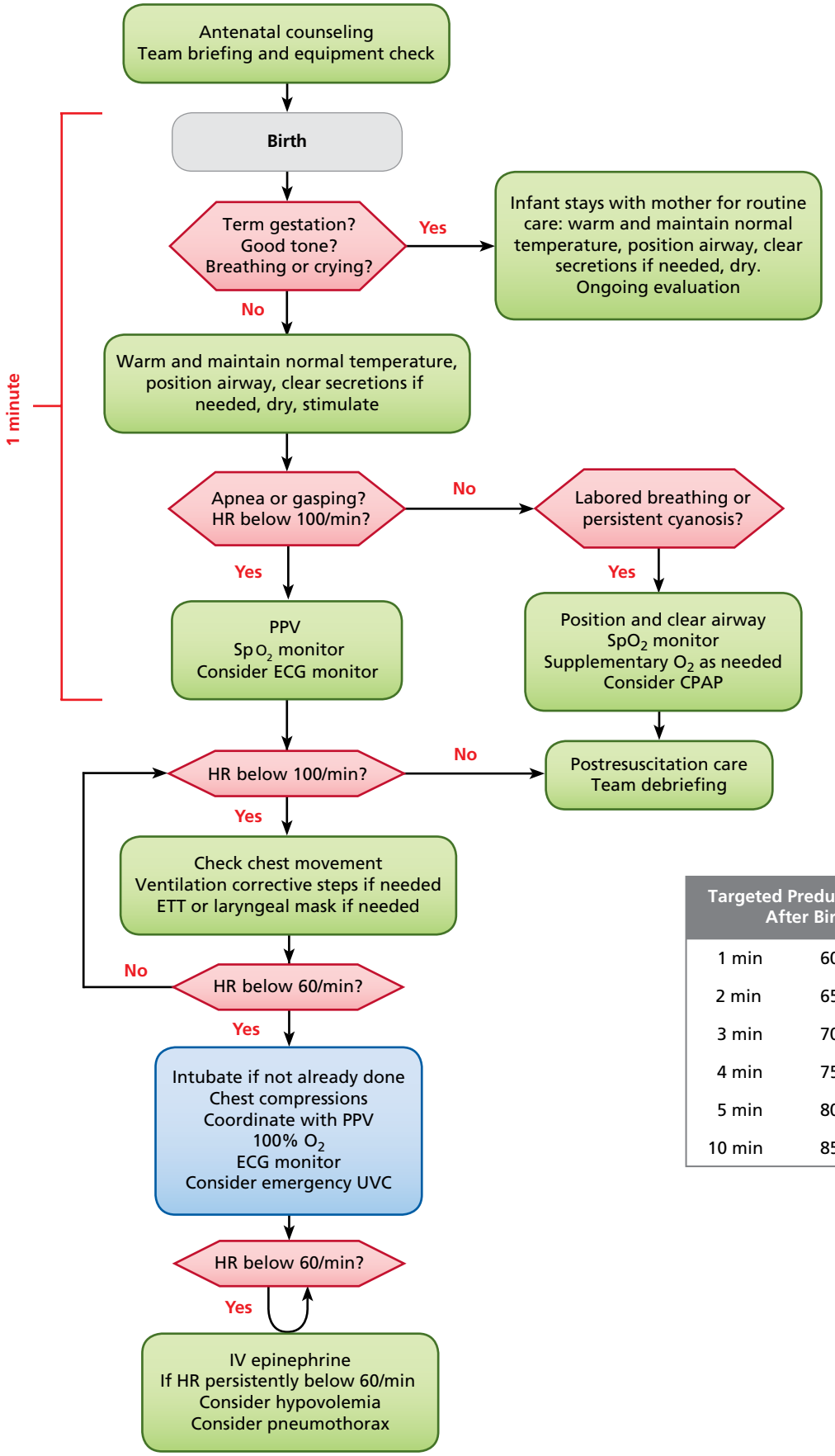
The algorithm in Figure 23.10 is taken from the 2015 guidelines [205] and remains unchanged in the 2017 update. The guidelines are still divided mainly into four broad categories of: (1) assessment, initial care, and observations; (2) ventilation and monitoring; (3) chest compressions; and (4) drug and fluid administration. These areas will be discussed with the emphasis on current significant evidence and recent trials. The first "golden" minute of assessment with progression to ventilation is emphasized to help reduce unnecessary delays. "Start the clock!" is the very first directive during newborn resuscitation.

Assessment and initial care

Immediate assessment and initial care includes drying and stimulating the baby and clearing and positioning the airway, which includes suctioning with a soft suction catheter and positioning the head in the "sniffing" position. The 2015 guidelines have changed the *order* of the three initial assessment questions. These now read: (1) Term gestation?; (2) Good muscle tone?; and (3) Breathing or crying? Tracheal suction of meconium has been shown not to improve outcome, so this is no longer recommended by the NRP. Evidence suggests that the resuscitation procedures should follow the same principles for meconium-stained aspiration as for clear fluid. There should always be some way of providing a source of warmth during resuscitation, and this is normally done under a radiant heat source or with a warming mat. Preterm infants and neonates with a very low birthweight (<1500 g) are recommended to have the additional warming technique of being placed in a plastic wrapping with a hat, as well as being placed under a radiant heat source or on a warming mat. This has been shown to decrease heat loss without hindering ongoing resuscitative measures [205,207,208]. Delayed umbilical cord clamping is recommended for all vigorous term and preterm newborns.

The immediate assessment is of respiratory effort, muscle tone, heart rate, and color. This in practice also includes

Neonatal Resuscitation Algorithm—2015 Update



Targeted Preductal SpO_2 After Birth	
1 min	60%–65%
2 min	65%–70%
3 min	70%–75%
4 min	75%–80%
5 min	80%–85%
10 min	85%–95%

Figure 23.10 Neonatal resuscitation algorithm. *Source*: Reproduced from Wyckoff et al [205] with permission of Wolters Kluwers.

saturation monitoring. The use of three-lead ECG monitoring of heart rate is also now suggested because clinical assessment of heart rate has been found to be unreliable in the resuscitation environment. The first major sign of tissue hypoxia in newborns is bradycardia (heart rate <100 as per the guidelines). Bradycardic episodes normally respond well to a brief period of positive pressure ventilation. This is done via a bag and mask, T-piece, or manually operated, gas-powered, pressure-regulated resuscitator (Neo-puff™, Fisher and Paykel Healthcare, Auckland, New Zealand). According to the NRP guidelines, it is then recommended to give supplemental oxygen. There are many studies comparing the risks and benefits of using oxygen to resuscitate neonates.

Oxygen versus air

First, there is evidence linking ventilation of neonates on high concentrations of oxygen, even for short periods of time, to ROP, chronic lung disease, oxygen free radical disease of the neonate, infection, and leukemia. Studies comparing initial resuscitation with air and varying concentrations of oxygen are beginning to show some evidence that using air alone can have outcomes comparable to using oxygen supplementation, thereby preventing the risks associated with oxygen therapy, but there is as yet insufficient evidence to resolve all questions [209].

Some studies have shown that room air may be superior to 100% oxygen as the initial choice for resuscitation [210]. The resuscitation algorithm recommends step-wise targeting of preductal saturations using supplemental oxygen as needed during the first 10 min after birth (see Fig. 23.10). It also further recommends starting resuscitation of *preterm* (under 35 weeks) neonates with low inspired oxygen concentrations of 21–30%. Standard practice would include decreasing the oxygen concentration as saturations rise to over 95%. It is also reasonable practice to start resuscitation of a term newborn with room air. The AHA guidelines recommend supplemental oxygen when giving positive pressure ventilation and free-flow oxygen to those spontaneously breathing with central cyanosis. Some studies suggest a compromise, aiming for 30–40% oxygen [211]. The use of oxygen blenders with either T-pieces or Neo-puff apparatus is recommended.

Temperature control – therapeutic hypothermia

A review of the literature looking at hypoxic ischemic encephalopathy of newborn infants found that there is evidence from trials to show that induced hypothermia helps to improve survival and development at 18 months for, specifically, term babies at risk of brain damage [212]. A great deal more research is needed into methods of cooling, whether it is isolated to the head or whole-body therapeutic hypothermia. There is also the difficulty of patient selection. It is unclear which patients would benefit from cooling and also to what temperature and for how long. This technique is only recommended in institutions with the appropriate expert personnel and equipment.

Ventilation

Improving bradycardia is the first sign that effective ventilation is being conducted during resuscitation. Improving color and muscle tone, with a return to spontaneous and regular breathing, normally follows this. Effective ventilation is achieved using a T-piece or self-inflating Ambu-bag®, however many centres now use the Neo-puff as it has an oxygen blender as part of its design. CO_2 monitoring is the gold standard method of confirming correct placement of the endotracheal tube. The use of a LMA may be considered in term neonates as an alternative to intubation in those that have had failed endotracheal intubation attempts who are requiring ongoing resuscitation.

Studies looking at resuscitation of asphyxiated neonates at birth have shown that term babies often require around 30 cmH_2O as initial inflation pressures [213] with preterm and low birthweight babies needing higher inflation pressures due to their underdeveloped lungs. Large-volume inflations can cause injury [214], however the inclusion of PEEP has been shown to have a protective effect against lung injury as well as improving lung compliance and gas exchange [215,216].

Chest compressions

Good ventilation strategies are the most effective way of successfully resuscitating a neonate. Chest compressions are only indicated if there is a continuing bradycardia <60 beats/min in the face of adequate ventilation and oxygenation. Chest compressions should be started after approximately 1 min of resuscitation as per the algorithm. There should be at least a period of 30 s where adequate assisted ventilation is delivered before starting chest compressions. The two thumb–encircling hands technique is the one recommended by the AHA for chest compressions as this should generate higher peak systolic and coronary artery perfusion pressures [205]. If access to the umbilicus is needed for umbilical catheter insertion during resuscitation, chest compressions can be continued with the two-thumb technique from the head of the cot.

Drugs

If bradycardia persists despite good ventilatory resuscitation with poor perfusion and no improvement in color, muscle tone, or saturations then volume expansion and administration of specific drugs, especially epinephrine, are indicated. Emergency umbilical vein access, where the catheter is inserted only 3–5 cm until blood return is obtained, is the preferred route for administration of emergency drugs and fluids [217]. The concentration of epinephrine used is 1:10,000 (0.1 mg/mL). The intraosseous route can be considered if umbilical access fails or is not possible.

Although there is a lack of data on the effectiveness of endotracheal epinephrine, it can be used as a route of administration while IV access is being obtained. The dose used for endotracheal epinephrine is 0.1 mg/kg. This is a 10-fold increase in concentration of the recommended dose for IV administration. The recommended IV dose is 0.01–0.03 mg/kg per dose. Higher doses are not used as they can cause a paradoxical decrease in myocardial function due to exaggerated hypertensive responses with subsequent poorer neurological outcome [218]. Other drugs are used during resuscitation but rarely.

Naloxone and other narcotic antagonists are not recommended due to a lack of clinical evidence during initial resuscitation and also because they may precipitate withdrawal seizures in newborns of mothers taking regular opioids.

The Resuscitation Council (UK) does recommend the administration of sodium bicarbonate when there is no effective cardiac output, or virtually none, prior to a second dose of epinephrine. There are no well-powered studies to support the potentially beneficial effects of sodium bicarbonate use and the NRP no longer recommends its use.

KEY POINTS: NEONATAL RESUSCITATION

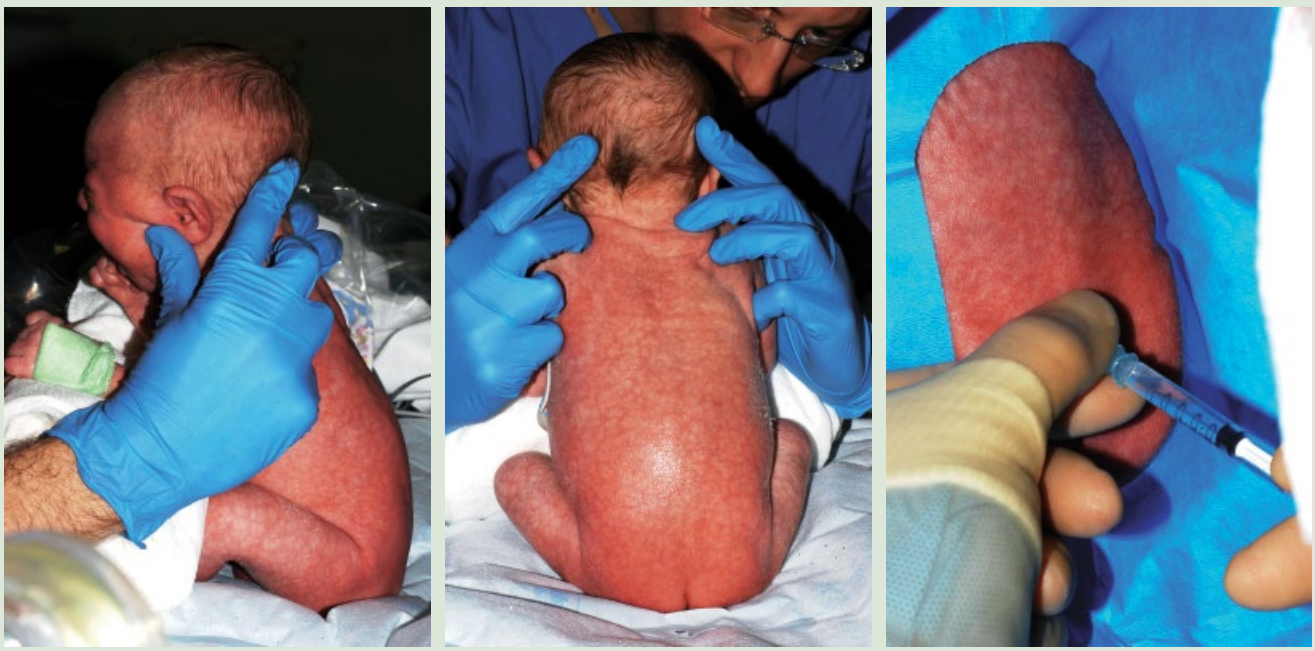
- The golden minute for assessment and implementation of appropriate resuscitation is vital
- Good ventilation strategies are the most successful way of resuscitating a neonate
- Preductal oxyhemoglobin saturation targets are helpful during the first 10 min of neonatal resuscitation
- FiO_2 is targeted to oxyhemoglobin saturation and excessive inspired oxygen levels avoided whenever possible

CASE STUDY

This case study illustrates the principles of anesthetic management of the ex-premature infant as detailed in this chapter and Chapter 22.

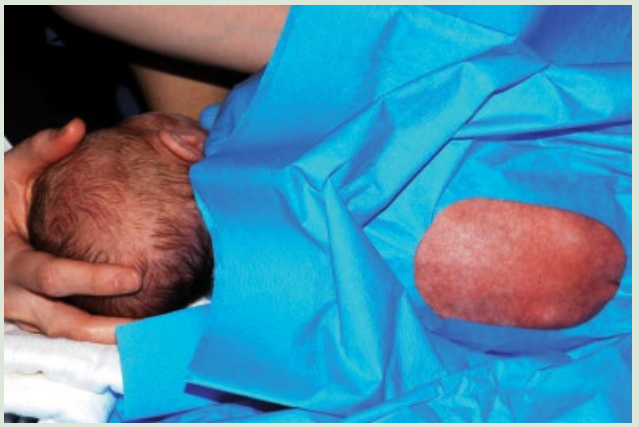
A 44-week ex-premature boy weighing 2 kg presented for surgical repair of a unilateral large but easily reducible inguinal hernia at 44 weeks' postconceptual age having been born at 28 weeks' postconceptional age by cesarean section after his mother went into premature labor with premature rupture of membranes. The mother had been given predelivery steroids to encourage lung maturation and surfactant production in the baby's lungs but the baby showed signs of *in utero* fetal distress and a decision was made to deliver early. The birthweight was 1 kg and the baby required exogenous surfactant therapy, intubation, and ventilatory support for 2 weeks using high-frequency oscillation for severe neonatal respiratory distress syndrome complicated by group B streptococcal septicemia. Weaning from ventilatory support was slow and it became evident that the baby had a patent ductus arteriosus. Medical treatment with nasogastric ibuprofen was unsuccessful. The PDA was clipped via a left mini-thoracotomy performed in the NICU and the baby's lung function improved but he continued to require oxygen therapy for several weeks. A right inguinal hernia was noted but was easily reducible. After discussion with the surgical team and parents, and because the baby lived locally, it was agreed to allow him home and readmit at around 44 weeks' postconceptual age when he had grown a bit more and been weaned from oxygen therapy for a number of weeks. He had no residual cerebral damage and echocardiography revealed normal cardiac anatomy with no residual ductal flow. His blood work-up prior to the hernia repair was normal except for a hemoglobin level of 9 g/dL. Thus this baby presents as an ex-preterm infant of 44 weeks' PCA with mild bronchopulmonary dysplasia and preoperative anemia. He does have a significant risk of postoperative apnea and arrangements are therefore made to admit him after his inguinal herniotomy to the high-dependency area adjacent to the NICU for monitoring overnight even though he was being considered as suitable for an awake regional block technique. The anesthetic options, benefits and risks, and postoperative monitoring and analgesia management were discussed with the parents who were concerned about potential adverse effects of anesthetic drugs on their baby's future development. It was mutually agreed to use a spinal anesthetic supplemented by a single-shot caudal block. The parents were initially concerned that their baby would be upset by being awake in the OR environment but were reassured by the discussion about the use of oral sucrose, topical local anesthesia for the spinal injection and IV cannula sites, and the use of a quiet, warm OR environment. The possibilities of failure of the technique or the need to supplement with or convert to general anesthesia were discussed and the anesthesiologist discussed his personal results for this technique, which were a failure rate of around 5% overall. The parents agreed to this option and to the postoperative plan for overnight admission for monitoring and ongoing pain control with intravenous or oral acetaminophen. The anemia was also discussed as it is an added risk factor for apnea but the parents were not keen on further blood transfusion if this could possibly be avoided. On balance it was felt that leaving this untreated was an acceptable risk. The anesthesiologist recommended that the baby should be given caffeine intravenously to help further reduce the propensity for apneic spells, and this was agreed. The anesthesiologist discussed this plan with the surgeon who was used to operating on these babies under regional blockade and preferred to do open rather than laparoscopic repairs in small infants. The baby was scheduled as the first case of the morning and the OR was prepared for a neonate with appropriate equipment, drugs, and fluids available for a full general anesthetic as well as regional block in case of block failure. The ambient temperature was set to 23°C. A warm air system and warming mattress were set up and the baby was given a breast feed 4 h in advance of the scheduled time and a clear fluid drink 2 h in advance. Tetracaine gel was applied to the back of each hand and to the lumbar region 30 min in advance of the procedure. The baby was brought in to the OR, an IV cannula was sited, and maintenance fluids were commenced at a rate of 8 mL/h. Caffeine 10 mg/kg was administered slowly IV. A neonatal pulse

oximetry probe was placed on the right hand and ECG leads applied. The local anesthesia tray was then prepared for a spinal and caudal block and the anesthetic machine and equipment were also made ready for a 2 kg baby including facemask, oropharyngeal airways, tracheal tubes, anesthetic and muscle relaxant drugs, atropine, and intravenous acetaminophen 7.5 mg/kg. For the spinal/caudal block, full aseptic technique was used including surgical scrub, gown, gloves and mask, skin prep and sterile drapes, equipment, and drugs. The local anesthetic used was isobaric levobupivacaine 5 mg/mL concentration at a dose of 1 mg/kg (0.2 mL/kg). An additional 0.1 mL was added to allow for the deadspace of the needle and its hub. For this 2 kg baby, that was a volume of 0.4 + 0.1 mL = 0.5 mL drawn into a 1 mL syringe. A 25 G neonatal lumbar puncture needle was used at the L5/S1 interspace with the baby sitting supported by a trained assistant who paid particular attention to supporting the baby's chin to avoid flexion of the head and neck on the trunk which can cause airway obstruction (this baby is too young to have head control) (Fig. 23.11A and B). After the spinal injection the baby was immediately placed in the left lateral position and a caudal cannula inserted (22 G) via the sacral hiatus (Fig 23.11C–F). Levobupivacaine at a concentration of 2.5 mg/mL was slowly injected to a dose of 2 mg/kg (0.8 mL/kg) via the sacral hiatus, which was a volume of 1.6 mL for this baby. The caudal cannula was then removed, small dressings applied to the spinal and caudal puncture sites, and the electrocautery grounding plate was applied to the baby's back. The baby was then turned supine and a blood pressure cuff applied to a lower limb and skin temperature probe applied to a toe. A pacifier with dextrose was given to the baby (50% dextrose via a pinhole made in the nipple) who fell asleep (Fig. 23.11G). The legs were straightened out and stayed straight. Gentle skin pinch testing showed a block to just above the umbilical level. The room lights were dimmed, noise levels were kept to a minimum, and monitor alarm volumes were minimized. After surgical prep and draping of the operation field, an open herniotomy was performed in conventional fashion via a 1.5 cm skin incision. The baby did not respond to the incision; he showed slight signs of arousal during dissection of the hernia sac but settled after sucking further on the pacifier. Oxygen saturation, respiratory rate, pulse, and blood pressure were stable throughout. The operation lasted a total of 20 min from prep to dressing. The spinal/caudal took a total of 20 min from patient arrival in the OR to start of skin prep for surgery. The baby was taken straight to the high-dependency unit and monitoring applied. No apneic episodes were observed overnight and the baby resumed breast feeding 1 h postoperatively. Acetaminophen was administered orally twice before discharge the following day after surgical review. The parents were delighted and felt this had been a very good option for their baby.

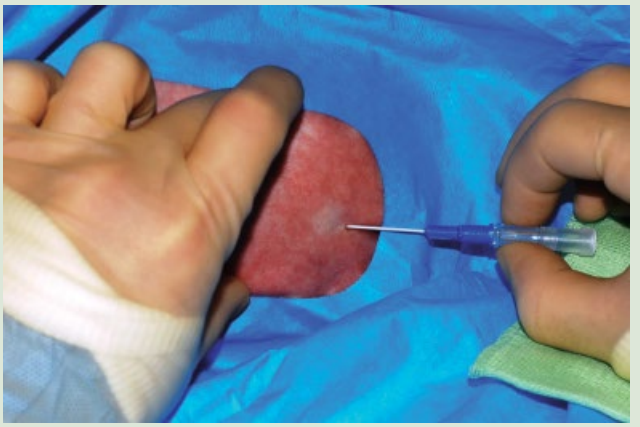


(A) (B) (C)

Figure 23.11 Case study sequence of awake spinal caudal anesthesia. (A) Baby supported in sitting position by trained assistant with head held in neutral position avoiding neck flexion, arms contained, and spine curved gently forward to open up the intervertebral spaces. (B) View of the back with the vertebral column in straight alignment. (C) Spinal injection using 25 G needle and 1 mL syringe at L5/S1 interspace. (D) Baby immediately placed in left lateral position for caudal injection. (E) Caudal cannulation using 22 G cannula. (F) Caudal injection of local anesthetic. (G) Pacifier with microdrip feed of 50% dextrose delivered via pin-hole in the nipple.



(D)



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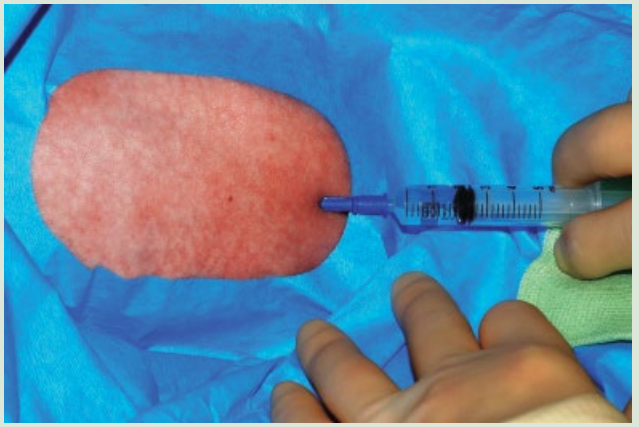

(F)

(G)

Figure 23.11 (*Continued*)

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CHAPTER 24

Anesthesia for the Adolescent and Young Adult Patient

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Introduction

Adolescence, defined as the time between puberty and adulthood, roughly ages 13–19, is a time of significant change for the child, even without significant health problems. Chronic diseases beginning in infancy and childhood may further complicate the transition to adulthood. The pediatric anesthesiologist cares for patients in both categories and may face a number of challenges in patients in this age group. This chapter first reviews developmental and behavioral issues in the adolescent, and then addresses the reproductive issues of the adolescent as they relate to anesthesia care. Then, common chronic adolescent and young adult illnesses are reviewed including cystic fibrosis, congenital heart disease, cancer, sickle cell anemia, diabetes, inflammatory bowel disease, and developmental disabilities and autism, emphasizing anesthetic care. Finally, obesity and bariatric surgery in the adolescent are reviewed, as is thyroid surgery.

Developmental/behavioral issues in the adolescent

Adolescence is a transitional period between childhood and adulthood that is generally characterized by ongoing cognitive development, greater emotional lability, increased risk-taking behavior, and inconsistencies in behavior modulation [1,2]. Non-compliance with medication administration, and other medical treatment regimens including subspecialty follow-up, is a form of risk-taking behavior. From an evolutionary perspective, this period is designed to prepare the person for independent survival, but it is also is a period of vulnerability. The social environment is changing so that more time is often spent with peers rather than adult family members; peer influence is greater, and may also influence emotional reactivity. Most of the time these changes are positive; however, of the more than 25,000 adolescent and young adult (ages 10–24) deaths in the USA annually, about 70% result from risk-taking behavior including automobile accidents, unintentional trauma, homicide, and suicide [3]. Several neurobiological hypotheses have been advanced to explain these changes; many have cited increased growth and activity in the prefrontal regions of the brain as the reason for progressively greater cognitive control and affective modulation as a person grows into adulthood. Newer theories based on functional brain magnetic resonance imaging (MRI) studies implicate the subcortical limbic areas (nucleus accumbens and amygdala) in the likelihood of engaging in risky behavior as teenagers, versus adults or younger children. Recent reviews emphasize that adolescents are more sensitive to this risk–reward behavior than adults, and, combined with reduced inhibitory control, this behavior is maximal in the early to mid-adolescent periods [4]. In addition, there are significant gender differences. For example, females have an earlier and lower magnitude peak in sensation seeking during mid-adolescence that is followed by a more rapid decline to stability by early adulthood. It has also been demonstrated that impulse control improved steadily in females following early adolescence, but males remained more impulsive than females through their mid-20s.

The dopaminergic (DA) system has been linked to reinforcement learning and to high-level cognitive processes and control. The DA system, including levels of the neurotransmitter and receptors, is undergoing rapid changes during adolescence, and some theories postulate that DA activity is greater in the frontal cortex of adolescents, which may result in greater propensity toward riskier (and perceived greater

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

reward) behavior. This neurobiological underpinning substantiates the clinical knowledge that despite their physical size and physiological (i.e. cardiac and pulmonary physiology) similarity to a mature adult, and tendency for healthcare providers to treat them like adults, adolescents indeed have substantial emotional and behavioral differences that may affect anesthetic care [5] (Fig. 24.1).

The ubiquitous presence of electronic devices, particularly smartphones, has become a major developmental influence for adolescents worldwide in the past few years. A recent report on media use of adolescents in the USA documented that they spend an average of 7.5 h per day engaged with electronic media, and 29% of that time is spent in media multitasking [6]. Social media use comprises a significant portion of this time, and the benefits have been documented, including use of social media in the service of critical adolescent developmental tasks, such as peer engagement and identity and aspirational development [7]. As adolescents strive for autonomy and seek intimacy with their peers, their online environments frequently reflect their offline lives. A number of negative effects of social media use have been reported, including cyberbullying, depression, social anxiety, and exposure to developmentally inappropriate content. Heavy users of media have been found to have lower performance on tests of sustained, goal-directed attention, relational reasoning, inhibition control, and long-term memory. Smartphone addiction in adolescents now has formal diagnostic criteria, and the same dopaminergic reward circuits involved in other addictions are active in this disorder [8].

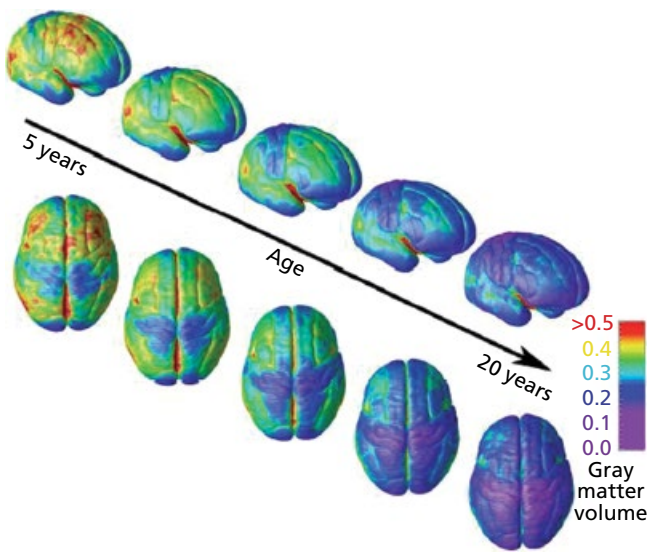

Figure 24.1 Structural changes in gray matter over time derived from serial MRI studies in children, adolescents, and young adults. Right lateral and top views of the dynamic sequence of gray matter maturation over the cortical surface. The side bar shows a color representation in units of gray matter volume. Fifty-two scans from 13 subjects each scanned four times at approximately 2-year intervals. The developmental trajectory of cortical gray matter follows a regionally specific pattern with areas subserving primary functions, such as motor and sensory systems, maturing earliest, and higher order association areas, which integrate those primary functions, maturing later. For example, in the temporal lobes the last part to reach adult levels is the superior temporal gyrus/sulcus, which integrates memory, audio-visual input, and object recognition functions. *Source:* Reproduced from Lenroot and Giedd [5] with permission of Elsevier.

Substance abuse and "recreational" use of alcohol and drugs (both legal and illegal) is one area of difference between the adolescent and mature adult. Annual surveys in the USA have generally reported a decline in the use of drugs (except marijuana) and alcohol over the past 5–10 years. Prevalence of alcohol use (any lifetime use) among 10th graders in the USA (age 15–16) was estimated at 42.2% in 2017, and any use of illicit drugs such as marijuana, cocaine, or methamphetamines was 34.3% [9]. Substance misuse is defined as a maladaptive pattern of use leading to clinically important impairment or distress, manifested by persistent or recurrent use of the substance despite interference with important functions such as school, home life, and interpersonal relationships, and issues such as legal problems and use in physically hazardous situations [10]. Substance dependence is much more limited, with daily use of alcohol reported by 0.7%, and of marijuana by 3.1% of 8th, 10th, and 12th graders [9]. Substance dependence is equivalent to addiction and usually is accompanied by physiological changes related to chronic drug administration, including tolerance, withdrawal, unsuccessful efforts to stop using the drug, interference with important daily activities, and spending a great deal of time and effort obtaining the drug. Alcohol and drug use and misuse in adolescence have important neurodevelopmental consequences. Functional MRI studies of adults dependent on cocaine have shown abnormal responses in the prefrontal cortex and basal ganglia, including the nucleus accumbens and related structures, and that the clinical effect of cocaine ingestion coincides with rapid saturation of dopamine transporters in the basal ganglia [10]. Other neuroimaging studies have found a smaller prefrontal cortex and hippocampus in young adults who had been dependent on alcohol during adolescence. Large epidemiological studies of US adults found that those who had their first alcoholic drink before age 14 or first drug use before age 15 were three times more likely to develop alcohol or drug dependence than those whose first use was at an older age. Regular use of marijuana before age 15 may be linked with increased risk of subsequent psychosis [10]. As noted previously, executive functions are developing in the adolescent, and recent research has confirmed associations between poor development of these functions and adolescents who are at high risk of developing alcohol/substance abuse problems. In addition, there is a familial or genetic component to substance abuse behaviors [11].

There is concern that the opioid use and overdose epidemic in recent years can have its origin for some of those affected in first-time use of medication prescribed for postoperative pain or for other people, either family members or diverted from other sources. A major US annual survey indicated that the annual incidence of non-medical use of hydrocodone decreased significantly in 2017 among 12th graders to about 2%, down from a high of 10% in 2002–2009 [9]. However, the overall tripling of overdose deaths in the USA from 1999 to 2014 has also been observed in late adolescence and early adulthood, with a combined rate of heroin and prescription opioid overdose mortality of about 10 per 10,000 in 20- to 21-year-olds in 2014 [12]. In a survey of 343 inpatients (two-thirds of whom were 8–21 years of age) prescribed opioid pain medication on postsurgical discharge, the median number of doses dispensed was 43, but 58% of doses were not consumed [13]. Only 4% of families disposed of leftover opioid.

This survey has brought attention to the potential for overprescribing of postoperative opioids to adolescent patients, and the risk that they could be diverted or misused.

Where there is concern that alcohol or substance use may affect the course of the anesthetic, the best solution is often to ask the parent or guardian if the anesthesiologist can ask the patient a few questions in private, and then take a history of drug or alcohol use by asking direct questions in a non-threatening, non-accusatory manner, emphasizing that this is necessary to provide the best possible care. In urgent or emergent surgery where the patient is suspected to be under the influence of alcohol or drugs, it is important to ascertain as far as possible what drugs were ingested. Acutely, central nervous system depressants will decrease minimum alveolar concentration (MAC) and other anesthetic requirements, whereas central nervous system (CNS) stimulants often have sympathomimetic effects and anesthetic requirements are usually increased and hemodynamic responses exaggerated, i.e. dangerous hypertension and tachycardia are possible. Chronic use of opioids will increase requirements for these drugs, and chronic use of alcohol and other CNS depressants will increase MAC [13–16].

Teen cigarette smoking

Recent US national surveys show that about 10% of 12th graders (17- to 18-year-olds) currently smoke cigarettes, defined as smoking on at least 1 day in the last month; of these, 4.2% smoke frequently, defined as smoking on at least 20 days in the last month. This represents a decline of over 75% since the late 1990s [9,17]. In the adolescent undergoing anesthesia and surgery, several potential adverse effects of smoking are possible. Airway and respiratory events after general anesthesia are more common in smokers. In a large prospective data collection in over 26,000 anesthetics, adverse events were compared in 7100 smokers and 19,000 non-smokers, patients being as young as 16. Respiratory events, including bronchospasm (the most frequent), laryngospasm, hypoxemia, and others, were 2.3 times more common in young smokers [18]. It is well known that carbon monoxide levels in the blood of heavy smokers may exceed 10%, impairing oxygen-carrying capacity and delivery. Cigarettes function as a means to deliver nicotine rapidly to the CNS. Nicotine activates several types of acetylcholine receptors, predominantly in the CNS, and is postulated to modulate neurotransmitter release, including dopamine. Despite its potential effects on pain modulation, and acute withdrawal of nicotine in the postoperative period, several studies in adults have demonstrated that nicotine withdrawal symptoms are minimal, and thus perhaps this is an opportunity to achieve sustained abstinence from tobacco [19]. An important effect of tobacco smoke exposure is to exacerbate asthma symptoms and precipitate bronchospasm; since asthma incidence is at its peak during adolescence, any teenager with asthma who smokes should be strongly encouraged to quit [20].

A recent trend among adolescents and young adults is use of electronic cigarettes, known as e-cigarettes. This practice is also termed "vaping," or using a device that results in the vaporizing of a liquid and gives the sensation of cigarette smoking. The majority of toxic chemicals present in tobacco smoke are not present; however, most of these liquids contain nicotine, and other substances can be incorporated, such as marijuana or hashish. Symptoms of chronic bronchitis or wheezing are increased 2-fold in adolescent e-cigarette users [21]. In 2017, about 28% of US 12th graders reported vaping, more than double the incidence of cigarette smoking [9]. A recent meta-analysis of over 17,000 adolescents and young adults aged 14–30 documented that use of e-cigarettes increased the risk of initiating and maintaining cigarette smoking 3- to 4-fold [22].

KEY POINTS: DEVELOPMENTAL/BEHAVIORAL ISSUES IN THE ADOLESCENT

- Adolescence (age 13–19) is a period between childhood and adulthood that is characterized by ongoing cognitive development, greater emotional lability, and increased risk-taking behavior
- Substance abuse has generally declined in recent years during adolescence
- Electronic device use, and electronic cigarette use, have increased dramatically in recent years

Pregnancy/reproductive issues in the adolescent and young adult

Teenage pregnancy testing before anesthesia is a controversial topic, but recent data and publications offer some guidance for pediatric anesthesiologists [23,24]. In the USA in 2013, 456,000 women younger than 20 became pregnant. The pregnancy rate was 43.4 pregnancies per 1000 women aged 15–19, meaning pregnancies occurred in about 4% of women in this age group. In general, the teen pregnancy rate has been declining for the past 30 years; in 2013, the US teenage pregnancy rate reached its lowest point in at least 80 years (43.3 per 1000), down 64% since its peak in 1990 (116.9) [25,26]. The teenage birthrate in 2013 was 26.7 births per 1000 women, a total of over 455,000 births. This was 57% lower than the peak rate of 61.8, reached in 1991. From 1986 to 2013, the proportion of teenage pregnancies ending in abortion declined over one-third, from 46% to 29% of pregnancies among 15- to 19-year-olds. These interesting data make the point that although the teenage pregnancy rate has declined, it is not a rare condition, and the anesthesiologist must consider the possibility when caring for adolescent females. Taking a history about possible pregnancy and missed menstrual periods is known to be inaccurate, thus many pediatric anesthesia departments have instituted policies for routine urine human chorionic gonadotropin (HCG) testing in menstruating females before anesthesia [27] (Table 24.1). At Texas Children's Hospital (TCH), parents are told that this urine pregnancy testing at age 12 or older, or in females who begin menstruation earlier than 12, is routine, and are asked to give consent, but exceptions can be made at the discretion of the anesthesiologist based on medical or cultural grounds. In practice, positive tests are rare, but, after confirmation by serum HCG testing, the policy is to have the surgeon, anesthesiologist, and social worker inform the parent with the patient, after permission has been obtained from the patient. Elective surgery is cancelled because of the potential effects of anesthetics, including benzodiazepines,

Table 24.1 Considerations in preoperative urine pregnancy testing in adolescents

Is it important to identify pregnancy before anesthesia or sedation?	Concerns include risk of congenital malformation, spontaneous abortion, medicolegal risk
What is the risk?	American Society of Anesthesiologists (ASA) Task Force on Preanesthesia Evaluation: the literature is inadequate to inform patients or physicians on whether anesthesia causes harmful effects on early pregnancy
	Pregnancy testing may be offered to female patients of childbearing age and for whom the result would alter the patient's management
What is the incidence of undiagnosed pregnancy?	Kahn et al [110]: five positive tests per 2588; three unrecognized pregnancies, one asymptomatic ectopic, one false positive
	Wheeler and Cote [23]: three positive tests per 235 (two were adults); all denied possibility
	Malviya et al [111]: test results correlated with history (*n* ~500)
What constitutes adequate informed consent?	ASA Committee on Ethics: routine pregnancy testing of all women and/or testing in the absence of informed consent is inconsistent with the privacy and autonomy rights of women making healthcare decisions about these sensitive issues
	"Mature minor" status may apply if patient believes herself to be pregnant
	Generally, parents need to consent for routine testing
Who can be informed if the test is positive?	Varies by state; essential to know local law
	Law may either require or prohibit informing parents
	Support structure (social work) and referral ability should be available if testing is performed
Logistical questions	Accuracy of test, turnaround time, cost, point-of-care credentialing requirements
	Most centers use urine testing unless unable to obtain sample
	Laboratory medicine notes lack of sensitivity early

Source: Reproduced from August and Everett [27] with permission of Elsevier.

halogenated anesthetic agents, and nitrous oxide, on early fetal development. Emergent surgery proceeds, avoiding agents that may be implicated in fetal malformations. At TCH, in 2008–2010, of over 91,000 anesthetics, approximately 9% were performed in menstruating females. During this period, only four of more than 6000 urine HCG tests were positive. Before implementing a policy concerning preoperative urine pregnancy testing, institutional, local, and state laws and regulations must be consulted. In general, reproductive confidentiality laws mandate that the pregnant teen under the age of 18 has the right to be informed first of a positive test, and to decide whether her parents are notified. In practice, this situation is rare, and the involvement of experts in social work, behavioral health, and adolescent medicine is highly desirable in this complicated situation.

Chronic diseases in the adolescent and young adult, and transition to adult care

Pediatric anesthesiologists care for a large number of patients for procedures caused by chronic diseases that are congenital or start in infancy or early childhood and continue through adolescence and into adulthood. Very often these patients and parents are very attached to their caregivers in the pediatric environment and have developed great trust and confidence in them. Expertise in a specialized pediatric field such as congenital heart disease is not widely available in the adult care environment, and many of these patients are understandably anxious about changing to a set of adult providers in an adult setting. Over 90% of children with chronic diseases now survive into adolescence and early adulthood, and so the concept of transition of care to the adult environment has assumed increasing importance in recent years. In a study of 283 patients aged 14–25 years with chronic conditions across a range of subspecialties who had not yet been transferred to adult healthcare, 50% of patients thought the best age to transfer care was 18–19 years; however, 14% felt that age 20 years or older was best. Some 39% of respondents felt that chronological age was the most important factor in deciding when to transfer care, and 34% said that feeling too old to see a pediatric specialist was the most important factor. Only 11% believed that their relationship with the pediatric specialist was a factor, and 3.5% felt that the severity of the chronic disease was important. Barriers to transition included: feeling at ease with the pediatric specialist, cited by 45%; anxiety because of not knowing the adult specialist (20%); and lack of information about adult services (18%) [28]. This ambivalence on the part of patients, parents, and pediatric caregivers leads to many young adults being cared for in the pediatric setting, and to variable policies about age limits for pediatric care, which are often different in different services in the same institution. In a study of 73 pediatric emergency departments (ED) in the USA, 79% had age limits for treatment, with 18 and 21 years the most often cited cutoffs. Those EDs with age limits over 21 years were most often associated with freestanding children's hospitals. There were many subspecialty-specific exceptions to the age policy allowing older patients to be cared for, with cystic fibrosis (64%), congenital heart disease (56%), and sickle cell disease (53%) the most common. Interestingly, underage exceptions, allowing care in the adult environment for patients less than 18 years, were made most frequently for teen pregnancy (79%), burn patients (50%), and psychiatric patients (40%). Only 18% of institutions had a specific transition of care policy [29]. Recommendations for transition of care plans for pediatric systems include starting education of the patient and family about transition several years in advance and having the patient acquire increasing age-appropriate information about the disease, taking increasing responsibility for their own care, i.e. medication administration and insurance information, and understanding the differences between the adult and pediatric systems [30–33]. It should also be noted that the mentally competent young adult patient (18 years in the USA) legally must sign their own consent for treatments.

Several of the most common chronic disease states presenting for anesthesia care in the transition period from adolescence to adulthood will be discussed.

Cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive disease that affects primarily the respiratory and gastrointestinal systems. Historically, CF was a uniformly fatal disease of childhood; however, it has become more a disease of adolescents and adulthood, with the median age of patients who die now at 28 years, and median predicted survival of 45.1 years [34]. In the United Kingdom, 60% of the people in the CF registry are over 16 years of age. This improvement in mortality is the direct result of more aggressive, standardized treatment involving many disciplines [35–38].

In the past, CF was considered a disease of the Caucasian population. Now the incidence in Caucasian, Hispanic, and African American births is 1 in 2500, 1 in 12,000, and 1 in 15,000 respectively. One thousand patients are newly diagnosed each year in the USA. The prevalence is growing quickly due to the increase in median survival age.

The fundamental defect in CF is a gene mutation on the long arm of chromosome 7 that encodes a protein, cystic fibrosis transmembrane receptor (CFTR), in the apical membrane of epithelial cells in submucosal glands. CFTR is important in the regulation of airway surface liquid. The CFTR mutation causes defective chloride secretion and excessive sodium reabsorption that results in loss of airway surface liquid [39,40]. Beyond the problems of regulation of surface liquid, a profound inflammatory response is present in patients with CF that is only partially explained by ongoing infection. The cumulative effect is persistent progressive symptoms and irreversible lung damage.

More than 2000 known mutations of the CFTR gene have been identified, but genotype and phenotype correlate poorly, especially regarding the severity of lung disease. Only about 200 of these mutations lead to the CF phenotype [34]. Certain genotypes are closely tied to the development of CF liver disease and portal hypertension (SERPINA1 A allele), while other genotypes increase the risk of developing type 2 diabetes with CF (TCF7L2) or of pancreatic insufficiency [41,42].

Pulmonary disease is the source of 90% of the morbidity and mortality. Pulmonary goblet cells exude a thick tenacious mucus that overwhelms mucociliary clearance. Patients develop a severe unremitting cough of secretions that are difficult to clear. The accumulation of secretions leads to airway occlusion, atelectasis, and hypoxemia. The retained viscid mucus is a fertile growth medium for bacteria, especially *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Pulmonary disease begins at a very early age with evidence of lower tract respiratory infections, neutrophilic inflammation, elevated IL-8, and elevated elastase present in infants (median age 3.6 months). Cough is a poor indicator of the presence of *Pseudomonas*, which can be cultured from over 50% of asymptomatic children. Left undetected or untreated, *P. aeruginosa* leads to an increased inflammatory cytokine response and poorer clinical status, made worse by the concomitant presence of *S. aureus*. In older patients, airway contamination with the fungus *Aspergillus fumigatus* and *Stenotrophomonas maltophilia*, an aerobic motile gram-negative rod of low virulence, develops as a consequence of recurrent use of antibiotics [40]. The infections trigger a neutrophilic inflammatory response that damages airways and culminates in bronchiectasis and later bronchomalacia.

The chest roentgenogram may show hyperinflation and flattened diaphragms, bronchiectasis, and cyst formation. Tram-track radiodensities are parallel lines from advanced peribronchial cuffing and bronchial wall thickening. Computed tomography (CT) scans reveal the extent of pulmonary involvement but may overestimate severity of disease as assessed by exercise tolerance.

Airway reactivity is common and may worsen in adolescence. The response to β-agonist bronchodilators may worsen expiratory flow due to progressive loss of airway cartilaginous support. The airway becomes more dependent on muscle tone for patency, and the airways become floppy similar to bronchomalacia. Further smooth muscle relaxation by bronchodilators increases airway obstruction.

Pulmonary function tests (PFT) reveal severe airway obstruction that may be poorly responsive to, or worsen with, bronchodilators. While PFT typically demonstrate increased residual volume/total lung volume (RV/TLV) ratios and decreased forced expiratory volume during 25–75% of expiration ($FEV_{25–75}$), the reduction in forced expiratory volume in 1 s (FEV_1) correlates with reduced survival [35]. Outcome predictors are rapid loss of pulmonary function, poor nutritional status, presence of *Pseudomonas*, persistent rales on pulmonary examination, and frequent clinical illness from infections [43].

Progressive bronchiectasis and airflow obstruction ultimately lead to hypoxemia and finally to hypercarbia. Destruction of pulmonary architecture and chronic hypoxia cause pulmonary hypertension, right ventricular hypertrophy, and eventually cor pulmonale. Patients may feel better with home oxygen and non-invasive ventilation support with continuous positive airway pressure or bilevel positive airway pressure (CPAP, BiPAP). These adjuvants may be very helpful during postoperative care.

All mucosal cells are affected by the defective CFTR, causing generalized mucosal hypertrophy. Nasal mucosal hyperplasia causes chronic sinusitis. Pedunculated nasal polyps are found in nearly half of patients and are most common during adolescence. Although surgical removal of polyps may be necessary, the use of rehydration therapy with hypertonic saline irrigation, topical or inhaled nasal rhDNase (dornase alfa; Pulmozyme®, Genentech Inc., San Francisco, CA, USA), and glucocorticoids may be helpful. The presence of nasal polyposis makes the use of nasopharyngeal airways or nasal tracheal tubes a higher risk than normal.

Pancreatic exocrine function is reduced in 90% of patients. Absent CFTR impairs bicarbonate secretion due to a dysfunctional chloride–bicarbonate exchanger. The volume and pH of pancreatic secretions are reduced. Pancreatic enzymes plug the pancreatic duct, and the retention of those enzymes causes inflammation and autodigestion of the pancreas.

Antenatal accumulation of viscid secretions from the intestinal mucosa glands causes meconium ileus, a bowel obstruction in neonates. Adolescents and adults may have recurrent gastrointestinal obstruction, a meconium ileus equivalent, caused by a similar mechanism. This condition is better termed distal intestinal obstruction syndrome because it may occur in the colon or the ileum. Advanced pancreatic disease,

dehydration, irregular use of pancreatic enzyme supplements, and use of medications that slow intestinal transport are precipitating factors of this condition.

Tenacious secretions obstruct pancreatic exocrine ducts, reducing overall pancreatic secretion of lipase, an enzyme necessary for the hydrolysis and subsequent absorption of fat. Inadequate absorption of fat-soluble vitamins (vitamins A, D, E, and K) worsens the patient's nutritional state and overall quality of life. Vitamin D deficiency leads to fractures from inadequate calcification of bones. Coagulopathy occurs due to reduced vitamin K supplies because of malabsorption and secondary to the effects of chronic antibiotics that reduce enteral bacterial synthesis of vitamin K. Vitamin E deficiency results in ataxia, decreased sensation to vibration, lack of reflexes, and paralysis of eye muscles. A decline in cognitive function is an early sign of vitamin E deficiency, particularly in the pre-teen years. Vitamin A deficiency causes predominantly eye and skin problems while excessive supplementation of vitamin A may cause harm to the respiratory and skeletal systems in children. A Cochrane review found no studies to show that giving vitamin A regularly to people with CF is beneficial [44].

Enteric-coated pancreatic enzyme supplements (Creon® (a delayed-release form of pancrelipase), Pancrease™ (lipase, amylase, and protease)) and fat-soluble vitamin supplements are essential elements of supportive care.

Pancreatic endocrine dysfunction gradually develops from the progressive autodigestion of the pancreas. The loss of islet cell function may become severe enough to trigger diabetes. Curiously, insulin resistance may be concurrent with insulin deficiency and complicate glucose homeostasis. Preparation for intraoperative care requires skilled management of both hyperglycemia and hypoglycemia. Microvascular deterioration of retina, kidney, and peripheral nerves becomes more frequent with prolonged poor glucose management.

The younger the age at diagnosis, the greater is the liver and pancreatic compromise. One-third of patients will have liver dysfunction with fatty infiltration, cirrhosis, and portal hypertension. Cirrhosis is the second most common cause of death in patients with CF. This progression typically occurs in specific histocompatibility complex genotypes, with male gender, or when nutrition is poor. If liver disease is suspected from function tests, preoperative evaluations for biliary fibrosis and cirrhosis may be necessary since they may cause coagulopathy and altered drug metabolism.

Bone demineralization is common in patients with CF. Poor nutritional status with malabsorption of vitamin D and the administration of steroids are precipitating factors for fractures and scoliosis. In addition, chronic pulmonary infections increase serum cytokines and stimulate bone resorption. Scoliosis and/or kyphosis in patients older than 15 years is seen in 75% of females and over 30% of males. Prevention of skeletal degeneration includes aggressive nutritional support with pancreatic enzyme supplements and fat-soluble vitamins, and treatment with growth hormone, calcium, and sex steroids.

Congenital absence of vas deferens with obstructive azoospermia causes infertility in 95% of males. Menstrual irregularity from chronic disease and thick cervical secretions reduce fertility in females. The natural history of CF is one of progressive deterioration. It is important to monitor carefully the quality of life indicators, the presence of depression, and the patient's ability to cope, as it will directly affect their compliance with treatment [45].

Treatment of cystic fibrosis

Inhaled hypertonic saline acutely increases mucociliary clearance and is a safe, inexpensive means of improving clearance of secretions. Chest physiotherapy, employing percussion via exhalation flutter valves or direct chest compression, serves to improve the efficacy of the patient's cough.

Although it has been used clinically for decades, the effectiveness of inhaled N-acetylcysteine (NAC) (Mucomyst® Bristol-Myers Squibb and others) has been questioned. NAC is thought to reduce mucus viscosity by splitting disulfide bonds that link proteins present in the mucus (mucoproteins), but evidence that this results in improved mucus clearance is absent [46]. However, high-dose oral NAC is thought to modulate inflammation in CF and may counter the intertwined redox and inflammatory imbalances [47].

Aerosolized antibiotics (i.e. tobramycin, aztreonam) decrease the population of *P. aeruginosa*, thereby reducing hospitalization and the rate of pulmonary deterioration. Even short-term use of inhaled aztreonam is effective in improving lung function [48] and quality of life indicators.

Oral azithromycin, an acid-stable derivative of the macrolide antibiotic erythromycin, is a component of standardized maintenance therapy for patients with CF. The drug's principal effects appear to be unrelated to its antibiotic effect, acting through modulation of proinflammatory effects of bacterial infection and alteration of the virulence of *Pseudomonas*. Azithromycin interferes with neutrophil recruitment, chemotaxis, and oxidative bursts, all of which injure airways during infections. With protracted use, azithromycin is associated with gradual improvements in FEV_1 and forced vital capacity (FVC). It appears especially useful in patients with persistent *Pseudomonas* infection, but this may not be due to its antibiotic potential. Subinhibitory concentration of azithromycin can be bactericidal to *P. aeruginosa* when exposed for protracted periods [49].

Bacterial growth in biofilms is associated with reduced sensitivity to antibiotics. Formation of biofilms is an iron-dependent process, and iron chelation therapy, when combined with antibiotics, reduces biofilm formation and leads to enhanced antibiotic susceptibility of *P. aeruginosa* [50].

Deoxyribonuclease I (DNase), a bovine recombinant enzyme, and its recombinant twin, rhDNase (dornase alfa, Pulmozyme®) catalyzes the hydrolytic cleavage of phosphodiester linkages in the DNA in white blood cells that accumulate in the mucus. When white cell DNA is hydrolyzed, the "stickiness" of the mucus is reduced, and it is much easier to clear from the lungs. The net effect is to reduce air trapping, improve FEV_1, and reduce the frequency of clinical infections. Although rhDNase is efficacious at reducing atelectasis, hyperinflation, and mediastinal shift over a period of 3 days, its use in the hyperacute setting of the operating room has not been demonstrated. Prolonged use of rhDNase does not reduce pulmonary colonization, and the timing of its administration to chest percussion is a subject of considerable debate. A recent meta-analysis of 19 randomized trials of dornase alfa in over 2500 CF patients demonstrated clear benefit of dornase alfa over placebo or hypertonic saline on FEV_{1at} 1, 3, and

6 months, and 2 years, and a decrease in pulmonary exacerbations. Daily dornase alfa is one of the newer treatments in recent years that is believed to be responsible for improved CF outcomes [51].

A new treatment option is to increase the amount of functioning CFTR at the cell surface. Phe508del is the most common CFTR mutation; approximately 45% of patients with CF are homozygous for this allele. A two-step process is felt to be ideal at restoring CFTR function: correction of cellular misprocessing to increase the amount of functional mutated CFTR, and potentiation to further increase channel opening. Ivacaftor is an approved oral CFTR potentiator that increases the probability that CFTR channels will be open *in vitro* and improves clinical outcomes in patients 6 years of age or older who have CF and at least one copy of most CFTR mutations [52]. Lumacaftor is an investigational agent that corrects CFTR misprocessing, increases the amount of the transporter protein, and increases chloride transport when used together with ivacaftor to a greater extent than either agent alone. In two phase III randomized trials, 1100 subjects were assigned to either both drugs, or lumacaftor, or ivacaftor alone, with placebo, for 24 weeks. Twenty-five percent of the patients were 12–18 years of age, and average age in the study was 24–25 years. The combination of both drugs resulted in a mean relative improvement in FEV_1 of 4.3–6.7% ($p < 0.001$). Pooled analyses showed that the rate of pulmonary exacerbations was 30–39% lower in the lumacaftor–ivacaftor groups than in the placebo group; the rate of events leading to hospitalization or the use of intravenous antibiotics was also lower in the lumacaftor–ivacaftor groups [53].

Gene therapy is another novel treatment approach, considered experimental at this writing but showing promise in improving the chronic course of CF. A randomized, blinded, placebo-controlled trial of a nebulized plasmid DNA encoding the CFTR gene in a liposome complex on a monthly basis for 12 months was recently reported [54]. There was a significant improvement in FEV_{1in} the CFTR gene group (3.7%, $p = 0.046$), proving the concept that this therapy can be delivered safely and improve lung function.

Sinus surgery in cystic fibrosis

The paranasal sinuses become infected before pulmonary contamination and infections begin. As patients age, they are more likely to have infection in both upper and lower airways. Bacteria spread from the sinuses to the lungs in CF [55]. Because the upper and lower respiratory tracts have the same mucosal lining, improvements in sinus health reduce the frequency and severity of lower tract infections.

Nasal obstruction and chronic rhinosinusitis are common otorhinological manifestations of CF. The altered viscoelastic properties of mucus result in impaired ciliary function and obstruction of sinus ostia. Chronic sinusitis and mucosal edema lead to sinonasal polyposis and nasal obstruction in nearly all adolescent and adult patients. The sinonasal disease increases the risks of pneumonia, the bacterial origin of which lies in the paranasal sinuses [56].

The prevalence of nasal polyposis in children with CF is 6–48% [56]. Nasal polyps begin as an edematous growth of mucosa as a consequence of an inflammatory mucosal reaction in the paranasal sinuses. They are commonly found bilaterally and lead to septal deviation, bulging of the nasal dorsum, and even hypertelorism [57].

Almost all CF patients have abnormalities on CT; the findings do not correlate well with symptom severity. Surgical intervention for sinus disease is based on symptom management, pulmonary status, and frequency of infection. Endoscopic sinus surgery is safe and at least temporarily effective at reducing these complications. Grading the severity of nasal polyposis can help predict the need for future sinus surgery [58]. A recent review reported that about 2–3% of pediatric CF patients undergo sinus surgery annually; indications and frequency of surgery vary widely by institution and short-term improvement is usually seen but there is a paucity of data about long-term outcomes [59].

Chronic high-dose ibuprofen in pediatric patients with CF appears to be effective in management of nasal polyposis in young adults [60]. Hypertonic saline lavages improve clearance of viscid secretions. Despite aggressive medical management, approximately one-quarter of patients with CF require sinus surgery. Paranasal sinus surgery in children and young adults with CF can be safely performed, resulting in symptom reduction and improving rhinosinusitis symptoms (less facial pain, headache, nasal obstruction, postnasal drip, and rhinorrhea). Although combined medical and surgical management may yield symptomatic relief, the infections, obstruction, and nasal polyposis can recur because CF is a chronic, unremitting disease.

Intraoperative management of CF patients undergoing open or endoscopic sinus surgery includes appreciation of the degree of nasal airway obstruction, avoiding instrumentation of the nares with tracheal tubes and nasal airways, management of vitamin K-deficient coagulopathy, and readily available equipment for suctioning tenacious mucus from the lungs.

Portosystemic shunts

Liver disease is the second most common death of patients with CF, occurring in over one-quarter of the patients [61]. The purported pathophysiological mechanism of liver injury is focal inspissation of bile due to its abnormal viscosity, decreased flow, and high concentrations in the liver tissue. The decreased bile flow obstructs small biliary ductules and induces collagen deposition in the portal tracts [62]. The spectrum of clinical liver disease in patients with CF runs from cholestasis to focal biliary cirrhosis to multilobular cirrhosis and, finally, to portal hypertension. Portal hypertension occurs in 7% of the most severely affected patients, with a preponderance of male gender. It causes massive splenomegaly, hypersplenism, ascites, and esophageal bleeding from varices [63]. Initial management of variceal bleeding may include sclerotherapy, while a portosystemic shunt in its various forms (Fig. 24.2) provides more definitive relief of the complications of portal hypertension [64]. Increasingly, liver transplantation is an option for CF patients with significant liver disease. See Chapter 30 for more detail about this approach.

Pulmonary surgery in cystic fibrosis

Pulmonary surgery in patients with CF requires special comment. Surgical treatment of bronchiectasis, whether segmental or diffuse, may be indicated to reduce cough sputum production and decrease the rate at which new areas of

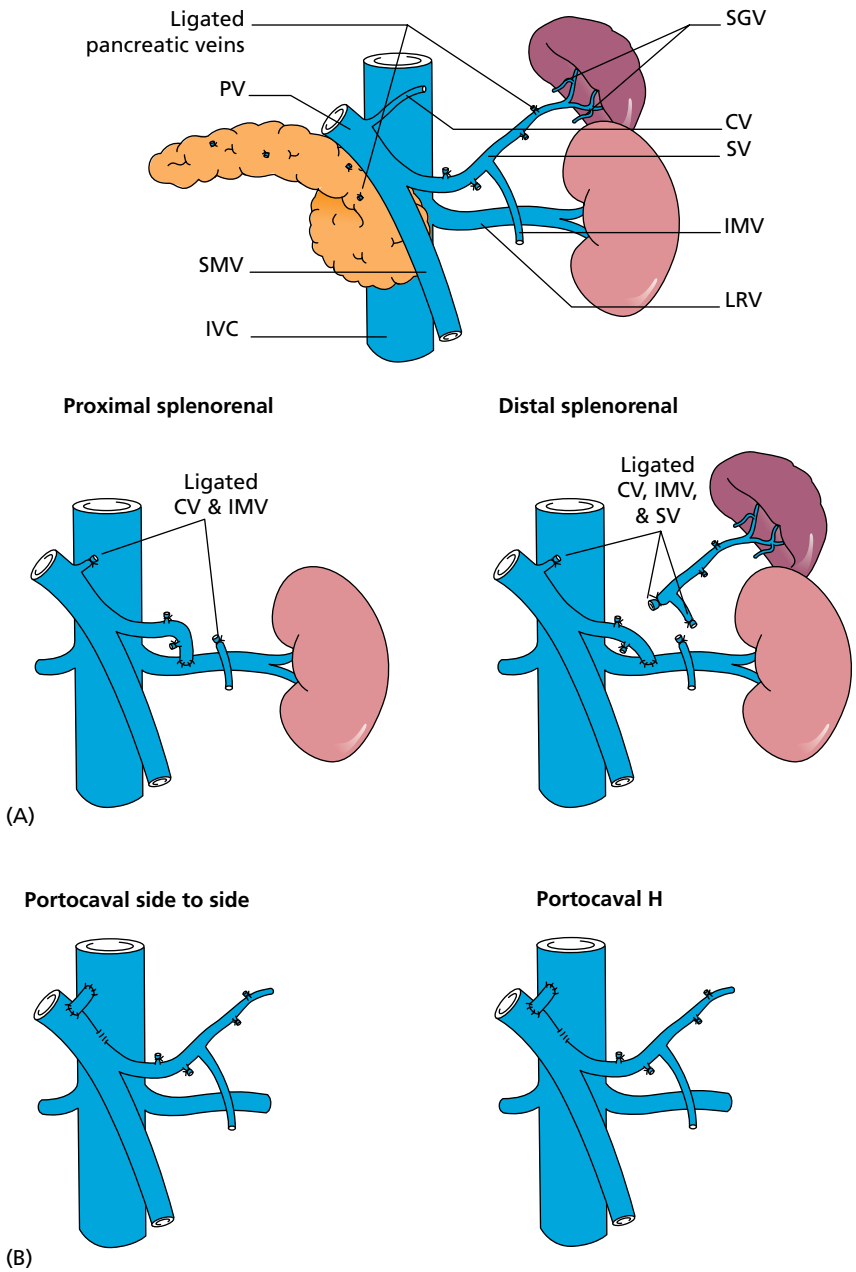

Figure 24.2 The four types of shunts. CV, cardiac vein; IMV, inferior mesenteric vein; IVC, inferior vena cava; LRV, left renal vein; PV, portal vein; SMV, superior mesenteric vein; SGV, short gastric veins; SV, splenic vein. *Source:* Reproduced from Lillegard [64] https://www.hindawi.com/journals/hpb/2010/964597/abs/. Licensed under CC BY.

bronchiectasis form. Pulmonary function is affected very little by the resection since the area of diseased lung contributes little to respiratory function. Resection may reduce the severity of symptoms and improve oxygenation. Even larger resections may be tolerated.

In severe or recurring cases of pneumothorax, bleb resection and/or multiple treatments with talc pleurodesis may be necessary. Talc creates an enhanced pleural reaction and causes the parietal and visceral pleural surfaces to adhere, thereby reducing the frequency of pneumothorax. This technique is particularly helpful in patients with bleb formation. Unfortunately, future surgical procedures (i.e. lobe resections, lung transplants) become extremely difficult.

CF is the third most common indication for pulmonary transplantation in adolescents and adults. The calculated survival must be less than 50%, or life expectancy <2 years, typically marked by FEV_1 <30%, PaO_2 <50 mmHg, and $PaCO_2$ >55 mmHg. The most common precipitating conditions for transplantation are progressive loss of FEV_1 <30%, severe hypoxemia and hypercarbia, increasing frequency of hospitalization, and hemoptysis. When transplantation is a consideration, bilateral lung transplants are usually required due to cross-contamination of the good lung. A review of 9 years of pulmonary transplantation revealed that older patients have improved cumulative survival when compared to younger patients [65]. Older patients have less infections, bronchiolitis obliterans, and graft rejection. Patients 6–10 years of age receiving transplants for CF have similar overall survival to patients of the same age being transplanted for other reasons. Evidence-based decision aids

help to improve expectations of lung transplantation and prepare patients for the post-transplantation experience [66]. See Chapter 30 for a detailed discussion of the anesthetic management of lung transplantation.

Anesthetic management in cystic fibrosis

The perioperative evaluation should be designed in accordance with the severity of clinical disease and the extent of the operative intervention planned. Routine chemistries, liver profile, and coagulation assessments are warranted. Exercise tolerance is a good prognostic indicator that may determine the risk for postoperative pulmonary complications. Pre-operative arterial blood gases are helpful to determine stage of disease and may help in guiding postoperative care.

The anesthetic should be designed to facilitate early extubation and avoid prolonged mechanical ventilation. Volatile agent anesthetics may be of benefit in patients with bronchospastic disease that is known to improve with bronchodilators. Total intravenous anesthesia may be best for patients whose degree of airway obstruction becomes more severe with bronchodilators or when vapor diffusion is severely affected by the extent of pulmonary disease.

Propofol normally has 30% first-pass metabolism in the lungs. Its clearance may be substantially increased in the presence of active inflammatory lung disease like CF and much larger doses may be required to achieve adequate anesthesia. Inadequate insulin supply, along with the presence of insulin resistance, makes intraoperative glucose monitoring imperative. The tracheal tube selected should be as large as possible to facilitate suctioning. Because of nasal mucosa hypertrophy and the potential for nasal polyps, nasal airway devices should be avoided if possible. Inspired anesthetic gases should be humidified, and frequent suctioning with or without bronchodilators may be required.

Use of neuromuscular blocking drugs (NMB) may complicate ventilation in patients who rely on muscle tone for airway patency. Avoiding prolonged administration of NMB, particularly in combination with adrenocorticosteroids, is essential to avoiding muscle weakness, prolonged ventilation support, and additional pulmonary infections.

Prior to extubation, tracheal suctioning, with or without aerosolized hypertonic saline treatment, and lung recruitment maneuvers are helpful to restore pulmonary function. Patients may need longer periods of observation postoperatively, until effective analgesia is balanced against the need for additional oxygen support.

Non-invasive ventilation support (CPAP, BiPAP) is helpful postoperatively. Aggressive pulmonary toilet including percussion postural drainage and flutter valve therapy is beneficial to improve postoperative function. Inhaled hypertonic saline or rhDNase may facilitate secretion clearance and be efficacious at treating atelectasis.

Postoperative pain control should not be provided exclusively with opioids because of their effect on intestinal transit and its potential to initiate distal intestinal obstruction syndrome. Acceptable analgesic adjuvants include non-steroidal anti-inflammatory drugs, continuous IV infusion of lidocaine (because of its ability to reduce inflammation), and low-dose ketamine (for modulation of pain via N-methyl-D-aspartate (NMDA) receptors). If the procedure and parameters permit, regional or neuraxial anesthetic techniques may lower the risks of altered drug metabolism and excretion.

KEY POINTS: CYSTIC FIBROSIS

- CF results from an autosomal recessive gene mutation on the long arm of chromosome 7 that encodes cystic fibrosis transmembrane receptor in the apical membrane of epithelial cells in submucosal glands, affecting primarily the lungs but with multiorgan effects
- Survival and lung function in CF have dramatically improved in recent years due to a standardized multisystem approach and new therapies such as dornase alfa and ivacaftor
- Endoscopic sinus surgery, portosystemic shunts, thoracic surgery, lung transplant, and liver transplant are performed in CF patients

Congenital heart disease

Congenital heart disease (CHD) is the most common birth defect requiring treatment, being present in 8 per 1000 births in the USA and Europe. Because of improved survival rates (now above 90%) for neonatal and infant cardiac surgery for complex lesions, the vast majority of these patients survive into adolescence and adulthood and present both for cardiac surgery and non-cardiac surgery for a range of procedures similar to patients without CHD. In the USA there are approximately 1 million children and 1 million adults over the age of 18 living with CHD. Of these survivors, 55% have simple disease, 30% moderately complex, and 15% complex lesions [67]. For patients with CHD it is crucial to have current, accurate information about the status of their cardiac condition and repair. Patients with complex and moderately complex lesions must have an evaluation by a cardiologist with expertise in CHD that is recent, and have their medical condition optimized for the surgery and anesthetic [68]. Patients with significant potential for instability and need for specialized care should undergo anesthesia only in facilities where such expertise is readily available whenever possible. Infective endocarditis prophylaxis guidelines must be followed [69]. For more detail about the preanesthetic evaluation and anesthetic management of patients with CHD for both cardiac and non-cardiac surgery, see Chapters 27 and 28.

Cancer

The most common new cancers diagnosed in the adolescent population in 2010–2014, in the 10–14-year and 15–19-year age groups, and their incidences per 1 million population, are: (1) leukemias (33 and 32 per million); (2) lymphomas (25 and 49 per million); (3) brain and spinal neoplasms (27 and 23 per million); (4) malignant bone tumors (13 and 14 per million); and (5) soft tissue and other extraosseous sarcomas (13 and 17 per million) [70]. Testicular cancer in 15- to 19-year-old males is - the most prevalent malignancy in that age/gender group at 40 per million [70]. Five-year survival for all cancers in childhood is improving, and in 2007–2013 was 84.8%, with leukemias and lymphomas having the best

survival at 85–97%, and malignant bone and CNS cancer the lowest survival at 74–75% [70]. These adolescent cancer patients will present for anesthesia for a wide variety of procedures, including primary and secondary resection of tumors (sometimes after initial chemotherapy) and metastatic lesions, vascular access procedures, bone marrow aspirations, and many others. The reader is referred to chapters elsewhere in this text for a discussion of anesthetic management of procedures in specific organ systems. Radiation therapy is common in these patients. Emergency radiation therapy in the patient with lymphoma or leukemia and an anterior mediastinal mass and airway obstruction is a rare occurrence, but fraught with the dangers of managing the airway coupled with transport to a remote location. See Chapter 26 for a discussion of the anesthetic management of the patient with a mediastinal mass. Many patients will require a number of follow-up imaging procedures, including MRI, CT, positron emission tomography/CT (PET/CT), and ultrasounds, but sedation is not needed for the vast majority of adolescent patients.

As with many other congenital and acquired conditions in childhood, survival for childhood cancers has increased dramatically over the past several decades. Many of these patients present for anesthetic care, either for procedures for follow-up or treatment of their cancer, or for completely unrelated issues. The residual medical and psychological problems that may be present in these adolescents are important for the pediatric anesthesiologist to understand [71]. When evaluating these patients, knowledge of their past treatments is important, particularly chemotherapy and radiation therapy, which can affect cardiac and pulmonary function (Table 24.2). For example, anthracycline chemotherapy may cause cardiomyopathy, and routine follow-up with echocardiography is performed on all these patients. Pulmonary and renal toxicity should also be sought out and the anesthetic planned accordingly. Cranial irradiation is used commonly to treat leukemia and CNS tumors and leads to a significant incidence of neurodevelopmental disability.

As with many chronic illnesses, survivors of childhood cancer have an increased incidence of psychological problems. In a review of psychological and quality of life studies in over 7000 adolescent and young adult cancer survivors, the cancer survivors were 80% more likely than the general population to report clinically relevant impairments in mental health, and twice as likely to report emotional distress [72]. Those with particularly high levels of anxiety and depression include patients with CNS tumors, bone tumors, leukemia, and lymphoma, and those who have undergone cranial irradiation. Chronic pain may also be an important component of the residual medical problems for cancer survivors.

Sickle cell disease

Sickle cell disease (SCD) is an autosomal dominant condition caused by a substitution of the normal glutamate by valine at the sixth position of the β-globin chain of

Table 24.2 Long-term effects of childhood cancer

System	Risk factor	Potential effect
Cardiac	Radiation therapy Anthracyclines	Valvular disease Pericarditis Myocardial infarction Congestive heart failure Sudden death
Pulmonary	Radiation therapy Carmustine/lomustine Bleomycin	Restrictive lung disease Exercise intolerance
Renal/urological	Radiation therapy Platinums Ifosfamide and cyclophosphamide Cyclosporin A Nephrectomy	Atrophy or hypertrophy Renal insufficiency or failure Hydronephrosis Chronic cystitis
Endocrine	Radiation therapy Alkylating agents	Growth failure Pituitary, thyroid, and adrenal disease Ovarian or testicular failure Delayed secondary sex characteristics Infertility
Central nervous system	Radiation therapy Intrathecal chemotherapy	Learning disabilities
Psychosocial	Childhood cancer	Post-traumatic stress disorder Employment and educational difficulties Insurance discrimination Adaptation and problem-solving difficulties Difficulties with transition to independence
Second malignancies	Radiation therapy Alkylating agents Epipodophyllotoxins Type of primary malignancy	Solid tumors Leukemia Lymphoma Brain tumors

Source: Reproduced from Henderson et al [71] with permission of the American Academy of Pediatrics.

hemoglobin, producing hemoglobin S instead of the normal hemoglobin A. Sickle cell anemia is most common in populations whose origins are from Africa, South or Central America (especially Panama), the Caribbean islands, Mediterranean countries (Turkey, Greece, and Italy), India, and Saudi Arabia. In the USA, an estimated 70,000–100,000 children and adults have a diagnosis of sickle cell anemia, mainly African Americans. The disease occurs in about 1 of every 500 African American births, and also occurs in more than 1 of every 36,000 Hispanic American births. More than 2 million Americans have sickle cell trait (heterozygous hemoglobin AS); this condition occurs in about 1 in 12 African Americans [73]. Worldwide, an estimated 300,000 babies are born with SCD annually, the majority in three countries: Nigeria, the Democratic Republic of the Congo, and India [74]. Homozygous hemoglobin SS causes abnormal aggregation of hemoglobin under conditions of low oxygen tension or acidosis, resulting in reduced red cell elasticity and causing the characteristic sickle shape of erythrocytes with homozygous SCD. This in turn leads to impedence of passage of deformed erythrocytes through capillaries in all organ systems, resulting in the myriad problems seen in this disease (Fig. 24.3). Red cell survival is shortened, leading to hemolysis and anemia, with most patients maintaining hemoglobin levels between 7 and 9 g/dL. Homozygous SS patients are usually significantly affected and have hemoglobin S concentrations that exceed 80%. In the USA, about two-thirds of SCD patients have this genotype. Other variants, such as hemoglobin SC disease, or hemoglobin S β-thalassemia, are also frequently encountered. In terms of severity of disease, hemoglobin SS and S-β° thalassemia genotypes generally are most affected, although symptoms vary. Heterozygous carriers with one copy of the hemoglobin S gene are usually relatively asymptomatic [75].

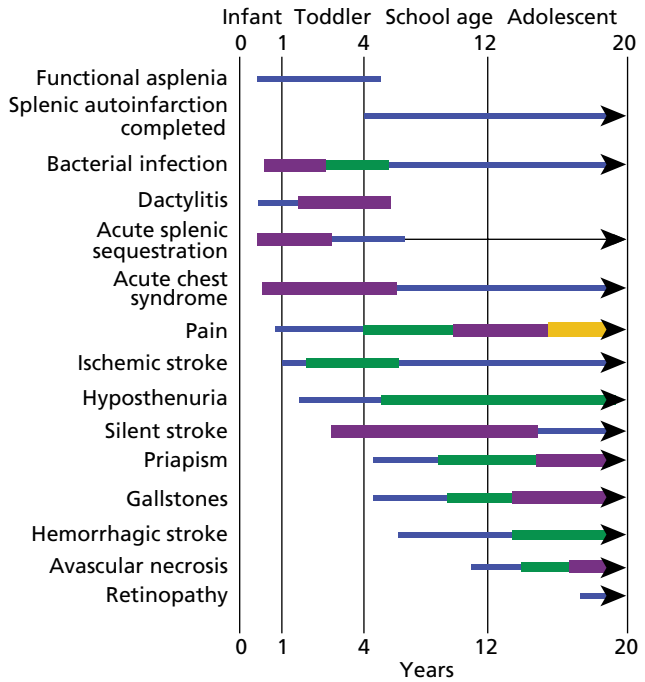

Figure 24.3 Sickle cell disease complications by age. Width and color of the arrow shaft signify the relative incidence of the complication. *Source:* Reproduced from Redding-Lallinger and Knoll [75] with permission of Elsevier.

Problems of particular importance for the adolescent with SCD are acute painful crises and chronic pain, strokes, priapism, cholelithiasis, and avascular necrosis of the hip and other joints [74] (Fig. 24.4). Acute chest syndrome episodes, resulting in pulmonary hypertension, are also seen in this age group. Current therapy for SCD often involves chronic transfusion therapy to maintain higher levels of hemoglobin A and lower levels of hemoglobin S. This therapy has been demonstrated to reduce episodes of painful crisis, stroke, priapism, and acute chest syndrome, and reduce risk for chronic pain and pulmonary hypertension. In recent years hydroxyurea treatment has been demonstrated to increase the percentage of hemoglobin F (fetal hemoglobin) and decrease the percentage of hemoglobin S, resulting in reductions in episodes of painful crises and acute chest syndrome. Leukopenia and thrombocytopenia are possible side-effects of hydroxyurea treatment. Packed red blood cell transfusion or exchange transfusion is used for acute problems such as acute chest syndrome, painful crises, priapism, and acute stroke. Erythrocytes for transfusion should be sickle negative, leukocyte-poor and matched for C, E, c, e, and Kell antigens as well as Rh D and ABO (extended cross-matching or partial phenotypic matching). This will reduce the risk of alloantibody sensitization against the many antigens the patient is likely to be exposed to during future transfusion therapy. Hematopoietic stem cell transplantation in children with SCD is 85% effective in curing the disease. Matched sibling donors are associated with a survival rate of >90%, with the lowest rates of rejection and graft versus host disease; unfortunately, only 20% of SCD patients have a matched donor sibling. Gene modification or replacement therapies are experimental and have shown some promise in SCD [76]. Gene therapy strategies include replacing the defective β-globin gene utilizing viral vectors, inserting γ-globin genes (increasing HbF production), and genome editing to reactivate silenced γ-globin genes. A summary of current approaches to treatment of sickle cell disease is presented in Table 24.3 [74].

The goal of perioperative anesthetic management in SCD is the prevention of excessive sickling of abnormal cells and thus significant complications such as acute chest syndrome, painful crises, stroke, and other major problems. The cornerstones of management are to avoid known precipitating factors for sickling, including hypoxemia, hypovolemia, acidosis, and hypothermia, which then set off a vicious circle of red cell adherence to endothelium, causing vaso-occlusion, further tissue hypoxia and ischemia, inflammation, activation of coagulation, and further vasoconstriction (Fig. 24.5). Among the most common surgical procedures that adolescents with SCD present for are cholecystectomy for cholelithiasis caused by chronic hemolysis, tonsillectomy, orthopedic procedures for avascular necrosis, and priapism. Case reports and case series of other major procedures, including cardiac surgery with cardiopulmonary bypass, have also been published [77–79]. The most recent consensus guidelines about perioperative management of SCD patients were published in 2014 by the US National Institutes of Health National Heart, Lung, and Blood Institute [80] (Box 24.1). Besides strict attention to preoperative hydration, oxygenation, temperature maintenance with warmed IV fluids and other warming measures such as forced air warming, and avoidance of acidosis and

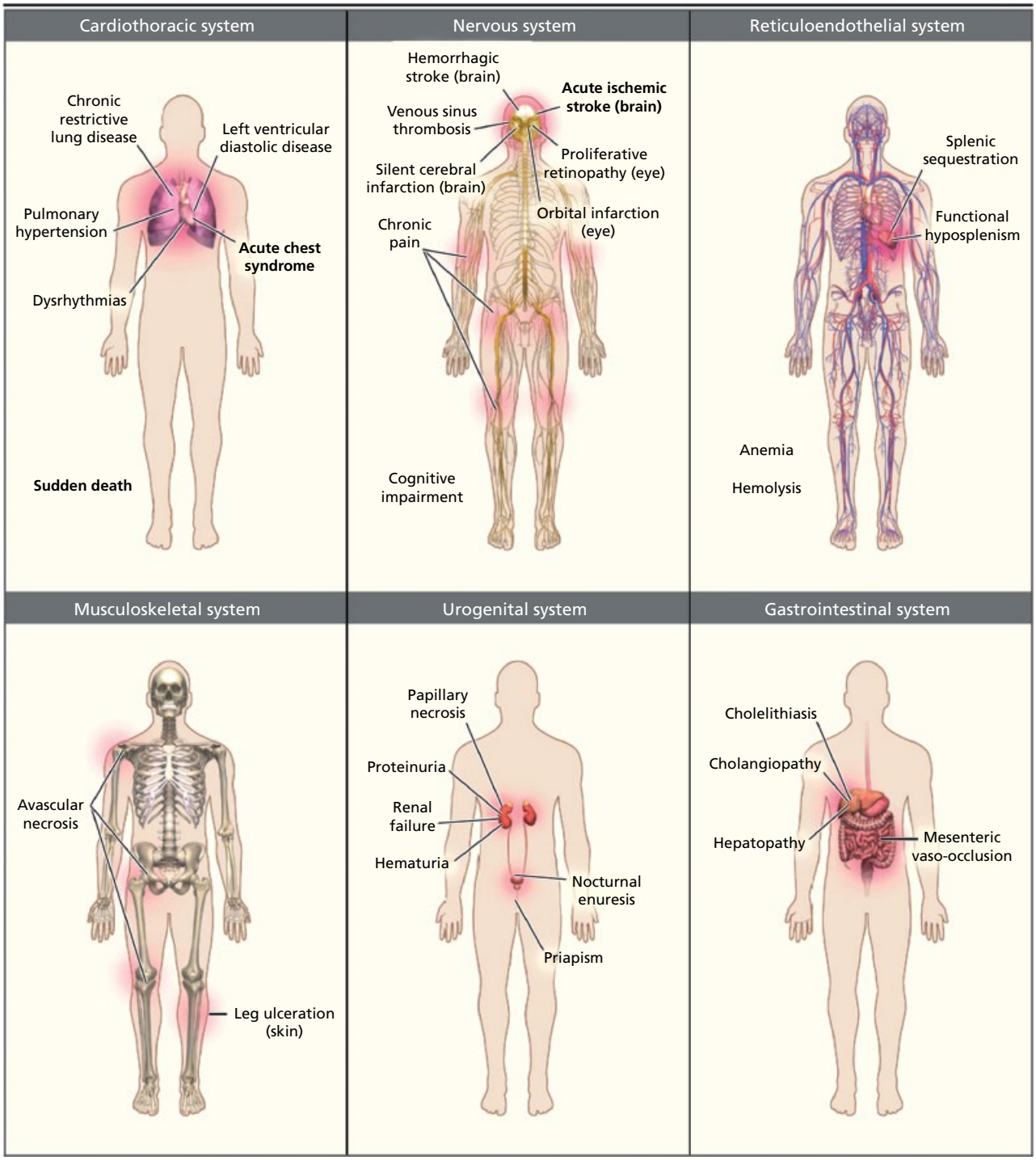

Figure 24.4 Common clinical complications of sickle cell disease. Acute complications are shown in boldface type. *Source:* Reproduced from Meier and Rampersad [76] with permission of Springer Nature.

hypovolemia, simple transfusion to a minimum hemoglobin of 10 g/dL is recommended for all but the simplest procedures. This includes tonsillectomy, open cholecystectomy, major orthopedic procedures, and other major surgery (see Box 24.1). Exchange transfusion is indicated only for very severely affected patients, or for open heart surgery. Perioperative analgesia is critically important to prevent severe pain, stress, catecholamine release, and the precipitation of further acute events. Attention to preoperative opioid and other pain regimens is important, and provision of intraoperative and postoperative pain relief must be carefully considered. Patient-controlled analgesia is often very effective in adolescents with SCD. Supplemental oxygen to maintain high oxygen saturations is important in the recovery period. For any sickle cell patient undergoing anesthesia and surgery, consultation with the patient's hematologist for perioperative recommendations is key in providing optimal care and outcomes. See Chapter 12 for more discussion of the perioperative management of patients with SCD.

Table 24.3 Summary of recommended treatment approaches for sickle cell disease

Treatment approach	Dose and frequency	Duration	Recommendation	Evidence quality
Prevention of infection				
Penicillin V	62.5–250 mg, twice daily	At least until 5 years of age	Strong	Moderate
Pneumococcal vaccines	Every 5 years, starting at 2 years of age	Lifelong	Strong	Moderate
Malarial prophylaxis when appropriate	Daily (e.g. proguanil), weekly (e.g. pyrimethamine), or intermittent (e.g. mefloquine–artesunate or sulfadoxine–pyrimethamine plus amodiaquine)	Lifelong (in malarial area)	Strong	Low
Blood transfusion				
Acute care				
Treatment of anemia	Simple transfusion; target hemoglobin level, 10 g/dL	Limited	Strong	Low
Preoperative transfusion (if hemoglobin <8.5 g/dL)	Simple transfusion, performed once; target hemoglobin level, 10 g/dL		Strong	Moderate
Ongoing care				
Primary stroke prevention	Target HbS, <30%; transfusions every 3–6 weeks	Indefinite	Strong	High
Secondary stroke prevention	Target HbS, <30% or <50%; transfusions every 3–6 weeks	Indefinite	Moderate	Low
Prevention of additional silent cerebral infarctions	Target HbS, <30%; transfusions every 3–6 weeks	Indefinite	Moderate	Moderate
Hydroxyurea				
Universal use	20–35 mg/kg/day	Indefinite	Moderate	Moderate
Prevention of acute complications	15–35 mg/kg/day	Indefinite	Strong	High
Primary stroke prevention	15–35 mg/kg/day	Indefinite	Strong	Moderate

Reproduced from Piel et al [74] with permission of NEJM.

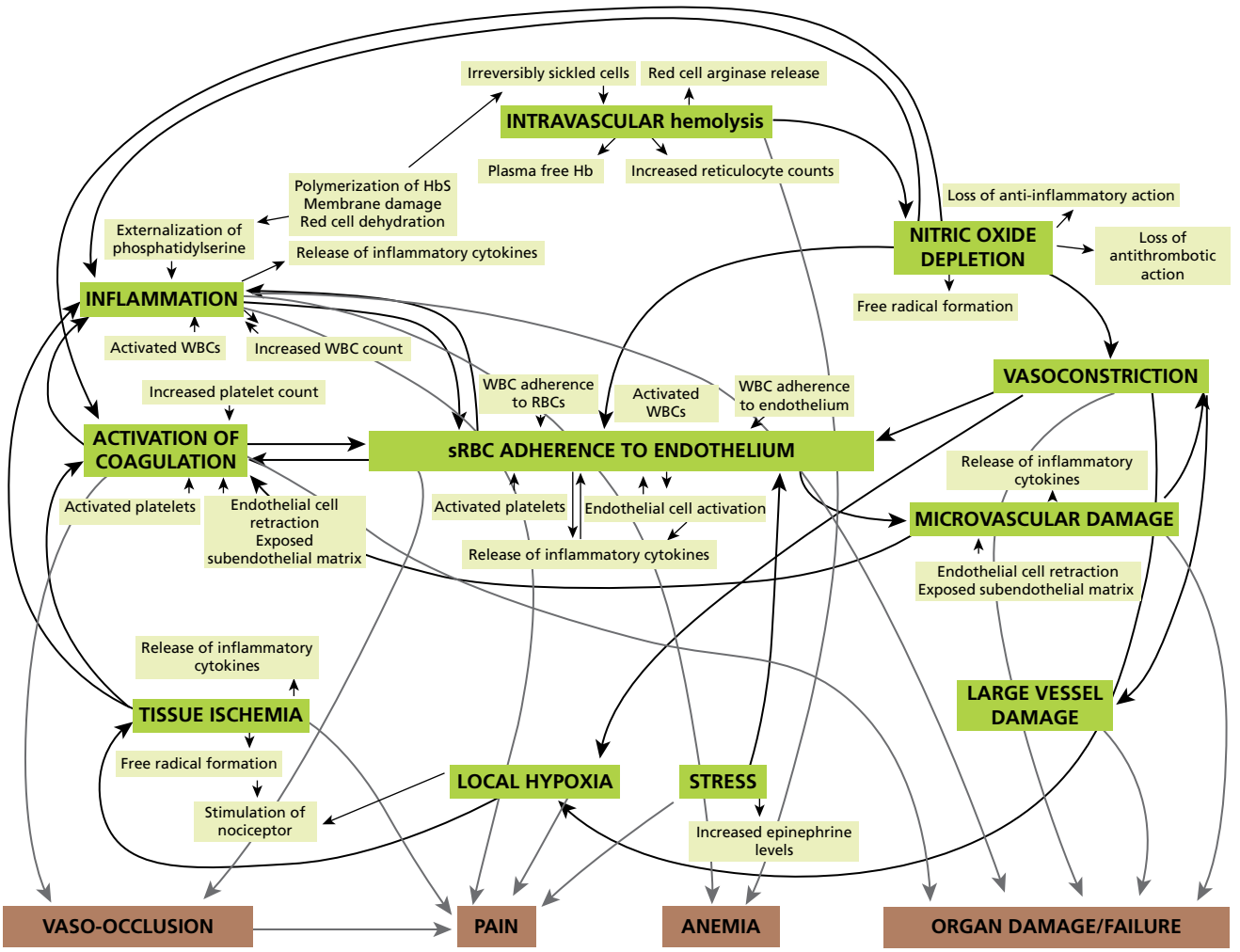

Figure 24.5 Elements of the pathophysiology of sickle cell disease and interactions between them. *Source:* Reproduced from Redding-Lallinger and Knoll [75] with permission of Elsevier.

Box 24.1: Perioperative transfusion recommendations for sickle cell disease

- In adults and children with SCA, transfuse RBCs to bring the hemoglobin level to 10 g/dL prior to undergoing a surgical procedure involving general anesthesia (*strong recommendation, moderate-quality evidence*)
- In patients with HbSS disease who require surgery and who already have a hemoglobin level higher than 8.5 g/dL without transfusion, are on chronic hydroxyurea therapy, or who require high-risk surgery (e.g. neurosurgery, prolonged anesthesia, cardiac bypass), consult a sickle cell expert for guidance as to the appropriate transfusion method (*strong recommendation, low-quality evidence*)
- In adults and children with HbSC or $HbS\beta^+$ thalassemia, consult a sickle cell expert to determine if full or partial exchange transfusion is indicated before a surgical procedure involving general anesthesia *(moderate recommendation, low-quality evidence)*

RBC, red blood cell; SCA, sickle cell anemia.

Source: Reproduced with permission of National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services [80].

KEY POINTS: SICKLE CELL DISEASE

- Sickle cell disease (SCD) is an autosomal dominant condition caused by a substitution of the glutamate by valine at the sixth position of the β-globin chain, producing hemoglobin S instead of the normal hemoglobin A
- Multiorgan effects include painful crises, acute chest syndrome, strokes, cholelithiasis, avascular necrosis of the hip, pulmonary hypertension, and priapism
- Survival and quality of life have improved recently due to chronic transfusions and hydroxyurea
- Simple transfusion to hemoglobin of 10 g/dL, along with hydration, oxygenation, temperature maintenance, and avoidance of acidosis are important intraoperative principles

Diabetes mellitus

In the adolescent population, diabetes mellitus is usually type 1, although the incidence of type 2 diabetes is increasing in this population (see section "Obesity in the adolescent"). Approximately 183,000 children age 0–19 had a diagnosis of diabetes in 2015 in the USA, or 0.24% of this population; 65% was type 1. In the 10- to 19-year age group, 85% of new diabetes in the non-Hispanic white population in the USA was type 1, while in the African American and Hispanic populations, the proportion of new type 1 versus type 2 cases was 37:63 and 45:55. In the Asian Pacific Islander (43:57) and Native American populations, new cases are predominantly type 2 (88%) [81]. The onset of type 1 diabetes usually occurs during childhood or adolescence, and it arises from T-cell-mediated autoimmune destruction of pancreatic β cells, resulting in failure of insulin production and hyperglycemia. The incidence of type 1 diabetes is also increasing in many parts of the world. Associated risk factors include genetics, diet, lifestyle, and immune responses to viral infection, with enterovirus most frequently implicated. Insulin therapy is the cornerstone of treatment for type 1 diabetes [82]. Type 2 diabetes results from resistance to the effects of insulin, causing hyperglycemia. Obesity, particularly adipose tissue deposits in the abdomen, and non-alcoholic fatty liver disease, are associated with this disease in adolescents. Treatment is primarily by diet, exercise, and in some cases, oral hypoglycemic drugs such as metformin, sulfonylureas or thiazolidinediones; insulin is rarely necessary in adolescence [83].

The secondary complications of diabetes, e.g. nephropathy, are rare in adolescents; most diabetics present for anesthesia for the standard surgical procedures seen in patients in this age group. In the insulin-dependent diabetic, there are myriad forms of insulin therapy, ranging from short, medium, to long acting insulin; dosing one, two, or more times per day; or sliding scales. Insulin pumps with continuous basal rates of subcutaneous insulin infusion, superimposed on programmable boluses at mealtimes, or in response to hyperglycemia, are also used [84]. The diabetic patient should have a preanesthetic visit, where gaining an understanding of the insulin regimen, history of diabetic ketoacidosis or hospitalization, and degree of glycemic control (hemoglobin A1C <7.5%) is important, as is coordination with the patient's endocrinologist [85]. Whenever possible, an insulin-dependent diabetic patient should be scheduled as the first case of the day. Generally, the night before surgery, the patient's normal meal and insulin regimen should be followed. Fasting guidelines are not different from non-diabetics for a morning case, i.e. nil per os (NPO) for solid food and non-clear liquids for 6 h preoperatively, and clear liquids allowed up to 2 h preoperatively. For insulin-dependent diabetics who are afternoon cases, a light early breakfast may be preferable. For patients on twice daily or more frequent insulin doses, the current recommendations are to omit short-acting insulin, and to give only 50% of the intermediate insulin dose in the morning. After measuring a baseline blood glucose, an infusion of 5% dextrose in ½ normal saline is started at maintenance rates 2 h preoperatively, or as soon as the patient arrives if an early morning case (1500 mL/ 24 h, plus an additional 20 mL/kg/24 h for each kg over 20 kg, maximum 2000 mL/24 h, i.e. 83 mL/h for a 50 kg patient). Also start an insulin infusion made with 1 unit regular insulin per 1 mL normal saline, at 0.025–0.1 unit/kg/h, depending on the baseline glucose. Glucose must be measured every hour while the patient is on an insulin infusion, and the insulin rate adjusted accordingly, with the goal of maintaining blood glucose 90–180 mg/dL. Additional boluses of IV regular insulin, 0.025–0.1 unit/kg, are given for glucose values above 180 mg/dL. Serum electrolytes, i.e. sodium and potassium, are measured at regular intervals and potassium replaced if needed. After surgery, the glucose and insulin infusion is continued, with the addition of potassium chloride at 20 mEq/L in the IV fluid, if the patient is maintained NPO. If oral intake is allowed, IV dextrose and insulin can be weaned, and the patient's normal evening meal and insulin regimen resumed, if glycemic control is adequate. Patients with infusion pumps must be managed in close consultation with the endocrinologist; pump use may be continued during anesthesia. These recommendations are summarized in Box 24.2. For type 2 diabetes patients on insulin the guidelines are the same. If the type 2 patient is taking metformin, it should be discontinued 24 h before elective surgery. If the patient is taking sulfonylureas or thiazolidinediones, these are stopped on the day of surgery.

Adolescent gynecological surgery

Adolescent gynecology is a growing field, and more of these patients are presenting for surgery. In recent years, most of these procedures have been done laparoscopically. Indications for laparoscopic surgery in females in this age group include congenital anomalies such as Mullerian anomalies and disorders of sex development that may require diagnosis and treatment. Adnexal masses such as ovarian torsion, tumors, or tubo-ovarian abscess are also diagnosed and treated with laparoscopy [86,87]. Other less frequent indications include diagnosis and treatment of endometriosis or pelvic inflammatory disease, and procedures to preserve ovarian function before pelvic irradiation [88,89]. See Chapter 31 for a discussion of the anesthetic management of patients undergoing laparoscopy.

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is classified as either Crohn's disease or ulcerative colitis, and the overlapping clinical features of these diseases often lead to lack of clarity in diagnosis in adolescents [90]. Of patients with IBD, 20–30% are less than 20 years of age, and the prevalence in this age group worldwide has recently been estimated to be 2–13 per 100,000 [91,92]. Crohn's disease is a transmural inflammatory disease of the mucosa with episodic progression. It can involve any part of the gastrointestinal tract from the mouth to the anus, but often is concentrated in the small bowel. Ulcerative colitis is a non-transmural inflammatory disease with episodic progression that is limited to the colon. The clinical features of the IBD depend on its localization and often include diarrhea, abdominal pain, fever, clinical signs of ileus, and the passage of blood and mucus per rectum. Patients with Crohn's disease often do not have bloody diarrhea but rather abdominal pain or non-specific abdominal symptoms, and about 25% have perianal disease on presentation. Table 24.4 summarizes the major features of Crohn's disease versus ulcerative colitis [92]. Growth failure is common in children and adolescents. IBD are autoimmune diseases, associated with susceptibility regions on at least 12 different chromosomes. Other associations include ethnic origin, with Northern European descent predominant, lifestyle, and geographical factors. Extraintestinal manifestations can also be observed, including joint and skin involvement (15–25% in Crohn's disease; 2–16% in ulcerative colitis) [93]. Medical treatment is similar for both Crohn's disease and ulcerative

Box 24.2: Guidelines for perioperative management of patients with insulin-dependent diabetes

NPO guidelines	**6 h preoperatively for solid food, non-clear liquids** **2 h preoperatively for clear liquids**
IV fluids	D5 ½ normal saline 2 h preoperatively at 1500 mL/24 h plus 20 mL/kg for every kg over 20 kg, maximum 2000 mL/24 h
Insulin regimen	No change the evening before surgery Omit short-acting AM insulin, give 50% of usual medium-acting insulin dose
Insulin infusion	Start at 0.025–0.1 unit/kg/h depending on baseline glucose
Glucose measurement	Q 1 h during insulin infusion
Glycemic control	Goal: 90–180 mg/dL; increase or decrease insulin infusion accordingly; may give regular insulin IV 0.025–0.1 unit/kg bolus for values >180 mg/dL, or stop insulin infusion briefly for values below 60 mg/dL
Insulin pump patients	Consult endocrinologist for plan
Postoperative treatment	Continue insulin and glucose infusion if NPO; add KCl 20 mEq/L to IV fluids Wean insulin and glucose and resume normal evening meal and insulin regimen if taking food

IV, intravenous; NPO, nil per os.

Source: Reproduced from Betts et al [85] with permission of John Wiley and Sons.

Table 24.4 Characteristics of Crohn's disease and ulcerative colitis

Clinical features	Crohn's disease	Ulcerative colitis
Sex distribution	Male > female	Male = female
Symptoms and signs	Abdominal pain, diarrhea, weight loss, anorexia, growth failure	Bloody diarrhea, abdominal pain
Location	Mouth to anus; involves all layers of gut: mucosa to serosa; most common: ileocolonic	Colon; involves only mucosa; most common: pancolonic
Endoscopic findings	Segmental distribution, aphthous ulcers, deep fissuring ulcers, cobblestoning, perianal disease, strictures, fistulas	Diffuse and continuous erythema, friability, granularity, loss of vascular pattern from rectum to variable extent
Histological findings	Pathognomonic non-caseating granulomas; patchy cryptitis, crypt abscesses, ileitis	Cryptitis, crypt abscesses, crypt architectural distortion, basal lymphocytosis, distal Paneth cell metaplasia
Radiological findings	Rigid stenotic segments, skip areas, and sinus tracts or fistulas	Dilatation of colon in toxic megacolon

Source: Adapted from Oliveira SB, Monteiro IM. Diagnosis and management of inflammatory bowel disease in children. BMJ 2017; 357: j2083; Conrad MA, Rosh JR. Pediatric inflammatory bowel disease. Pediatr Clin North Am 2017; 64(3): 577–91.

colitis: oral or rectal mesalamine, corticosteroids, purine analogs (6-mercaptopurine, azathioprine), and methotrexate, in varying combinations depending on severity of disease and acute relapse status. Newer treatments include anti-tumor necrosis factor (TNF)-α antibody drugs (infliximab, adalimumab) or, in severe cases, cyclosporine. In addition, Crohn's disease patients are usually receiving antibiotics (metronidazole, ciprofloxacin). A summary of current drug treatment approaches is presented in Table 24.5 [92].

Adolescents with IBD often present for surgery for complications of the disease or failed medical management. Indications include bowel perforation/abscess, obstruction, stricture, perianal fistula, toxic megacolon, or malignancy. Over 50% of IBD patients will ultimately require bowel resection. Recurrence of disease and reoperation are frequent (in Crohn's disease 50% at 1 year and 77% at 10 years [92]), and so bowel conservation is very important to avoid the complications associated with short bowel syndrome and long-term dependence on total parenteral nutrition. Ostomy formation may be necessary for more severe cases. Complications after surgery for IBD include wound infection, anastomotic leak, anastomotic stricture, fistula, recurrence of disease, small bowel obstruction, and bleeding; these complications are seen particularly in Crohn's disease surgery. For ulcerative colitis, total proctocolectomy is curative; 8–26% of children with UC will require colectomy in the first 5 years from diagnosis [92]. The procedure used depends on the clinical status of the patient but usually involves a total colectomy with or without an ileostomy. Creation of a reservoir in the small bowel with an ileoanal anastomosis is the definitive procedure. These patients also present frequently for upper and lower gastrointestinal endoscopy for diagnosis and treatment, and for cancer surveillance, and may require sedation or anesthesia provided by the pediatric anesthesiologist.

Preanesthetic evaluation and care must consider nutritional status, chronic pain, medications including corticosteroids and other immunosuppressant drugs, and history of anesthesia and surgery. The extraintestinal manifestations of the disease must be carefully sought out. As with any chronic disease in the teenage population, psychosocial distress is common in patients with IBD, and anesthetic care must take this into consideration.

Developmental disabilities/autism

Chapter 43 contains an extensive listing of the genetic causes of developmental delay, including autism spectrum disorder. Acquired causes of developmental delay may include hypoxic-ischemic brain injury from cardiac or respiratory arrest secondary to a disease state, hypoxemic insults from cardiopulmonary bypass or the perioperative period for congenital heart surgery, trauma, near-drowning, cranial irradiation, toxic exposures, and many other etiologies. Clearly it is important to understand fully the patient's history and level of functioning and communication; the parent or other caregiver is essential in the preoperative evaluation and preparation and approach to the anesthetic. Developmentally delayed adolescents present for a variety of procedures including dental care, orthopedic procedures, brain imaging, and many others. Involving the parent by having them present for IV placement or mask induction of anesthesia may be extremely helpful. Premedication, either oral (benzodiazepines, barbiturates) or intramuscular (ketamine or midazolam), may be necessary to accomplish induction of anesthesia in the large, uncooperative, developmentally delayed adolescent.

Obesity in the adolescent

Obesity in children and adolescents is defined in a variety of ways, but one commonly used definition is that of the US Centers for Disease Control: a body mass index (BMI) above the 95th percentile for age as defined by the 2000 CDC growth charts for normal children [94].

Using this definition, the prevalence of adolescent obesity has increased dramatically in the USA between 1976–1980 and 2011–2014, from 5.0% to 20.5% in children aged 12–19 years [95] (Fig. 24.6). For boys and girls, respectively, this corresponds to a BMI of 24–25 at age 12, 27–28 at age 15, and 29–30 at age 18. Morbid obesity is often defined in the adult population as BMI >40. Epidemiological studies suggest that over 90% of cases of adolescent obesity are not accompanied by an underlying medical condition or syndrome, but primarily represent excess intake of calories, accompanied by relative lack of physical activity and often social/psychological inputs, genetic and environmental factors, as well as possibly

Table 24.5 Dosing for commonly used drugs in pediatric inflammatory bowel disease

Drug	Dose	Side-effects
Prednisone (oral) or methylprednisolone (intravenous)	1–2 mg/kg daily, maximum 40–60 mg/day	Growth suppression, adrenal suppression, immunosuppression
Budesonide	9 mg orally daily	Same as above but lower
5-aminosalicylate	50–80 mg/kg/day orally up to 4 g daily	May mimic acute exacerbation, interstitial nephritis
Azathioprine	2–3 mg/kg/day orally	Immunosuppression, myelosuppression, pancreatitis, lymphoma
6-mercaptopurine	1–1.5 mg/kg/day orally	
Methotrexate	15 mg/m^2/day to maximum 25 mg/day	Nausea, hepatic fibrosis
Infliximab	5 mg/kg intravenously at 0, 2, and 6 weeks, then every 8 weeks; dose can be increased to 10 mg/kg and interval be shortened to every 4–6 weeks	Immunosuppression, psoriasis, lymphoma
Adalimumab	Induction: 2.4 mg/kg (maximum 160 mg) at baseline, 1.2 mg/kg (maximum 80 mg) at week 2; maintenance: 0.6 mg/kg every other week	

Source: Adapted from Oliveira SB, Monteiro IM. Diagnosis and management of inflammatory bowel disease in children. BMJ 2017; 357: j2083; Conrad MA, Rosh JR. Pediatric inflammatory bowel disease. Pediatr Clin North Am 2017; 64(3): 577–91.

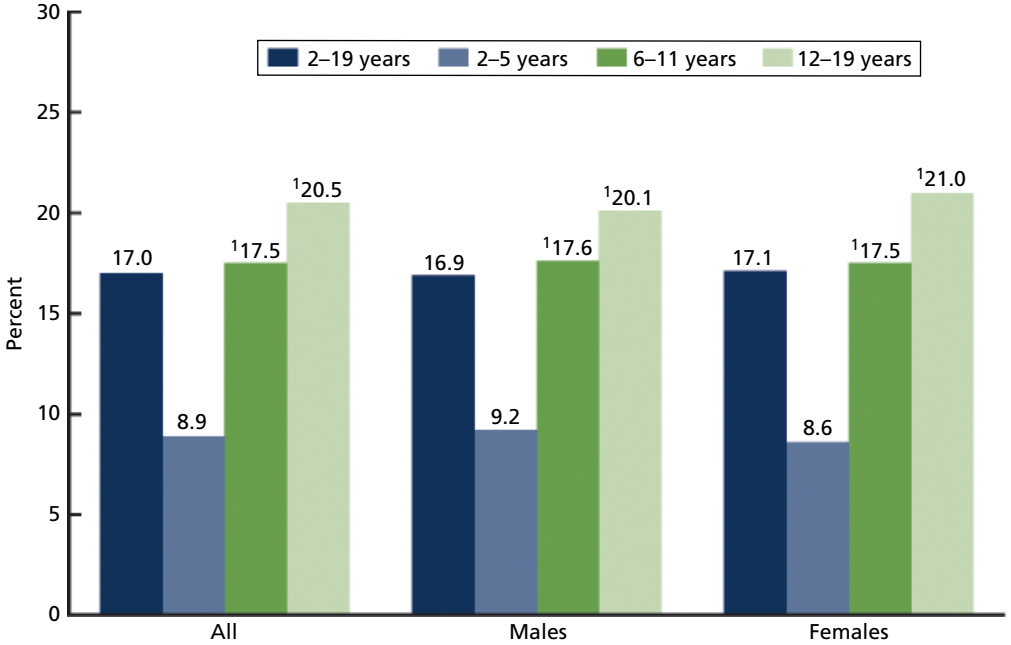

Figure 24.6 Prevalence of obesity among youth age 2–19 years, by sex and age: United States 2011–2014. *Source:* Reproduced with permission from US Centers for Disease Control: National Center for Health Statistics [95].

a deficiency of the hormone leptin in some cases. However, in about 5% of cases in adolescence there is an accompanying genetic syndrome, including Prader–Willi and Laurence–Moon–Biedl syndromes, a glycogen storage disease, medical cause such as chronic corticosteroid administration, or physical inactivity such as accompanies severe muscular dystrophy [96]. Obesity is a complex endocrine state in which the adipose tissue communicates with the brain and peripheral tissues by releasing hormones and cytokines such as leptin, C-reactive protein (CRP), interleukin (IL)-6, TNF-α, lipoprotein lipase, renin, and adiponectin. Significant obesity leads first to insulin resistance and then, if well established, to the metabolic syndrome, consisting of central obesity, hyperinsulinemia, systemic hypertension, and hypertriglyceridemia. Obesity can be considered a chronic inflammatory state. It can lead to multisystem complications including respiratory (asthma, obstructive sleep apnea (OSA), atelectasis, hypoxemia), cardiovascular (systemic hypertension, left ventricular hypertrophy, pulmonary hypertension), endocrine (insulin resistance and type 2 diabetes, polycystic ovary syndrome), gastrointestinal (delayed gastric emptying, gastroesophageal reflux, non-alcoholic fatty liver disease), and psychological (depression, poor body image, loss of self-esteem) [97]. Table 24.6 summarizes the pathophysiology of obesity in adolescents. Diet and behavioral therapy are always attempted, but achieve variable success rates. Drug therapy is sometimes attempted (orlistat to reduce fat absorption). Bariatric surgery is increasingly recommended for morbid obesity in older adolescents when other measures have failed.

Overweight adolescents present for surgery and anesthesia for a range of disorders, including orthopedic (Blount disease or tibia vara, slipped capital femoral epiphysis) [98], cholecystectomy from cholesterol-induced cholelithiasis, tonsillectomy for OSA, and bariatric surgery. Preoperative evaluation must carefully search for co-morbid disease, especially OSA. Some adolescents may require bilevel continuous positive airway pressure (BiPAP), most often at night. Obesity is a known significant risk factor for OSA. See Chapter 34 for a detailed discussion of the perioperative patient with OSA. If the patient is managed with BiPAP, this therapy should be reinstituted in the postanesthesia recovery area if the trachea is extubated, until the patient is awake and demonstrates ability to maintain a patent airway. The obese teen with moderate or severe OSA should most often be admitted after anesthesia, even for a minor procedure, and may require observation in the intensive care unit (ICU) [99,100]. Severe pulmonary hypertension merits very careful planning of the anesthetic, in consultation with the patient's cardiologist or pulmonologist; ICU admission should be arranged for patients with this condition. See Chapter 27 for anesthetic management of patients with pulmonary hypertension. In addition, airway management may be complicated by adipose tissue in the tongue, pharynx, and neck that collapses with decreased muscle tone, causing airway obstruction. Most often this can be managed with an oral airway to assist mask ventilation. In the vast majority of obese teens, mask ventilation, direct laryngoscopy, and tracheal intubation are not difficult. See Chapter 16 for a discussion of management of the difficult airway. Vascular access may be difficult in the obese adolescent: often it is possible to place a small peripheral intravenous catheter preoperatively; larger intravenous access can be secured after induction of anesthesia. Gastroesophageal reflux disease is common in obese teenagers; if the patient is not already on therapy, consideration can be given to prophylaxis for reflux including oral clear antacids, IV histamine-2 blocking agents, and gastrointestinal motility agents. Intravenous drug dosing is problematic, but there are now some data and recommendations that offer more definitive guidance on administering doses based on actual versus ideal bodyweight; this may be different for

Table 24.6 Pathophysiological changes in organ systems associated with obesity and concerns from an anesthesia perspective

System	Effects of obesity	Concerns
Respiratory system	• In children, there is no clear relationship between measures of obesity such as BMI and waist circumference and the presence of restrictive pulmonary function • Fat accumulation on the chest wall produces decreased lung and chest wall compliance • Increased work of breathing • Increased risk of upper airway infections • Increased prevalence of asthma	• Decreased time to desaturation during apnea • Increased risk for hypoxemia and atelectasis • Hypoventilation, especially in the supine spontaneously ventilating patient • General anesthesia and muscle relaxation in obese children leads to atelectasis, severe respiratory mechanics alterations, and increased hypoxemia risk. Atelectasis formation correlates with bodyweight and may be sustained into the postoperative period
	Obstructive sleep apnea (OSA) • The prevalence of OSA in obese children is 13–59%, compared with 2–3% in normal-weight children. Obesity increases soft tissue surrounding the pharyngeal airway and for each increase of 1 kg/m^2 of BMI above the mean in children, the risk of OSA increases by 12% • Factors responsible for increased risk of OSA include airway narrowing, increased critical airway closing pressures, decreased chest wall compliance and abnormal ventilatory control	• Careful history of sleep-disordered breathing and use of oxygen or pressure support ventilation • Overnight oximetry or polysomnography • CBC (for polycythemia due to hypoxemia); increased serum bicarbonate levels (compensation for respiratory acidosis) • Airway concerns • Evaluation for right heart disease • Disposition concerns
Cardiovascular system	• Increased risk for coronary artery disease, carotid intima–media thickening, hypertension and dyslipidemia • Increased left ventricular mass • Pulmonary hypertension in those with OSA	• Increased risk for biventricular failure in patients with OSA • Cardiology evaluation in the presence of history of multiple episodes of desaturation <70%, systemic hypertension or signs of right ventricular dysfunction
Endocrine system	• Excess fat accumulated in muscle cells and hepatocytes secretes bioactive molecules (adipokines), interfering with insulin signaling and increasing risk of type 2 diabetes mellitus (incidence of 1–2%) and impaired glucose tolerance (incidence of 7–25%). Excess body fat accumulation also predisposes obese children to growth and thyroid hormone deficiency as well as pseudohypoparathyroidism	• Perioperative glucose control • Increased risk for infection
Hepatic system	• With every 5-cm increase in waist circumference, the odds of liver steatosis are increased 1.4- fold • Pediatric non-alcoholic fatty liver disease (NAFLD) has a prevalence between 3% and 10% in obese children. When associated with inflammation and cellular hepatocyte damage, it is called non-alcoholic steatohepatitis (NASH)	• NAFLD is usually asymptomatic • NASH may lead to cirrhosis and hepatocellular carcinoma, with the consequent need for liver transplantation
Renal system	• Larger kidney size, an independent predictor of chronic kidney disease progression	• Drug clearance may be increased or unchanged
Metabolic syndrome	• The odds of developing metabolic syndrome in children are 1.55 times more for every half-unit increase in BMI z score. The two most commonly used definitions include the presence of at least three out of five criteria (elevated triglycerides, low high-density lipoprotein, central obesity/abdominal circumference by sex, elevated fasting glucose, and high blood pressure). Since metabolic syndrome predisposes to coronary artery disease, congestive heart failure, obstructive sleep apnea, pulmonary dysfunction, and deep venous thrombosis, its presence carries increased perioperative morbidity	

BMI, body mass index; CBC, complete blood count.
Source: Reproduced from Chidambaran et al [97] with permission of Elsevier.

lipophilic drugs, such as propofol, and ionized drugs such as non-depolarizing muscle relaxants [97]. Pharmacokinetic effects on different drug classes resulting from obesity are summarized in Table 24.7. Current recommendations for common anesthetic drug dosing in the obese adolescent are shown in Table 24.8 [97]. Often the best practice is to start with doses based on ideal bodyweight and to titrate additional doses based on the individual patient's pharmacodynamic response.

Bariatric surgery in the adolescent

In the mature adolescent who is morbidly obese, when diet, exercise programs, and behavioral interventions have failed, there is increasing evidence that bariatric surgery effectively brings about weight loss and reverses significant co-morbidities, including type 2 diabetes, OSA, non-alcoholic fatty liver disease, pseudotumor cerebri, quality of life, and depression [101]. Selection criteria are very important, and all must be met before bariatric surgery can be offered to the adolescent

Table 24.7 Effect of the pathophysiological changes in childhood obesity on drug pharmacokinetics

Physiological change in obese children	Effect on drug pharmacokinetics
Increases in lean body mass (LBM) accounting for 20–40% of the increase in total bodyweight	Increased clearance (CL) of lipophilic drugs: increased V_d for especially lipophilic drugs Saturation of tissue and possible accumulation with prolonged administration
Increase in blood volume, cardiac output, and capillary networks to nourish the excess body fat	Increased volume of distribution – need for higher initial dose
Increase in α1-acid glycoprotein	Decreased free form of drugs that are highly protein bound
Increase in liver volume, fatty infiltration, and non-alcoholic steatohepatitis lead to sinusoidal narrowing; compensated by increase in cardiac output and blood flow	Affects clearance of drugs that have high hepatic extraction ratio depending on extent of contrasting changes
Expression and function of cytochrome P enzymes are largely not affected except CYP3A which has decreased and CYP2E1 which shows increased activity	Affects clearance of drugs metabolized by CYP3A and CYP2E1

General dosing recommendations based on drug solubility:
- Loading doses should be based on IBW when drug distribution is restricted to lean tissues.
- Loading doses based on IBW + % of TBW or LBM when distribution to lean tissue and partially to fat tissue.
- Loading doses based on TBW when distributed to lean and fat tissues or markedly in fat tissue.
- Maintenance doses depend on ability to clear medications. If CL is decreased, dose based on IBW.

IBW, ideal bodyweight; TBW, total bodyweight.
Source: Reproduced from Chidambaran et al [97] with permission of Elsevier.

Table 24.8 Recommendations for dosing of commonly used drugs for obese patients in pediatric anesthesia

Drug	Recommended scalar for dosing	Comments
Propofol		
Induction dose	?LBM	Titrate to clinical effect for induction
Maintenance infusion	TBW (allometric)	Allometric weight = 70 × (TBW/70)^x where exponents (x) of 0.72–0.8 have been proposed
Fentanyl	LBM/PK	Lipophilic, elevated V_d in obese; clearance linearly related to PK mass
Remifentanil	LBM/IBW	Pharmacokinetics unaffected in obese, but more side-effects if dosed by TBW
Morphine	IBW	Hydrophilic, V_d does not change with obesity, does not accumulate in body fat
Sufentanil	TBW	Lipophilic; increased V_d in body fat, but risk for accumulation. Loading dose based on TBW, decrease maintenance doses
Alfentanil	LBM/TBW	
Succinylcholine	TBW	May max out dose at 150 mg
Non-depolarizing muscle relaxants (vecuronium, rocuronium, cisatracurium)	IBW	No differences in pharmacokinetic parameters between lean and obese patients. However, prolonged duration of action when dosed by TBW
Benzodiazepines	Loading: ABW/LBM Maintenance: IBW	Lipophilic; CYP3A4 metabolism decreased in obese; higher than IBW, less than TBW – no particular scalar has been studied. Daily clinical retitration recommended
Lidocaine		
Initial dose	TBW	Intermittent doses may be preferable to infusions.
Maintenance infusion	IBW	Monitor clinically
Ketamine	—	Lipophilic; limited pharmacokinetic studies in obese
Acetaminophen (oral)	—	Similar plasma levels with normal doses as non-obese
Acetaminophen (intravenous)	—	Lower levels achieved with usual doses in obese, but higher CYP2E1-mediated metabolite production may preclude dose adjustment. Check liver enzymes
Ibuprofen	—	V_d increased in obese; increase dose without changing dosing intervals
Neostigmine	TBW	Maximum dose 5 mg

ABW, actual bodyweight; IBW, ideal bodyweight; LBM, lean body mass; PK mass, pharmacokinetic mass; –, no recommended scalar; TBW: total bodyweight; V_d, volume of distribution.
Source: Reproduced from Chidambaran et al [97] with permission of Elsevier.

(Table 24.9). The most important criteria are BMI >35 with serious co-morbidities, or >40 with milder co-morbidities, skeletal maturity, and stable and mature psychosocial evaluation, with parental support and high likelihood of compliance with diet and medical follow-up regimens. Evaluation by a multidisciplinary team consisting of gastroenterologists, dieticians, nurse specialists, surgeons, psychologists, and social workers is the standard of care.

Several forms of bariatric surgery have evidence of positive outcomes and low complication rates in adolescents [102] (Fig. 24.7). The first was the Roux-en-Y gastric bypass (RYGB), initially performed as an open procedure but now performed laparoscopically through five or six small incisions by experienced surgeons. This operation involves the creation of a small gastric pouch of 10–30 mL, division of the small intestine and creation of a jejunojejunostomy, and finally connection of

the gastric pouch to the Roux limb (gastrojejunostomy). This operation has the effect of bypassing most of the stomach, and weight loss occurs mostly through restriction of caloric intake from the small gastric pouch. It is intended as a one-time intervention. In recent adolescent case series there were no perioperative deaths and a low complication rate comparable to adult series. The second operation is the adjustable gastric band (AGB; performed in less than 5% of adolescents), also placed laparoscopically, which involves the placement of an inflatable silicone band with an inner inflatable balloon that encircles the top of the stomach, thus creating a virtual gastric pouch 1–2 cm below the gastroesophageal junction. A catheter leads from the balloon to a subcutaneous pouch where a port is implanted, allowing adjustment of balloon size by adding or removing saline. The US Food and Drug Administration has not approved this device in patients under the age of 18; any use of the device in adolescent patients should therefore be in the context of Investigational Device Exemption studies for the purposes of reporting clinical safety and outcomes [103]. In recent adolescent series, complication rates were 6–10%, with no deaths. Reoperation rates, including band removal, were 8–10%. Laparoscopic sleeve gastrectomy has also been performed in adolescents. In terms of weight loss outcomes, RYGB leads to the most significant weight loss, with average BMI reduction around 17 kg/m^2. Clinically significant reduction in BMI is also seen for sleeve gastrectomy and AGB (average reductions of 15 and 11 kg/m^2, respectively) [104]. Other operations, such as biliopancreatic diversion with or without duodenal switch, are not recommended in adolescents.

Table 24.9 Selection criteria for bariatric surgery in adolescents

BMI (kg/m^2)	Co-morbidities
>35	*Serious:* type 2 diabetes mellitus, moderate or severe obstructive sleep apnea (AHI >15 events/h), pseudotumor cerebri, and severe steatohepatitis
>40	*Other:* mild obstructive sleep apnea (AHI ≥5 events/h); hypertension, insulin resistance, glucose intolerance, dyslipidemia, impaired quality of life or activities of daily living, among others
Eligibility criteria[a]	
Tanner stage	IV or V (unless severe co-morbidities indicate WLS earlier)
Skeletal maturity	Completed at least 95% of estimated growth (only if planning a diversional or malabsorptive operation, including RYGB)
Lifestyle changes	Demonstrates ability to understand what dietary and physical activity changes will be required for optimal postoperative outcomes
Psychosocial	Evidence for mature decision making, with appropriate understanding of potential risks and benefits of surgery
	Evidence for appropriate social support without evidence of abuse or neglect
	If psychiatric condition (e.g. depression, anxiety, or binge eating disorder) is present, it is under treatment
	Evidence that family and patient have the ability and motivation to comply with recommended treatments pre- and postoperatively, including consistent use of micronutrient supplements. Evidence may include a history of reliable attendance at office visits for weight management and compliance with other medical needs

AHI, apnea-hypopnea index; RYGB, Roux-en-Y gastric bypass; WLS, weight loss surgery.
[a] All of the eligibility criteria must be fulfilled.
Source: Reproduced from Pratt et al [101] with permission of John Wiley and Sons.

KEY POINTS: OBESITY AND BARIATRIC SURGERY

- Obesity prevalence has increased to 20% of children aged 12–19
- Obesity can lead to the metabolic syndrome and insulin resistance/type 2 diabetes, obstructive sleep apnea, non-alcoholic fatty liver, and depression
- Bariatric surgery consisting of laparoscopic Roux-en-Y gastric bypass, sleeve gastrectomy, or adjustable gastric band can be performed with low complication rates and successful weight loss

Thyroid surgery in the adolescent

Thyroid surgery is infrequently performed in adolescents, but the pediatric anesthesiologist will encounter patients having thyroid lobectomy or total thyroidectomy. The two broad categories of diseases in which thyroid surgery is indicated are thyroid nodules and carcinoma, and hyperthyroidism. Characteristics of 91 total thyroidectomies at Texas Children's Hospital are displayed in Table 24.10 [105]. The risk of a thyroid nodule being malignant is 5–15%, depending on age, gender,

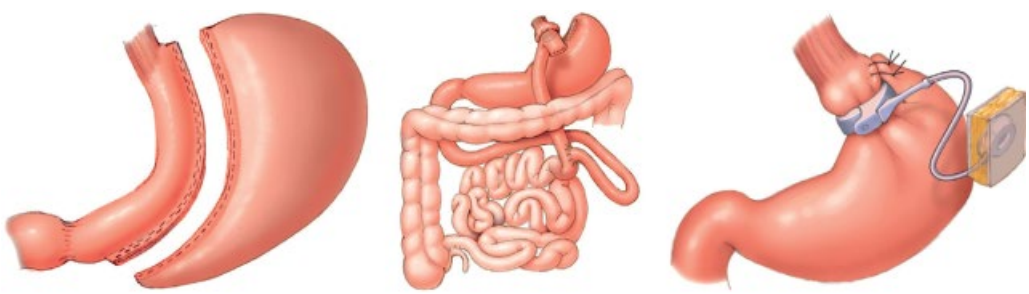

Figure 24.7 Bariatric surgery procedures for adolescents. (A) Sleeve gastrectomy. (B) Roux-en-Y gastric bypass. (C) Adjustable gastric band. *Source:* Reproduced from Kumar and Kelly [102] with permission of Elsevier.

Table 24.10 Demographic and clinical characteristics of pediatric patients undergoing total thyroidectomy

Variable	Total patients (*n* = 91)
Gender	
Female	70 (77%)
Male	21 (23%)
Age (mean)	13.7 ± 4.4 years
Diagnosis	
Malignancy	47 (52%)
Graves' disease	24 (26%)
Hashimoto's thyroiditis	3 (3%)
Multiple endocrine neoplasia (MEN) 2A/2B	6 (7%)
McCune–Albright Syndrome	2 (2%)
PTEN hamartoma syndrome	1 (1%)
Enlarging goiter/mass	5 (5%)
Refractory hyperthyroidism	3 (3%)
Ultrasound	72 (79%)
Biopsy	54 (59%)
Lymphadenectomy	31 (34%)

Source: Reproduced from Yu et al [105] with permission of Elsevier.

family history, radiation exposure, and other risk factors [106]. The risk of malignancy in the adolescent is equal to or higher than that in adults. The approach to a thyroid nodule is to confirm the diagnosis by ultrasound, measure thyroid function tests, and perform fine needle aspiration. If the resulting pathology is suspicious or confirmed to have malignant features, surgery is performed – either lobectomy or total thyroidectomy with possible lymph node dissection depending on other characteristics such as size and suspected lymph node involvement. There are approximately 300–400 new cases of thyroid cancer in children and adolescents annually in the USA. Of 1753 total cases in children reported to the major US cancer registry, 83% were papillary thyroid cancer, 10% follicular thyroid cancer, 5% medullary thyroid cancer, and 2% other types [106].

Hyperthyroidism in adolescents is most commonly caused by Graves' disease, an autoimmune thyroiditis that results from autoimmune binding to the thyroid stimulating hormone (TSH) receptor on follicular cells, elevation of T3 and T4, and signs of hyperthyroidism including weight loss, fatigue, palpitations, tremor, goiter, and changes in behavior. Hashimoto's thyroiditis is a similar autoimmune condition, caused by antibodies against thyroglobulin or thyroid peroxidase and accompanied by invasion of thyroid tissue by T-lymphocytes. A female preponderance of autoimmune thyroiditis of about 7:1 exists in adolescents. Medical treatment consists of antithyroid drugs such as methimazole (propylthiouracil should no longer be used in children because of the risk of liver failure), radioactive iodine, or, in refractory cases, thyroidectomy [107]. Thyroid storm results from uncontrolled secretion of thyroid hormones and results in hypertension, tachycardia, and potentially cardiovascular collapse. Treatment is with antithyroid drugs, radioactive iodine, and β-blockers to control hemodynamic changes until thyroid function is normalized.

Preoperative evaluation of the adolescent undergoing thyroid surgery should elicit any symptoms of current hyper- or hypothyroidism and review thyroid function tests (TSH, T4, T3 (free and total)) and any thyroid medications. Baseline evidence of tachycardia or hypertension should be ascertained. Examination of the neck and airway for large nodules or goiter is important to determine any potential difficulty with airway management. Most adolescent thyroid surgery patients do not present airway concerns. It is important to discuss the surgical plan with the surgeon to ascertain whether the procedure will be a partial or total thyroidectomy, and whether neck dissection is planned. In addition, because of the risk of injury to the superior laryngeal and recurrent laryngeal nerves, discussion about whether intraoperative neuromonitoring is planned is important.

Because of the need to monitor the recurrent laryngeal and superior laryngeal nerves, muscle relaxation beyond initial tracheal intubation is often avoided in thyroid surgery. In addition to direct nerve stimulation, neuromonitoring via a specialized endotracheal tube with implanted electrodes (NIM® Trivantage EMG tube, Medtronic Corp., Minneapolis, MN, USA) can be utilized to monitor vocal cord function during surgery (Fig. 24.8) [108]. The tube must be placed correctly so that the electrodes are in contact with the vocal cords. A meta-analysis of over 9000 patients demonstrated a 20% reduction, both short- and long-term, in recurrent laryngeal nerve palsy with intraoperative neuromonitoring. The overall incidence of short-term injury was 1.82%, and long-term injury 0.67% [109]. Besides avoiding neuromuscular blockade, there are no other specialized anesthetic drug requirements. Another method to check the integrity of the recurrent laryngeal nerve is to observe bilateral vocal cord movement with a videolaryngoscope after extubation of the trachea with deep anesthesia. Intraoperative and postoperative analgesia can be provided with a superficial cervical plexus block or local anesthetic wound infiltration by the surgeon.

Other than recurrent laryngeal nerve injury, acute complications of thyroid surgery include airway and neck swelling from extensive dissection or hematoma, and hypocalcemia if the parathyroid glands are also removed. In the series from

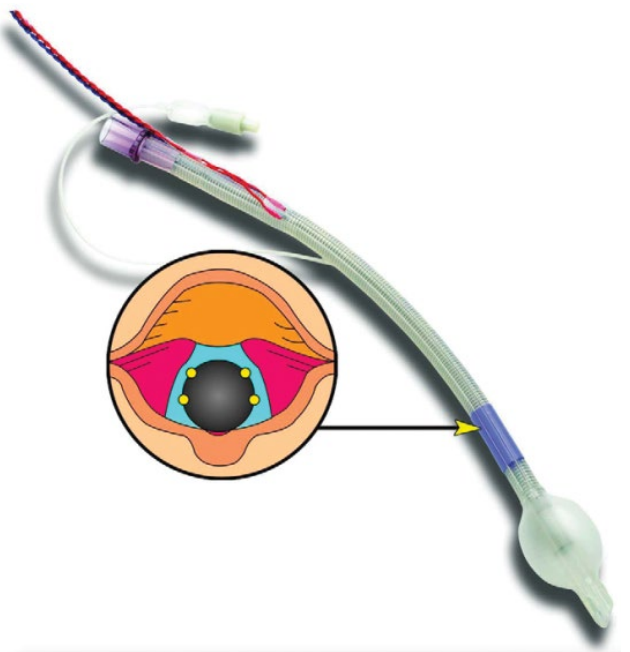

Figure 24.8 Endotracheal tube equipped with two pairs of electrodes (NIM® Trivantage EMG tube, Medtronic Corp., Minneapolis, MN, USA) with a diagram illustrating the contact points between the electrodes and the vocal folds. *Source:* Reproduced from Julien et al [108] with permission.

Texas Children's Hospital, 31 of 91 (34%) total thyroidectomy patients developed transient hypocalcemia (ionized calcium <1.0 mmol/L or total calcium <8.0 mg/dL) [105]. Ten patients were symptomatic, and 13 received IV calcium gluconate supplementation. Signs and symptoms of hypocalcemia include paresthesias, wheezing, dysphagia, voice changes, tetany, and seizures. Pre- and perioperative calcium supplementation reduces the risk of this complication, and these patients should have serum calcium monitored in the immediate postoperative period.

Conclusion

Adolescence is a time of rapid growth and change, and a number of anesthetic challenges occur that are unique to this age group. Knowledge of physiological and psychosocial development and the disease processes and procedures common in these patients is important to providing anesthesia care to maximize favorable outcomes. A direct, honest, positive approach that is distinct from that toward the younger child, empathetic to the adolescent's developmental stage and disease process, is usually greatly appreciated by these patients and their parents. This approach also facilitates the establishment of trust with the anesthesiologist in the often brief time for preoperative evaluation and preparation. Transition to adult care of patients with chronic pediatric diseases such as congenital heart disease and cystic fibrosis is variable, and the pediatric anesthesiologist should be prepared to care for young adults with these conditions.

CASE STUDY

The patient was a 16-year-old girl presenting for laparoscopic Roux-en-Y gastrojejunostomy. Current BMI was 47.8 (height 165 cm, weight 130 kg). Review of her growth charts revealed that the patient had been above the 99th percentile on the US Centers for Disease Control 2000 growth charts since age 10. She had attempted diet and behavioral therapy for the past 4 years without success. Co-morbidities included type 2 diabetes treated with metformin, gastroesophageal reflux disease treated with pantoprazole, and OSA with apnea-hypopnea index of 9 (moderately severe OSA) on sleep study that was treated with BiPAP 10 cm at night by nasal mask. She also had early polycystic ovary syndrome with facial acne and mild hirsutism. After a full evaluation by the bariatric surgery team, including a psychological evaluation, full explanation of the procedure and follow-up required, and contract signed by the patient and parents to adhere to the follow-up guidelines, the patient was accepted for surgery. She had not had anesthesia or surgery previously, there was no family history of anesthetic problems, and she had no medication allergies. She did not smoke, drink alcohol, or use illegal drugs. Menses were irregular, with last menstrual period 6 weeks previously.

Physical examination revealed an alert, anxious, morbidly obese teenager. Room air SpO_2 was 94% without BiPAP, heart rate 80 beats per minute, respiratory rate 16, and blood pressure 145/86. Airway examination revealed a Mallampati Class II examination, full range of neck motion, and intact dentition. Lung examination revealed no respiratory distress, distant clear breath sounds, and decreased breath sounds at both bases. Cardiac examination revealed regular rate and rhythm, with no murmurs. Peripheral veins were difficult to identify. Preoperative laboratory values included hemoglobin 14 g/dL, hematocrit 42%, and white blood cell count 8500/mm^3 with normal differential. Electrolytes were normal, blood urea nitrogen 18 mg/dL, creatinine 1.0 mg/dL, and blood glucose 125 mg/dL. Urine human chorionic gonadotropin test was negative. Chest radiograph revealed mild cardiomegaly and clear lung fields with the exception of some volume loss at both bases. The patient was informed of the anesthetic procedures, that the plan would be to extubate her trachea in the operating room when she was awake and able to follow commands, that she would have her BiPAP reinstituted in the postanesthesia care unit (PACU), and that she would have patient-controlled analgesia (PCA).

A 20 ga peripheral IV was started in the dorsum of the left hand on the second attempt. Metformin had been stopped 2 days preoperatively. Oral sodium citrate and IV metoclopramide and pantoprazole were given in the holding area, along with IV midazolam, 2 mg, which provided anxiolysis. The patient was transported to the operating room (OR) where she was positioned on the OR table with a foam wedge under the back and shoulders to optimize airway alignment. Difficult airway adjuncts were in the OR, including a videolaryngoscope, large adult intubating laryngeal mask airway, and fiberoptic bronchoscope. After application of standard monitors and preoxygenation for a full 5 min, IV induction was achieved with fentanyl 100 μg and propofol 150 mg IV, which was 2 mg/kg based on ideal bodyweight of 75 kg. Eyelash reflex was lost in 45 s. Mask ventilation was easy once an oral airway was inserted, and rocuronium 80 mg was given to facilitate tracheal intubation, which was accomplished easily with a MacIntosh 3 blade achieving a grade I Cormack and Lehane view of the larynx. Anesthesia was maintained with desflurane, 6–12% end-tidal concentration. Positive end-expiratory pressure of 8 cmH_2O was used to prevent atelectasis, and the patient was ventilated with tidal volumes of 750 mL, and FiO_2 50% with an air–oxygen mixture, achieving an SpO_2 of 95–98% during the surgery. A second 18 ga IV was placed after induction. Laparoscopic Roux-en-Y-gastrojejunostomy proceeded via five separate incisions for ports and instruments, and CO_2 insufflation to achieve a pressure of 15–20 cmH_2O was used. The patient was hemodynamically stable throughout the procedure; minute ventilation had to be increased during the insufflation to achieve end-tidal CO_2 of 35–40 mmHg by increasing the rate. After 3 h and 15 min of operating time, estimated blood loss 15 mL, and achieving an excellent surgical result and hemostasis, the incisions were closed after infiltrating

the fascia, subcutaneous tissue, and skin with a total of 30 mL of 0.25% bupivacaine. Ketorolac 30 mg IV, morphine 6 mg IV, and ondansetron 4 mg IV were given during the last hour of the procedure. Neuromuscular blockade was reversed, the patient's respirations were at first assisted with pressure support ventilation of 15 cmH_2O, and when she was awake, following commands, and taking unassisted tidal volume breaths of 500 mL or more, the trachea was extubated, with the patient in semi-Fowler position with head elevated 45°. She was assisted with facemask CPAP, achieving good tidal volumes and SpO_2 94–96% without distress, and was transported to the PACU where her BiPAP was instituted at end-expiratory pressure of 10 cmH_2O and inspiratory pressures of 15 cmH_2O. Patient-controlled analgesia with morphine was instituted in PACU, with no basal rate, and a PCA dose of 1.5 mg morphine with 10 min lockout interval. Ketorolac 30 mg IV Q 6 h × five additional doses and ondansetron were also ordered. Pneumatic sequential compression stockings for deep vein thrombosis prophylaxis were fitted in PACU. After 2 h of monitoring in PACU with several visits by the anesthesiologist to ensure satisfactory airway, pulmonary, and pain control status, the patient was transferred to an intermediate-care monitored unit. She was mobilized out of bed and into a chair the night of surgery, and every 4 h during the first postoperative day. Incentive spirometry exercises commenced the first night after surgery. On the second postoperative day she was out of bed walking around her room every 4 h. Pain control was adequate, with visual analog scale scores 3–5 on a 10-point scale, with a total of 22.5 mg morphine used during the first 24 h. Respiratory status was adequate, with no episodes of OSA or desaturation below SpO_2 90%, and she was able to discontinue the BiPAP while awake after 24 h, thereafter using it only while sleeping. Clear liquid intake and metformin and pantoprazole orally commenced on postoperative day 1. Serum glucose was adequately controlled at 120–200 mg/dL. She was discharged to the surgical ward on postoperative day 3, transitioned to oral pain medication with acetaminophen/hydrocodone oral solution, and discharged home on postoperative day 4.

At 6-month follow-up the patient was doing well, had lost 25 kg, and was compliant with her diet regimen and clinic follow-up visits. Her blood pressure had decreased to 130/80 mmHg. Her endocrinologist was considering discontinuing the metformin.

This case illustrates the principles of preanesthetic evaluation of morbidly obese teenage patients, and the comorbidities they suffer, including OSA and type 2 diabetes. Careful preoperative preparation for a possible difficult airway, gastrointestinal prophylaxis preoperatively to prevent aspiration of acid gastric contents, and proper positioning to facilitate laryngoscopy, allowed appropriate airway management. Dosing lipid-soluble induction agents (propofol) based initially on ideal bodyweight, maintaining functional residual capacity with positive end-expiratory pressure during laparoscopy with CO_2 insufflation, using an insoluble anesthetic gas (desflurane) to minimize uptake by adipose tissue that would delay emergence, minimizing intraoperative opioids, using local anesthesia and non-steroidal anti-inflammatory agent, extubating the trachea with the patient awake, and directly instituting BiPAP immediately after extubation, helped avoid obstructive apnea and hypoxemia. A pain management regimen of PCA without basal rate, continued ketorolac administration, and early mobilization and ambulation all aided in avoiding pulmonary and airway morbidity in this patient.

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 25

Anesthesia for Neurosurgical Procedures

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Introduction

As with many areas of surgery and anesthesiology, the specialized care of patients with neurological and neurosurgical conditions presents an interesting challenge to the anesthesiologist [1]. As in the patient in the case study at the end of this chapter, neurological conditions may be dynamic, and recognition of perioperative events, selection of specific anesthetic agents, and a collaborative approach with intensivist, surgeons, and neurologists may profoundly reduce or prevent significant morbidity. Contemporary neuroanesthetic practice is based on the understanding of cerebral physiology and how it can be manipulated in the presence of intracranial pathology (see Chapter 8). In addition to managing common problems of administering anesthesia to a diverse general pediatric population, the neuroanesthesiologist must give special consideration to the effects of anesthesia on the central nervous system (CNS) of children with neurological diseases. This chapter reviews the fundamentals of clinical management in neurosurgical patients. Discussion of specific neurosurgical conditions and their respective anesthetic management is designed to highlight the common and sometimes unique problems encountered by the pediatric neuroanesthesiologist.

Neuropharmacology

General principles

Evidence from animals suggests that the lethal dose in 50% of the animals (LD50) for many medications is significantly lower in the neonatal and infancy periods than in adults [2]. The sensitivity of the developing human newborn to most of the sedatives, hypnotics, and opioids is increased, probably owing to brain immaturity (incomplete myelination and blood–brain barrier) and to increased permeability for some medications (i.e. the lipid-soluble drugs used in anesthesia) [3]. In addition, the effect of volatile anesthetic agents is influenced by the age of the patient. The minimal alveolar concentration (MAC) in the neonate (0–30 days) is much lower than in infants aged 31–180 days [4]. Although there is an increase in anesthetic requirements in infancy, it must be emphasized that there is a smaller margin of safety between adequate anesthesia and severe cardiopulmonary depression in the infant and child compared with the adult [5]. Therefore, dosages must be appropriately calculated and therapeutic effects must be monitored to avoid inadvertent adverse clinical consequences and prolonged effects.

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

Inhalational anesthetic agents

All modern, volatile anesthetic agents have variable degrees of cerebrovascular effects, primarily vasodilatation and increased cerebral blood flow (CBF). The increase in intracranial pressure (ICP) observed with volatile anesthetics can be partially mitigated by mild hyperventilation and lower inhaled concentrations. Historically used agents are not discussed; instead the focus of this section is on those inhalational agents most widely used in contemporary clinical practice.

Isoflurane

Isoflurane is the most commonly used volatile anesthetic for neuroanesthesia. Its widespread use is based on the fact that it affects CBF less than other inhaled anesthetics at equivalent MAC doses [6] and on the belief that it may provide neuroprotection [7,8]. Compared to other volatile anesthetics, isoflurane has a minimal effect on cerebral autoregulation [6] and reduces cerebrospinal fluid (CSF) through increased resorption [9]. Studies in children suggest that an end-tidal concentration of isoflurane between 0.5 MAC and 1.5 MAC did not change CBF velocity and had minimal effects on the cerebrovascular reactivity to CO_2 [10]. Furthermore, there were no time-response effects of 1 MAC isoflurane on CBF velocity in anesthetized children [11–13]. Of note, the net impact of most volatile anesthetics (like isoflurane) is greatest on CBF, and increased ICP can be mitigated by increased ventilation [14]. Table 25.1 compares the different effects of various anesthetic agents on neurophysiology.

Sevoflurane

Sevoflurane is similar to isoflurane with regard to its effects on CBF, cerebral metabolic rate of O_2 ($CMRO_2$), and ICP in adults (see Table 25.1) [15]. In children, there appears to be no effect on CBF during hypo- and normocapnia under 1 MAC concentrations of sevoflurane [16]. Comparison between isoflurane and sevoflurane showed no difference on elevation in ICP and reduction in arterial blood pressure resulting in clinically similar reduction in cerebral perfusion pressure [17]. Also, sevoflurane has a similar neuroprotective effect as isoflurane during incomplete ischemia, compared with fentanyl and nitrous oxide techniques in rodents [18].

Desflurane

Desflurane increases CBF and decreases $CMRO_2$ in animals. One MAC desflurane has been shown to increase ICP significantly in neurosurgical patients with supratentorial mass lesions, despite hypocapnia [19], although larger studies have not demonstrated this finding [20]. Data in children are limited, though Sponheim et al demonstrated only a modest rise in ICP and a greater reduction in blood pressure which resulted in a decrease in calculated cerebral perfusion pressure compared to isoflurane and sevoflurane. This reduction in mean arterial pressure is perhaps most problematic for managing neurosurgical patients with obvious and subtle issues of increased ICP. When quicker emergence is desired, the use of desflurane with elevated ICP and reduction in perfusion pressure makes intravenous anesthesia a potentially safer option, though this remains a subject of debate [17].

Table 25.1 Effects of volatile anesthetic agents on cerebral metabolic rate for oxygen ($CMRO_2$), cerebral blood flow (CBF), cerebrospinal fluid (CSF) dynamics, and intracranial pressure (ICP)

Volatile agent	$CMRO_2$	CBF	CSF	ICP
Isoflurane	Decrease	Increase	Decrease	Increased
Sevoflurane	Decrease	Increase	No change	Increased
Desflurane	Decrease	Increase	No change	Increased
Nitrous oxide	Increase	Increase	No change	Increased

Nitrous oxide

The effect of nitrous oxide (N_2O) on cerebral circulation and its use in neuroanesthesia remain controversial. The reported variability of its effects on CBF and ICP is probably due to differences in experimental species, background anesthesia, and control of respiration. Subanesthetic doses of N_2O (60–70%) cause excitement, cerebral metabolic stimulation, and increased CBF [21]. Leon and Bissonnette showed that in infants and children 70% N_2O in oxygen with fentanyl–diazepam caudal epidural anesthesia increased CBF significantly compared with an air/O_2 mixture [22]. This increase in CBF was not associated with significant changes in mean arterial pressure (MAP), heart rate, or cerebrovascular resistance. However, other studies have suggested a direct effect of N_2O on increasing $CMRO_2$ in both animals and humans. Clinically, N_2O has been shown to increase CBF and ICP in adults and children [23–25], although the co-administration of intravenous agents (with or without induced hypocapnia) can mitigate these N_2O induced increases in CBF [26,27]. In contrast, volatile agents can further increase CBF [28]. Although N_2O is commonly used, it remains a controversial agent that is best avoided in the clinical scenarios of a brain that is tight or when cerebral ischemia is known to be present.

Intravenous anesthetic agents

There is increased interest in total intravenous anesthesia for some neurological procedures such as awake craniotomy, and the anesthesiologist must be familiar with and utilize the nuanced differences in effect between various intravenous anesthetic agents on neurophysiological parameters (Table 25.2) to provide adequate anesthetic effects.

Table 25.2 Effect of intravenous anesthetic agents on cerebral metabolic rate for oxygen ($CMRO_2$), cerebral blood flow (CBF), cerebrospinal fluid (CSF) dynamics, and intracranial pressure (ICP)

Intravenous agent	$CMRO_2$	CBF	CSF	ICP
Barbiturates	Decrease	Decrease	No change	Decreased*
Etomidate	Decrease	Decrease	No change	Decreased
Propofol	Decrease	Decrease	No change	Decreased*
Benzodiazepines	Decrease	Decrease	No change	Decreased
Opioids	No change	No change	No change	No change
Ketamine	Increased+	No change	No change	Increased
Dexmedetomidine	No change	Increase	No change	No change

* Decreased ICP is a summation on lowering of $CMRO_2$ and reduction in CBF; +, intermittently observed depending on degree of neuronal excitation.

Barbiturates

Barbiturates are a broad class of drugs that bind to the γ-aminobutyric acid (GABA) receptor on the α subunit, creating sedation and amnesia. In addition, barbiturates reduce epileptiform and EEG activity, lower ICP, lower CBF, and reduce $CMRO_2$ in a dose-dependent manner [29,30]. A major problem with barbiturates is that they can significantly reduce myocardial contractility, systemic arterial blood pressure, and cerebral perfusion pressure (CPP) [31]. In non-clinical doses (10–55 mg/kg), thiopental produces an isoelectric EEG and decreases the $CMRO_2$ by 50% [31]. Barbiturates can prevent an increase in ICP [32] during laryngoscopy and tracheal intubation owing to their ability to decrease CBF. Cerebral autoregulation and cerebrovascular reactivity to CO_2 are preserved with barbiturates. Production and reabsorption of CSF are not altered [33]. As mentioned, barbiturates are effective in controlling epileptiform activity, apart from methohexital, which may activate seizure foci in patients [34].

Etomidate

Etomidate is a carboxylated imidazole that binds to the GABA receptors, resulting in hypnosis and amnesia with a reduction of CBF (34%) and $CMRO_2$ (45%) [35]. Etomidate appears to directly vasoconstrict the cerebral vasculature, even before the metabolism is suppressed [36]. Thus, administration of etomidate can potentially lower ICP by reducing cerebral blood volume (CBV) while augmenting or maintaining CPP. Studies of etomidate administration have been primarily in adults; studies in children are limited. However, the clinical applicability of etomidate was perhaps best illustrated in a small clinical study of intubated pediatric patients with traumatic brain injury with elevated ICP (>20 mmHg for over 5 min). After intravenous etomidate administration, all patients had an increase in MAP from baseline, with a significant lowering of measured ICP and improvement in CPP [37]. Other studies have demonstrated that cerebrovascular reactivity to CO_2 is maintained following administration of etomidate [35]. Although etomidate has a great advantage over other intravenous agents, like barbiturates, because of minimal cardiovascular depression, it has two significant disadvantages that limit its use outside airway management: suppression of the adrenocortical response to stress, and increased myoclonic activity, especially after prolonged infusion [38].

Propofol

Propofol is a rapidly acting GABA agent that reduces CBF and $CMRO_2$ [39]. Although administration of propofol either by bolus or infusion can reduce ICP, the cardiovascular effects of a dose-dependent reduction in MAP may have the net result of lowering CPP in the patient with brain trauma [40]. CO_2 cerebrovascular responsiveness is maintained during propofol anesthesia, but the observed reduction in CBF and CBV is not augmented by hyperventilation (end-tidal CO_2 <30 mmHg) in normal children [41]. Although it is routinely a part of neuroanesthetic management in children and adults, the use of propofol outside the operating room in critically ill pediatric patients is limited by concerns about morbidity and mortality related to propofol infusion syndrome [42].

Benzodiazepines

Benzodiazepines bind to the GABA receptor, resulting in amnesia and anxiolysis. In addition, benzodiazepine administration has been reported to decrease CBF by a 25% decrease in $CMRO_2$, reduce ICP, and slow seizure foci [43–45]. However, the sedating effects and relatively short duration of action (compared to barbiturates) have led to their widespread use in patients in both the operating room and intensive care unit (ICU). The benzodiazepine antagonist, flumazenil, has been demonstrated to reverse the beneficial effects of benzodiazepines on CBF, $CMRO_2$, and ICP. Consequently, administration of flumazenil should be undertaken with caution in neurological patients with high ICP, abnormal intracranial elastance, and/or a predisposition to seizure [46].

Opioid analgesics

The opioid agents have little or no effect on CBF, $CMRO_2$, and ICP [47]. However, if patients are experiencing pain, opioids cause a modest reduction in these variables through indirect effects on the sympathetic nervous system [48]. Fentanyl combined with N_2O decreases CBF and $CMRO_2$ by 47% and 18%, respectively [30]. Cerebrovascular reactivity to CO_2 and cerebral autoregulation are preserved with opioids. Fentanyl has no effect on CSF production, but it reduces CSF reabsorption by at least 50% [49]. Fentanyl has no effects on the cerebral circulation of neonatal animals, but alfentanil increases CSF pressure in patients with brain tumors [50]. This effect was less than that observed with sufentanil, but greater than that observed with fentanyl. Alfentanil has the greatest effect on MAP and CPP [51]. Some studies reported a decrease in CBF and $CMRO_2$ [52], whereas others suggested an increase in CBF and ICP [53]. Remifentanil, with an ultrashort elimination half-life, offers the advantage over other opioids of not delaying perioperative neurological assessment [54]. Equipotent infusions of remifentanil and fentanyl were studied in patients undergoing supratentorial tumor surgery in combination with a balanced inhalational anesthetic. Remifentanil appeared to have the same preservative effects as fentanyl on CBF and cerebrovascular reactivity [55,56].

Ketamine

Ketamine is a mixed N-methyl-D-aspartate (NMDA) receptor agonist/antagonist that results in a dissociative anesthetic state [57]. Ketamine appears to be a potent cerebral vasodilator capable of increasing CBF by 60% in normocapnic humans, and thus an increase in ICP [58]. Studies have reported clinical deterioration in patients with increased ICP after ketamine administration [32]. Despite alterations in cerebral tone and CBF, ketamine has a negligible effect on the $CMRO_2$. Although it is suggested that ketamine may have some cerebral protective effects, studies in animal models of brain development have shown it to increase neuronal apoptosis even in the absence of brain injury [59]. The use of ketamine is generally contraindicated in neuroanesthesia.

Dexmedetomidine

Dexmedetomidine, an α_2-adrenergic agonist, causes a unique kind of sedation, acting on the subcortical areas, which resembles natural sleep without respiratory depression. The most common cardiovascular effects are bradycardia and

transient hypotension [60]. All effects are typically responsive to slowing the infusion and/or giving fluid boluses with or without a vagolytic (i.e. atropine). Experimental data demonstrate both cerebral vasoconstriction and vasodilatation, depending on the model and dose studied [61]. In clinically relevant dosages that produce sedation, dexmedetomidine has been shown to reduce CBF in humans and animals, unrelated to hemodynamic changes. In early animal investigations, $CMRO_2$ was unchanged, suggesting the possibility of increasing cerebral vascular resistance [62]. However, additional studies in humans and animals demonstrate that dexmedetomidine maintains a decrease in CBF proportional to its effect on decreasing $CMRO_2$. Further, it appears that CO_2 reactivity of the cerebral vasculature is unaffected by dexmedetomidine. In a study of healthy adults, the relative middle cerebral artery blood flow velocity to CBF and $CMRO_2$ relationship was unchanged following dexmedetomidine administration [63]. Using clinically relevant doses, the researchers confirmed that dexmedetomidine decreases CBF and $CMRO_2$ proportionally in healthy humans. In adult patients with brain injury, it appears that dexmedetomidine is more effective than propofol in providing sedation while preserving functionality [64]. Clinical experience with dexmedetomidine use in functional neurosurgery is limited to small case series [65]. However, these reports suggest that use of dexmedetomidine does not appear to interfere with electrophysiological monitoring, and has permitted brain mapping during awake craniotomy and microelectrode recording during implantation of deep brain stimulators in adults [66] and children [67]. Studies are underway to investigate the pharmacokinetics and pharmacodynamics of dexmedetomidine in infants and children.

Muscle relaxants

Muscle relaxants have little effect on cerebral circulation.

Succinylcholine

Succinylcholine produces an initial fall in ICP followed by a rise, especially in patients with decreased intracranial compliance resulting from increased CBF [68,69]. The increase in ICP is probably related to cerebral stimulation caused by increases in afferent muscle spindle activity [70]. The increase in ICP and CBF with succinylcholine is reduced by prior administration of deep general anesthesia or by precurarization [71]. However, the benefits to pediatric patients with increased ICP from rapid control of the airway and hyperventilation offset the slight increase in ICP caused by succinylcholine. It is important to remember that life-threatening hyperkalemia may occur after administration of succinylcholine to patients with closed head injury even though they do not have conditions classically associated with this adverse effect, including motor deficits, severe cerebral hypoxia [72], subarachnoid hemorrhage [73], cerebrovascular accident with loss of brain substance [74], and paraplegia [75].

Rocuronium

Rocuronium offers an alternative to succinylcholine for rapid-sequence intubation, but it does delay the return of spontaneous respiration and neurological assessment provided by succinylcholine [76,77]. However, with the availability of sugammadex in some countries including the European Union, Japan, and now the USA for reversal of neuromuscular blockade by non-depolarizing agents, this issue may be less relevant [78,79]. Like the other neuromuscular blocking agents, rocuronium has no effect on CBF or hemodynamics [80].

Pancuronium, atracurium, and cis-atracurium

These agents have no effect on CBV, ICP, or $CMRO_2$ in the presence of volatile anesthetics [81]. Large doses of *d*-tubocurarine, atracurium, or metocurine may release histamine and cause transient cerebrovascular dilation, which could account for a slight increase in ICP. However, a slight decrease in MAP may offset any change in intracerebral blood volume [82]. Use of *cis*-atracurium should not result in histamine release and has demonstrated improved cardiovascular stability. In addition, the metabolism of the agent by Hoffman degradation allows for its rapid clearance in patients with impaired renal and hepatic function [83]. Studies in healthy adults have shown rocuronium and *cis*-atracurium to have no effect on CBF [80].

Vecuronium

Vecuronium is known for its cardiovascular stability and its relatively short duration of action. In patients with reduced intracranial compliance, vecuronium slightly decreased ICP, probably because there was a concomitant decrease in central venous pressure (CVP) [84].

Reversal of neuromuscular blockade

Historically, reversal of neuromuscular blockade (NMB) by non-depolarizing agents has been primarily with train-of-four monitoring, timed to see an optimal effect with neostigmine administration. Neostigmine (an acetylcholinesterase inhibitor) has minimal effects on $CMRO_2$ and CBF, however cerebral vascular resistance and CPP are lowered, suggesting a central cholinergic influence of cerebrovascular dilation. Notably, these findings were from higher-concentration infusions into the cerebral vasculature via the carotid or intervertebral artery in non-human primates [85]. That said, early reversal of paralysis after rapid-sequence intubation is preferable to neurological monitoring. Sugammadex is a novel pharmacological agent that was approved for clinical use in December 2015 by the US Food and Drug Administration. It reverses NMB with a mechanism that differs completely from acetylcholinesterase inhibitors by encapsulating rocuronium or vecuronium and thereby may provide complete recovery even when there is a profound degree of NMB [86]. Although experience in children is limited to case series and reports, initial experience suggests the medication to be relatively safe with only minimal side-effects of nausea, hypotension, bradycardia, and anaphylaxis in <1% of patients. In these case reports, sugammadex was able to reverse dense NMB with vecuronium and rocuronium in children without any response on the train-of-four. This has implications for use in neurological patients to facilitate neurological examination and to improve neuromonitoring (as with motor-evoked potentials) [86].

KEY POINTS: NEUROPHARMACOLOGY

- Isoflurane, sevoflurane, and desflurane all decrease $CMRO_2$, increase CBF, and increase ICP; increasing minute ventilation and producing mild hypocapnea can overcome the effects on ICP
- N_2O use is controversial; it is best avoided in clinical scenarios of "tight brain" or when cerebral ischemia is a risk
- Barbiturates, etomidate, propofol, and benzodiazepines all decrease $CMRO_2$, CBF, and ICP; opioids and dexmedetomidine do not effect these parameters; ketamine increases $CMRO_2$ and ICP
- Depolarizing and non-depolarizing neuromuscular blocking agents have little effect on cerebral circulation or metabolism

General anesthetic considerations

The following sections discuss the anesthetic management of pediatric neurosurgical procedures. Topics common to most procedures are reviewed first, followed by discussion of specific considerations and surgical procedures.

Preoperative assessment of the neurosurgical patient

Ongoing developments in neuroimaging and neuromonitoring have increased understanding of cerebral pathophysiology and improved the preoperative assessment of neurosurgical patients. However, the cornerstone of assessment of neurological function is still the history and physical examination. The preoperative anesthetic work-up of the neurosurgical patient includes a complete baseline neurological examination, an assessment of ICP, assessment of the function of vital respiratory and cardiovascular centers that can be affected by neuropathological processes, either in the brainstem or in the spinal cord, and assessment of specific disturbances in neurological function [87]. Important to many neurological procedures is to assess and document preoperative recognition of intracranial hypertension and major neurological deficits. Notably, the history, symptoms, and physical findings of intracranial hypertension differ somewhat according to the age group. In general, the clinical presentation of patients with intracranial hypertension varies with the duration of increased ICP (Table 25.3). Sudden massive increases in ICP often cause coma. In a less acute case, however, there may be a history of headache on awakening, suggestive of vasodilation caused by sleep-induced hypercapnia and reduced intracranial compliance. Vomiting is a common sign. Neonates and infants often present with a history of increased irritability, poor feeding, or lethargy. A bulging anterior fontanelle, dilated scalp veins, cranial enlargement or deformity, and lower extremity motor deficits are also common signs of increased ICP in this age group [88]. Increased ICP in children is frequently caused by a tumor. As ICP reaches critical levels, vomiting, decreased level of consciousness, and evidence of herniation may develop. Other symptoms include diplopia due to oculomotor or gaze palsies (sunset sign), dysphonia, dysphagia, and/or gait disturbances. Injury to the third cranial nerve may result in ptosis. Injury to the sixth cranial nerve produces a strabismus caused by loss of abduction. Nausea and vomiting usually occur, and older children complain of morning headache. Papilledema and lack of venous pulsation of the retinal vessels may be seen on funduscopy.

Neurogenic pulmonary edema is a syndrome that includes acute hypoxia, pulmonary congestion, pink, frothy, protein-rich pulmonary edema, and radiological evidence of pulmonary infiltrates [89], and is associated with a variety of intracranial pathological occurrences, including hemorrhage [90], head trauma [91], and seizures [92]. The mechanisms responsible for activating the sympathetic nervous system and the vagal centers, which lead to pulmonary edema, are related to ischemia of the medulla and distortion of the brainstem [93]. Cranial nerve function and the patient's ability to protect the airway must be evaluated. During the preoperative assessment, the possibility of spinal cord dysfunction must be determined. Neurological dysfunction arising from cervical spinal cord injury may affect the respiratory and cardiovascular centers. Some coexisting conditions may warrant additional anesthetic considerations if neurological problems occur (see Table 25.4).

Laboratory tests may yield evidence of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and of electrolyte abnormalities or volume contraction from protracted vomiting. Diabetes insipidus may result in hypernatremia [94]. Disturbances in metabolism, such as hypo- or hyperglycemia, may be present. The preoperative history and chart review may reveal that the patient is receiving steroids to reduce tumor edema. If so, steroids will be required during surgery. Neurosurgical patients may be receiving anticonvulsant medication, either to treat seizures or to prevent them. These drugs may have profound effects on the metabolism of other drugs (e.g. barbiturates, narcotics). Patients with suprasellar tumors, such as craniopharyngioma, frequently have pituitary dysfunction and should have a complete endocrine evaluation before surgery.

Table 25.3 Signs and symptoms of increased intracranial pressure (ICP) in infants and children

	Infants	Children	Infants and children
Symptoms	Irritability Poor feeding	Headache Vomiting	Lethargy
Physical examination	Bulging fontanelle Separated sutures Large head circumference	Diplopia Papilledema	Decreased level of consciousness Cushing's triad Pupillary enlargement Absent upward gaze Cranial nerve III and VI palsies

Table 25.4 Perioperative concerns for infants and children with neurological disease

Condition	Anesthetic implications
Congenital heart disease	Hypoxia and cardiovascular collapse
Prematurity	Postoperative apnea
Upper respiratory tract infection	Laryngospasm and postoperative hypoxia/pneumonia
Craniofacial abnormality	Difficulty with airway management
Denervation injuries	Hyperkalemia after succinylcholine Resistance to non-depolarizing muscle relaxants
Chronic anticonvulsant therapy for epilepsy	Hepatic and hematological abnormalities Increased metabolism of anesthetic agents
Arteriovenous malformation	Potential congestive heart failure
Neuromuscular disease	Malignant hyperthermia Respiratory failure Sudden cardiac death
Chiari malformation	Apnea Aspiration pneumonitis

Skull radiographs, ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) aid in the assessment of intracranial hypertension. Skull radiographs may show the "beaten copper sign" and widening of the sagittal sutures in response to chronic increased ICP and universal suture stenosis. In infants and young children, the width of the cranial sutures should not exceed 2 mm, and they should not have bridges or closures [95]. Ultrasonography of the brain is useful in premature infants and neonates because it is relatively inexpensive, does not require sedation, and can be performed at the bedside through the fontanelle. However, the CT scanner can visualize virtually all parts of the brain and is the preferred method for imaging for hydrocephalus [96]. Development of CT scanning and MRI has revolutionized the investigation of brain disease.

Given their complexity and potential need for optimization and integration of both the evaluation and treatment by multiple services, neurosurgical diseases have become a focus in the pediatric perioperative surgical home (PPSH, see Chapter 15). At Texas Children's Hospital we have used this for perioperative care planning for scoliosis surgery and craniosynostosis, with a future focus on epilepsy, arteriovenous malformation (AVM), and glioma surgery [97,98].

Premedication

Most anesthesiologists avoid sedation in pediatric neurosurgical patients. If sedatives and opioids are given as part of premedication for surgery, the patient must be closely monitored because the drugs may precipitate respiratory depression, hypercarbia, loss of airway integrity, and increased ICP. Exceptions to this rule include patients with intracranial vascular lesions (with no increase in ICP) who may benefit from sedation to reduce the likelihood of precipitating increased blood pressure from anxiety or crying that could potentially precipitate a preoperative hemorrhage. Sedation can be accomplished in small children with midazolam (0.5 mg/kg), pentobarbital (4 mg/kg), or chloral hydrate (50 mg/kg) administered orally or rectally 1 h before surgery. Emotional preparation is essential and is accomplished by the anesthesiologist and the parents working together. In older children, a simple explanation of what to expect before induction of anesthesia will reduce the element of surprise and the incidence of hemodynamic instability in a threatening environment.

Patient positioning

Planning of a successful anesthetic includes the preparation of the operating table with proper equipment to protect the patient after positioning. The anesthesiologist's preoperative visit should provide information on patient positioning during surgery.

Although patient positioning varies according to the neurosurgical procedure, the general principles remain the same. The eyes must be securely taped closed and, if the patient is prone, the face and other vulnerable areas must be padded to prevent localized pressure. Since ventilation may be compromised by incorrect positioning, it is mandatory to ensure that chest excursion remains adequate, especially when the patient is prone. This can be achieved by using suitable bolsters or a frame that allows the abdomen to be pendulous and facilitates respiratory movement during intermittent positive pressure ventilation. The endotracheal tube (ETT) should be taped securely in place, most notably in the prone position as secretions may loosen the tape. A 10° head-up position is usually advisable to improve cerebral venous return and reduce venous congestion. Rotation of the head to one side may kink the jugular veins and reduce venous return. This kinking can be avoided by rotating the trunk to maintain the axial position. During any surgical procedure, it is important for the anesthesiologist to be able to inspect the ETT and circuit connection and to have access to the ETT for possible endotracheal suctioning. In addition, it is desirable to have a body part, such as a hand or foot, visible during surgery so that peripheral perfusion and color can be readily assessed. General effects of patient positioning are listed in Table 25.5.

Monitoring

Basic monitoring consists of a precordial/esophageal stethoscope, electrocardiography (ECG), a non-invasive blood pressure measuring device, a temperature probe, a pulse oximeter, and capnometry. In addition, an arterial catheter allows continuous monitoring of peripheral perfusion on a beat-to-beat basis and provides an accurate measurement of blood pressure. A peripheral nerve stimulator for monitoring NMB is desirable. A urinary catheter is required for long surgical procedures and is mandatory if osmotic diuretics are administered.

Induction of anesthesia

The anesthetic technique chosen and recognition of perioperative events may have profound effects on morbidity and approach to induction [17]. Consideration of the developmental, anatomical, and physiological differences of pediatric patients who range from premature neonates to 16- to 18-year-old young adults is critical. Knowledge of normal physiology in these differing age groups is essential. Neonatal anesthesia differs from that in the older child and adult,

Table 25.5 Physiological effects of patient positioning for neurosurgical procedures

Position	Physiological effect	Risks
Supine	Easiest position Typical pulmonary and cardiac mechanics	Axial rotation of the head can cause jugular venous compression Peripheral nerve padding of ulnar with arms tucked
Head-elevated	Enhanced cerebral venous drainage	Increased venous air embolism (VAE) risk
	Decreased cerebral blood flow	Increased hypotension
	Increased venous pooling in lower extremities Postural hypotension	Increased pneumocephalus
Head-down	Increased cerebral venous and intracranial pressure	Increased bleeding
	Decreased functional residual capacity (lung function) Decreased lung compliance	Increased desaturation
Prone	Venous congestion of face, tongue, and neck Decreased lung compliance	Increased risk of eye injury Increased risk of skin injury
	Increased abdominal pressure can lead to venocaval compression	Difficult airway access
Lateral decubitus	Decreased compliance of down-side lung	Brachial plexus injury Decreased perfusion dependent arm

particularly with regard to the respiratory system, the cardiovascular system, and thermoregulation.

Most important is to recognize the neurological status of the patient and modify the induction accordingly. Anesthesia for patients with elevated ICP is fraught with danger. In patients with altered mental status secondary to elevation in ICP, the goal is to safely control the airway, with minimal effect on increasing ICP. As with other patients with lethargy or increased somnolence, a rapid-sequence technique for induction and intubation is preferred to minimize aspiration risk and allow for endotracheal intubation and controlled ventilation (such as hyperventilation) to help control and lower the ICP. The systemic hypertension associated with laryngoscopy may be avoided by giving IV lidocaine at induction of anesthesia. Rapid-sequence induction of anesthesia with propofol, atropine, lidocaine, and succinylcholine, followed by carefully applied cricoid pressure and manual hyperventilation, is recommended [99]. When succinylcholine is contraindicated (i.e. pre-existing spinal cord, stroke injury, congenital myopathy), large-dose rocuronium or vecuronium can be administered as an alternative neuromuscular blocking agent in conjunction with a modified rapid-sequence technique. With appropriate cricoid pressure, manual ventilation can be performed without distention of the stomach. Cricoid pressure reduces the likelihood of aspirating gastric contents; delayed gastric emptying is often associated with increased ICP. Historically, succinylcholine has been used to produce satisfactory intubation conditions because the speed of onset and offset outweighs the small increase in ICP that it causes. Rocuronium (1–1.2 mg/kg) produces intubation conditions comparable to succinylcholine [76]. In patients without ready IV access, anesthesia can be induced via a small butterfly needle that can be inserted with minimal patient stress or hemodynamic fluctuation. Failing this, it is probably less injurious to children with raised ICP to perform a skillful inhalation induction of anesthesia than it is to subject them to a difficult IV placement. Anesthesia is best maintained with air in oxygen, isoflurane, and a suitable muscle relaxant. Intermittent positive pressure mechanical ventilation is provided. Hypoventilation and hypercarbia are best avoided. An IV opioid can be used in children. Most importantly, deep levels of anesthesia are not needed and are relatively contraindicated for achieving the best neurophysiological conditions and the best neurological examination after the procedure.

Fluid management and intracranial pressure control

Fluid management

Fluid administration to neurosurgical patients depends on the pathology or brain insult being treated. A frequent result of these insults is the development of brain edema, with a resultant increase in ICP. It is essential for the neuroanesthesiologist to understand the principles of fluid movement in the injured brain to administer the proper fluid regimen. Edema formation occurs when there is inequality of net movement of fluid between the intra- and extracellular compartments. The blood–brain barrier (BBB) is composed of capillary endothelial cells, which are connected in continuous fashion by tight junctions. The BBB also excludes polar hydrophilic molecules. Thus, the BBB has tight endothelial junctions of 7 angstroms, as opposed to 65 angstroms in other tissues of the body. This junction is small enough in the brain to prevent sodium from moving into the cells. Essential molecules, such as glucose and amino acids, cross the BBB by energy-mediated transport systems. Only water molecules freely communicate with both sides of the membrane. This passive movement of water is regulated by oncotic, osmotic, and hydrostatic pressure changes across the barrier. The colloid oncotic pressure is a relatively weak driving force. A reduction of 50% of the colloid oncotic pressure (normal 20 mmHg) results in a pressure gradient across the membrane, which is less than that caused by a transcapillary osmolarity difference of 1 mOsm/L. As an example, reduction in the colloid oncotic pressure of the brain does not have the same impact as that observed in the bowel. This is because the brain's extracellular space is poorly compliant, due to its network of glial cells, and discourages edema formation, even in the presence of a severe colloid oncotic pressure gradient. Administration of Ringer's lactate alone will lead eventually to hemodilution and reduced plasma osmolarity (osmolarity 273 mOsm/L), which would encourage cerebral edema [100].

The choice of fluid must be dictated by the neuropathological process involved, and there is no formulaic solution for volume replacement in these cases. The goal should be to maintain an isovolemic, iso-osmolar, and relatively iso-oncotic intravascular volume. For example, a patient with increased ICP and/or a brain mass requires a fluid regimen that balances adequate intravascular volume against efforts to dehydrate the brain mass. In a patient undergoing insertion of a ventricular shunt and/or repair of myelomeningocele, fluid management should replace third-space losses.

An osmolar gradient can be maintained only in areas where the BBB is intact. Under normal circumstances, osmotic diuretics and plasma expanders, such as albumin, are excluded. Unfortunately, areas that might benefit the most from dehydration therapy, such as tumor edema, exhibit BBB incompetence. Agents of high osmolality move into these tissues and increase the edema.

Efforts to dehydrate the brain are complicated by the need to maintain adequate circulating blood volume. In many neurosurgical procedures, a substantial portion of the blood loss is onto the drapes and is difficult to measure. Furthermore, the use of large amounts of irrigation solution makes it difficult to assess blood loss accurately. The initial phase of any neurosurgical procedure produces blood loss, especially scalp incisions. Infiltration of the scalp with bupivacaine 0.125% with 1:200,000 epinephrine reduces blood loss and reduces hemodynamic responses (increased heart rate and blood pressure) during incision. In all cases, bupivacaine blood levels were within the therapeutic range [101]. Resection of a vascular malformation may require massive volume replacement. Placing large-bore IV catheters and having available sufficient blood products are part of appropriate planning for anesthesia and surgery. Urine output in the face of aggressive diuresis is a misleading indicator of adequate volume replacement. In this instance, CVP monitoring is very useful.

There is no perfect protocol for fluid replacement in neurosurgical patients with increased ICP. However, maintenance of cerebral perfusion pressure should represent the optimal goal of fluid therapy. Most anesthesiologists start osmotic diuretic therapy at the beginning of anesthesia and measure the resulting urine output. As surgery and blood loss progress, volume replacement usually consists of a mixture of crystalloid and colloid solutions to maintain an isovolemic, iso-osmolar, and iso-oncotic intravascular volume. After an initial 20 mL/kg of crystalloid solution, normal saline or hypertonic saline can be given. Lactated Ringer's and hypotonic fluids should be avoided. Administration of albumin remains controversial. A recent study in adults found that administration of albumin in the resuscitation of patients with traumatic brain injury was associated with a higher mortality than crystalloid-only resuscitation [102]. As described earlier, the brain that has sustained a recent insult (primary lesion) is vulnerable to so-called "secondary insult" (penumbra area) by a minor episode of hypotension, hypoxia, or ischemia related to mechanical insult [103] (retraction [104]) or ischemia (hemodynamic instability) [105]. Although rapid administration of normal saline (10 mL/kg) has little effect on CBV and ICP, it may reinstitute hemodynamic stability. Blood products should be administered only on the basis of hemodynamic instability and diminished oxygen-carrying capacity.

Dextrose-containing solutions are associated with a poorer neurological outcome and are best avoided unless hypoglycemia has been confirmed [106]. Stressed neonates have reduced glycogen stores, and patients from the ICU may have high glucose loads in their parenteral nutrition. Abrupt cessation of high-dextrose solutions can precipitate an insulin-induced hypoglycemia. In these patients, blood glucose levels should be sampled frequently and normoglycemia maintained.

Osmotic and diuretic therapy to reduce intracranial pressure

Hypertonic saline

Some investigators have suggested that extracellular volume dehydration can be accomplished by raising serum osmolality with hypertonic saline (3% saline) [107]. Hypertonic saline solution (typically 3 mL/kg bolus) has been shown to be effective for volume resuscitation, while resulting in less cerebral edema and/or ICP elevation [108]. In children with severe traumatic brain injury, resuscitation with hypertonic saline (sodium 268 mmol/L, 598 mOsm/L) was superior to resuscitation with lactated Ringer's solution (sodium 131 mmol/L, 277 mOsm/L) [109]. Although children treated with the hypertonic saline solution had shorter ICU stay and fewer ICP interventions, the overall survival rate and duration of hospitalization were no different between groups. In another study of children after traumatic brain injury, 3% hypertonic saline significantly reduced ICP when compared to normal saline resuscitation [110]. Based on these findings and others, there is no difference in recommendation between hypertonic saline or mannitol in the current pediatric brain trauma guidelines [111].

Mannitol

Mannitol (20% solution) remains the most popular diuretic for reducing ICP and providing brain relaxation. Small doses, such as 0.25–0.5 mg/kg, will raise osmolality by 10 mOsm and reduce cerebral edema and ICP [112]. The effects of mannitol begin within 10–15 min of its administration and persist for at least 2 h. Mannitol-induced vasodilation affects intracranial and extracranial vessels and transiently increases CBV and ICP while simultaneously reducing systemic blood pressure. In particular, some children may show transient hemodynamic instability (during the first 1–2 min) after rapid administration of mannitol [113]. Therefore, the drug should be given at a rate not exceeding 0.5 g/kg over 20–30 min. The initial period of hypotension will be followed by increases in cardiac index, blood volume, and pulmonary capillary wedge pressure, all of which reach peak values 15 min after infusion [114]. The changes in intravascular volume last for about 30 min before a return to normal levels. Administration of furosemide before giving mannitol may increase venous capacitance, reduce transient increases in intravascular volume, and provide more effective dehydration. There is, however, a danger of producing profound dehydration and severe electrolyte imbalance [115]. Larger doses of mannitol produce a longer duration of action, but there is no scientific evidence that they reduce ICP further. In animal studies, larger doses of mannitol have significantly decreased the rate of CSF formation [116]. In the presence of cerebral ischemia, larger doses of mannitol 2 g/kg can be used with a presumed added benefit of free radical scavenging. In addition, higher mannitol

dosages have been shown to increase CBF [117] and cardiac output [118] probably by reducing blood viscosity (rheology) [119] or acutely increasing intravascular volume. Through the combination of these effects, it has been suggested that mannitol may cause cerebrovascular vasoconstriction and further reduce CBV. Regardless, the net effect is a multifactorial reduction in ICP from mannitol administration that most directly correlates with a reduction in CBV [120].

Loop diuretics

The loop diuretics, such as furosemide and ethacrynic acid, may reduce brain edema by inducing a systemic diuresis, decreasing CSF production [121], and improving cellular water transport [122]. Although furosemide can reduce ICP without increasing CBV or blood osmolality, it is not as effective as mannitol [123]. The initial dose of furosemide should be 0.6–1 mg/kg if administered alone, or 0.3–0.4 mg/kg if administered with mannitol to children [124]. In the setting of co-administration with mannitol, it is thought to mitigate rebound cerebral edema [125,126]. It has been suggested that ethacrynic acid reduces secondary brain injury by decreasing glial swelling [127]. Raising serum osmolality above 320 mOsm may precipitate acute renal failure and water retention, and create a scenario with the negative consequences that follow from a declining serum osmolality during recovery. Periods of aggressive dehydration may be followed by rebound intracranial hypertension during the recovery or normalization period.

Corticosteroids

Corticosteroids are an important part of the therapeutic regimen in neurosurgical patients with raised ICP. They reduce edema around brain tumors, but hours or days may be required before effects are seen. However, the administration of dexamethasone preoperatively or at the induction of anesthesia frequently improves neurological status before the ICP decreases. It has been suggested that this is in response to a partial restoration of BBB function [128].

Temperature homeostasis

In general, extremes of temperature should be avoided and situations of hypothermia and hyperthermia managed aggressively. Often, a normothermic temperature goal of 35.5–36.5°C should be used, with warming measures started below and cooling measures started above these temperature margins. Although hypothermia reduces the $CMRO_2$, it frequently delays drug clearance, slows reversal of neuromuscular blocking agents, decreases cardiac output, causes conduction abnormalities, attenuates hypoxic pulmonary vasoconstriction, alters platelet function, causes electrolyte abnormalities, and can induce postoperative shivering [129]. In addition, the intraoperative vasoconstriction produced by hypothermia reverts to vasodilation and redistribution of body heat upon rewarming, causing a redistribution of heat and a transient fall in core temperature [130].

Neonates and infants are at greatest risk of hypothermia because of their large surface area relative to body mass. Despite a warm operating room, body temperature falls immediately after induction of anesthesia owing to internal redistribution of body heat from the central compartment to the periphery [131]. As heat loss continues, pediatric patients trigger non-shivering thermogenesis in an attempt to rewarm themselves [132]. In the paralyzed and ventilated patient, body temperature and end-tidal CO_2 ($ETCO_2$) concentration may increase at constant minute ventilation [133]. This phenomenon may not be readily apparent because of cold fluid administration. Temperature monitoring is essential, but the actual site of the probe placement is less important than probe reliability. For this reason, we usually place the probe in the esophagus or rectum. During induction of anesthesia and placement of IV lines and monitors, a large body surface area is exposed, and premature infants and small infants should be placed under a radiant heat lamp. Extremities can be covered with plastic wrap or sheet wadding. Dry inspired gases should be warmed and moisturized with a heat exchanger [134,135]. Although the usefulness of warming blankets has been questioned, they appear to work well as long as they are positioned below the patient. Forced air warming blankets that are placed underneath the patient are now available and can be very useful to maintain temperature. Blood warmers should always be used if substantial fluid replacement is required. Rewarming measures such as a forced warm air system can be used in the postoperative period.

Hyperthermia (>38.5°C) in the setting of pediatric traumatic brain injury has been associated with poor outcomes. Studies in both animal models and in patients have shown that during and immediately after brain trauma or ischemia, temperature powerfully influences neurological recovery and increases $CMRO_2$ [136]. The association between the development of hyperthermia and increased morbidity and mortality has been described in adult and pediatric patients with ischemic stroke and closed head injury [137]. Based on these data, aggressive cooling strategies with forced air systems at ambient air temperature, circulating cooling blankets, and cold gastric lavage combined with antipyretic therapy with acetaminophen and non-steroidal anti-inflammatory agents (NSAIDs) may be required to treat and prevent hyperthermia [138]. Further, some institutions have hypothermia protocols to maintain patient temperature in the range 32–34°C in the setting of severe brain injuries or refractory elevation of ICP [139,140]. The current (4th edition) of the Brain Trauma Foundation guidelines does not recommend prophylactic cooling, specifically citing two negative pediatric trials [138]. At our institution, the main thermostasis goal is avoidance of hyperthermia with acetaminophen, forced air cooling, and cooling blankets to targeted temperature of 36°C.

Venous air embolism

Venous air embolism (VAE) is one of the most serious complications of anesthesia and surgery. In neurosurgical cases, various positions place the operative site above the heart, creating increased risk of VAE. This risk increases as the height difference increases. Classically, VAE is associated with posterior fossa surgery in the sitting position, but it is not confined to this procedure. VAE has been reported in infants and children during procedures involving the skull, such as morcellation of the cranial vault, craniectomy for craniosynostosis, and spinal cord procedures [141]. It has also occurred with the patient in the lateral position [142]. The incidence of VAE has been reduced considerably by use of the prone position for

Table 25.6 Relative risk for venous air embolism (VAE) in neurosurgical procedures

Neurosurgical procedure	Relative risk
Craniotomy – sitting position	High
Posterior fossa/neck surgery	High
Craniosynostosis repair	High
Spinal fusion	Medium
Cervical laminectomy	Medium
PRBC infusion	Medium
Peripheral nerve surgery	Low
Anterior neck surgery	Low
Burr hole/ICP monitor placement	Low

Approximate expected reported incidence: high >25%, medium 5–35%, and low <5%.
ICP, intracranial pressure; PRBC, packed red blood cells.
Source: Reproduced from Mirski et al [144] with permission of Wolters Kluwer.

posterior fossa surgery [143] and by use of mechanical ventilation. Table 25.6 presents the relative risk for air embolization based on various surgical procedures [144].

Air entrainment occurs when a number of conditions are met, including (1) venous pressure at the operative site that is below atmospheric pressure, (2) a vein that is open to the atmosphere, and (3) a vein that is prevented from collapsing. It most commonly occurs during the first hour of surgery, and the most frequent sites of air entrainment are the cranial diploic veins, the emissary veins, and the intracranial venous sinuses, which are kept open by their dural attachment. VAE can also occur from veins in muscles and from the puncture site of the multipoint head-holder used in children over 3 years of age [145]. Detection of VAE depends entirely on the sensitivity of the monitors used (Fig. 25.1). The reported incidence of air emboli varies widely [146]. Using highly sensitive precordial Doppler, the reported incidence of air embolus is as high as 58% in adult patients undergoing posterior fossa surgery in a sitting position [147]. Less than half of the cases of detected emboli produce systemic hypotension [148]. In pediatric neurosurgery the incidence of detectable air emboli is about 33% [149] but systemic complications occur in more than half of the cases. Although children are not more prone to air emboli than adults, they are more susceptible to them. For example, the incidence of air embolism during craniosynostosis repair in supine infants may be as high as 67% [150].

This may explain why, without any obvious reason, some patients experience periods of hypotension. In addition, the increased right-sided pressure may cause air to pass from the right side of the heart to the left via an atrial septal defect, causing paradoxical air embolus. Anatomically, some 27% of patients have a patent foramen ovale and are potentially at risk for embolization to the left heart. Air also may reach the systemic circulation without the presence of an intracardiac septal defect [151] and may result in cerebral or myocardial infarction.

It is essential to take measures to avoid this potentially disastrous complication. Meticulous avoidance of a pressure gradient between the open tissue and the heart and the routine use of positive pressure ventilation are mandatory. On detecting air entrainment, the anesthesiologist must: (1) advise the neurosurgeon to discontinue surgery, flood the surgical field with fluid, compress the jugular veins, and position the operative field lower than the heart to prevent further ingress of air; (2) ventilate the lungs with 100% oxygen; (3) attempt to withdraw air through the central venous catheter; (4) treat any hemodynamic consequences; and (5) if hemodynamic instability persists, turn the patient into a left-side-down position. When venous air is detected during craniotomy in children, air can be successfully aspirated from veins 38–60% of the time [149] (Fig. 25.2).

Intravenous fluids [152], appropriate antiarrhythmic and inotropic agents, or vasopressors may be necessary and should be administered as needed. Nitrous oxide must be discontinued because it increases the size of the embolus several-fold, causing further physiological compromise. Some authors have proposed that a positive end-expiratory pressure (PEEP) of 10 cmH_2O might decrease the rate of air entry by increasing venous pressure, but less than 10 cmH_2O pressure is not adequate to do so [153]. It is possible that the

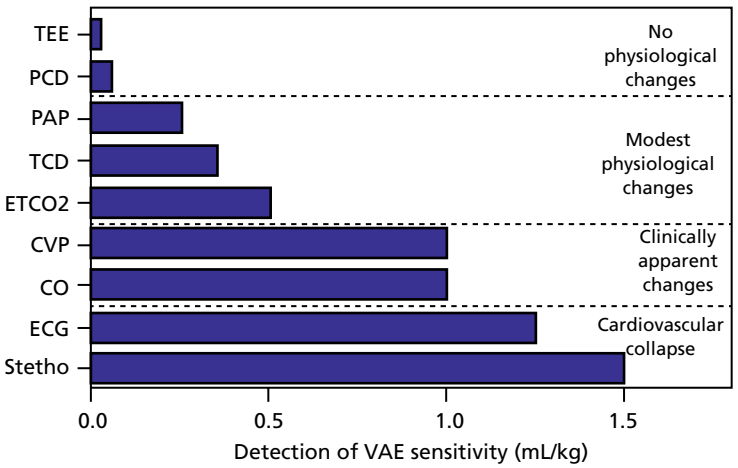


Figure 25.1 Methods of venous air embolism (VAE) detection listed from highest to lowest sensitivity based on smallest detectable volume of air. Those techniques with the highest sensitivity may detect VAE prior to clinical or physiological instability, while those with the lowest sensitivity may only detect VAE when hemodynamic changes and physiological instability are present. Clinical availability of VAE monitoring techniques is low for intraoperative transesophageal echo (TEE) and moderate for precordial Doppler (PCD), pulmonary artery pressure by catheter (PAP), and transcranial Doppler (TCD). Routine clinical monitors such as electrocardiography (ECG) and auscultation with a stethoscope (Stetho) are late detectors and unable to prevent decompensation. CO, carbon monoxide; CVP, central venous pressure; $ETCO_2$, end-tidal CO_2. *Source*: Reproduced from Mirski et al [144] with permission of Wolters Kluwer.

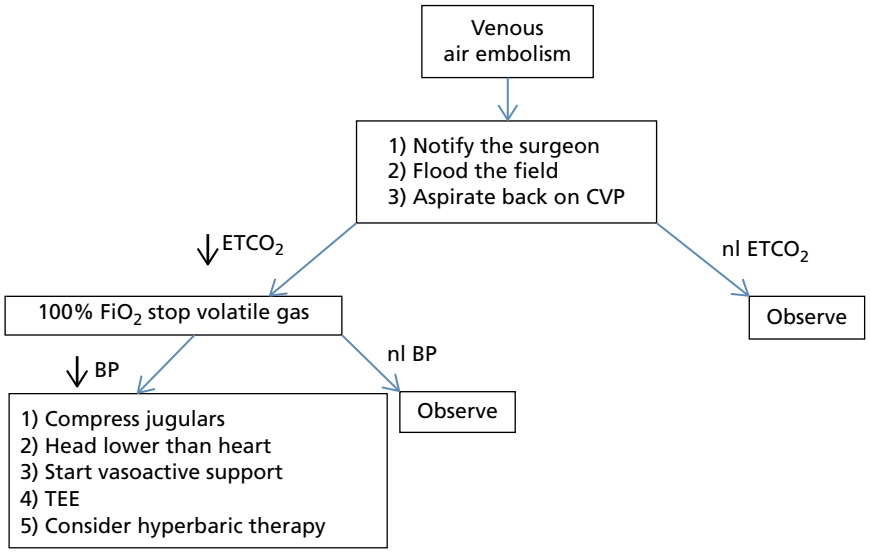


Figure 25.2 Algorithm for management of a suspected venous air embolism (VAE) event. Ideally, suspected increased VAE and detection source of suspected VAE are communicated with surgeon. Steps to prevent ongoing air entry are discussed, along with evaluation for other confirmation of VAE (like $ETCO_2$). If there is increasing hemodynamic instability from VAE, progress quickly to initiation of supportive measures such as repositioning and vasoactive support. BP, blood pressure; CVP, central venous pressure; $ETCO_2$, end-tidal CO_2; FiO_2, fraction of inspired oxygen; TEE, transesophageal echocardiography.

use of PEEP may cause paradoxical air embolism and decrease venous return to the heart, resulting in additional hemodynamic instability and necessitating additional fluid and vasopressor support [154].

KEY POINTS: GENERAL ANESTHETIC CONSIDERATIONS

- Preoperative assessment should focus on neurological examination, detecting increased ICP, reviewing neuroimaging studies, and understanding co-morbid conditions such as seizure disorder
- Premedication, if given, should be administered judiciously and patients with elevated ICP monitored carefully until anesthetic induction
- Careful positioning with attention to all pressure points and securing the endotracheal tube is essential; prone positioning is common; avoiding sitting position and head more than 10° elevated are important to avoid VAE
- Careful fluid administration, arterial monitoring, airway and ventilation management to avoid hypercapnia, and osmotic diuresis with hypertonic saline or mannitol are integral approaches to intracranial neurosurgery

Specific anesthetic considerations

Neuroradiology

Children and infants, unlike adults, frequently require general anesthesia or sedation for neuroradiological diagnostic or interventional therapeutic procedures. Several special problems are related to the administration of anesthesia in this context. Among these are the delivery of care in a remote area away from skilled help, the limitations imposed by cumbersome equipment, the need to be at a distance from the patient during the procedure, and the occasional adverse effects of contrast agents. The principal indication for anesthesia in these circumstances is to provide total immobility for extended periods for young patients who cannot cooperate. The most common procedures are CT scanning, cerebral angiography, lumbar myelography, radiation therapy, and MRI. Specific anesthetic considerations for these procedures depend on the patient's condition and the radiological demands. Chapter 41 presents further discussion of neuroradiology procedures.

Skull abnormalities: craniosynostosis

Craniosynostosis is the most common skull anomaly encountered by the pediatric anesthetist. The condition consists of premature fusion of one or more cranial sutures. The incidence is about 1 in 2000 livebirths with a male predominance. While it can be an isolated anomaly, it may be associated with a variety of genetic syndromes. Special considerations for patients with craniosynostosis include increased ICP and blood loss. Children and infants undergoing craniectomy may have increased ICP, and induction of anesthesia should proceed as discussed previously. The degree of blood loss is increased in patients with multiple suture synostoses and in those more than 6 months old with thicker bone tables. Most craniosynostosis surgery is performed between 2 and 6 months of age, a period that coincides with physiological anemia. Transfusion may therefore be required to maintain an acceptable hemoglobin level. Simple suture craniectomy in the young child with normal ICP seldom requires arterial line placement. However, adequate IV access for fluid and blood replacement is essential. Children with elevated ICP and those undergoing extensive multiple suture procedures usually require arterial line placement. Endoscopic craniosynostosis repairs are increasingly undertaken and usually reduce blood loss substantially. See Chapter 36 for a more detailed discussion of these procedures.

Hydrocephalus

Hydrocephalus is a congenital or acquired pathological condition with many variations but always characterized by an increase in the amount of CSF that is now, or has been, under increased pressure (Fig. 25.3). It can occur at any age. It is caused by one of four basic disease processes: congenital anomalies (e.g. Arnold–Chiari malformation), neoplasms, inflammatory conditions, and overproduction of CSF (e.g. choroid plexus papillomas). Hydrocephalus is the most common neurosurgical condition requiring intervention. Besides the underlying etiology, it can be further classified into obstructive/non-communicating (CSF cannot flow around the spinal cord) or non-obstructive/communicating forms (CSF can flow normally). Patients who cannot be medically managed require an external ventricular drain and/or internalized ventricular shunt, or endoscopic third ventriculostomy.

Ventricular shunts

Three types of internalized ventricular shunts are in current use: ventriculoperitoneal, ventriculoatrial, and ventriculopleural. Each has its indications and anesthetic implications. Often, as the pediatric patient grows, the shunt must be revised. It must be replaced if it malfunctions or becomes infected. Placement or revision of shunts is common in both severely neurologically impaired children and in otherwise healthy patients. These children may present to the operating room multiple times and may request a specific anesthesia induction technique. Patients who present for CSF shunting procedures may exhibit a broad spectrum of symptoms and clinical signs, ranging from an apparently healthy child with minimal disability to a seriously ill, comatose patient for whom surgery is urgent.

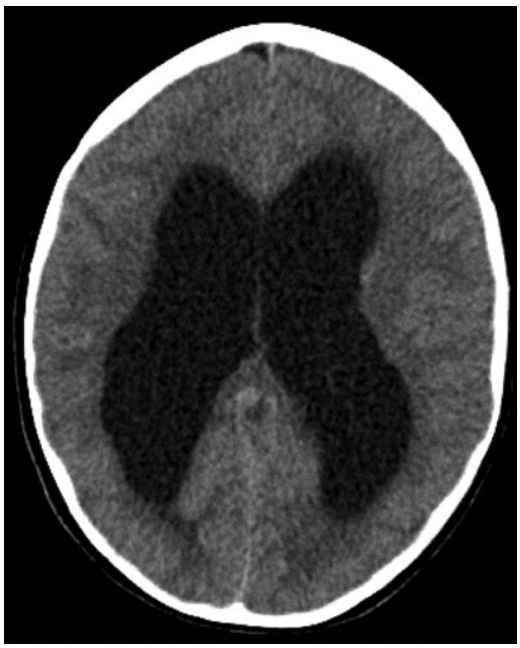


Figure 25.3 This 12-year-old boy was noted to have increasing headache and vomiting. This axial CT scan reveals severe supratentorial hydrocephalus. This was due to the presence of a posterior fossa mass (pilocytic astrocytoma) obstructing the fourth ventricle and cerebral aqueduct (not shown).

Endoscopic third ventriculostomy

Endoscopic third ventriculostomy (ETV) has emerged in recent years as an effective alternative treatment for hydrocephalus, especially in patients with non-communicating hydrocephalus. This procedure is performed by placing a flexible endoscope into the frontal horn of the lateral ventricle, through the foramen of Monro, into the third ventricle [155]. A ventriculostomy is then created in the floor of the third ventricle, creating a direct communication into the prepontine cistern for CSF drainage (Figs 25.4, 25.5). Choroid plexus cauterization is now usually added to the procedure, particularly in young infants. The obvious advantage to this approach is that a shunt is not used, eliminating a mechanical device that can fail or become infected. However, long-term follow-up studies of standard CSF shunts versus ETV have not consistently demonstrated a clear advantage, and a recent prospective study of ETV with a matched historical control group undergoing shunt in infant hydrocephalus demonstrated a worse intervention-free success rate with ETV in the first 6 months (36% versus 80%, $p < 0.001$) [156]. A recent randomized controlled trial in Uganda demonstrated similar treatment success rates at 12 months (65% for ETV versus 76% for shunting, $p = 0.28$), and similar neurodevelopmental outcome scores between groups [157].

Anesthetic considerations

Preanesthetic assessment must include the following:

- *Level of consciousness*. Patients presenting for primary shunting, shunt revision, or malfunction may exhibit severe elevations in ICP that require aggressive treatment.
- *Full stomach*. Evidence of vomiting or delayed gastric emptying is an indication to take precautions against aspiration of gastric contents (e.g. a rapid-sequence induction).
- *Coexisting pathology*. Does the child have evidence of other significant organ system compromise, such as the cerebral palsied child who frequently aspirates?
- *Age-related pathophysiology*. Is the patient likely to have apnea, poor pulmonary compliance, or immature renal function?

Monitoring

Routine monitoring has been discussed previously. Arterial line placement is usually reserved for the patient with uncontrolled ICP and hemodynamic instability.

Preinduction

Typically, a CT scan to assess the degree of hydrocephalus and a radiographic shunt series to look at the course of the shunt will be performed by the neurosurgeon to evaluate shunt integrity and function. Accessing the shunt (also called a "shunt tap") can help to determine the site of malfunction. In some cases, the increased ICP caused by shunt malfunction can be reduced acutely by tapping the proximal reservoir. Infiltration of the skin with local anesthetic allows the tap to proceed with minimal trauma to the patient. The needle can be left in place to monitor ICP during induction. In the patient at risk for emesis during induction of anesthesia, placement of a nasogastric tube may precipitate coughing and bucking and increase ICP. Severely neurologically compromised children often have gastrostomy tubes, and opening these tubes before induction of

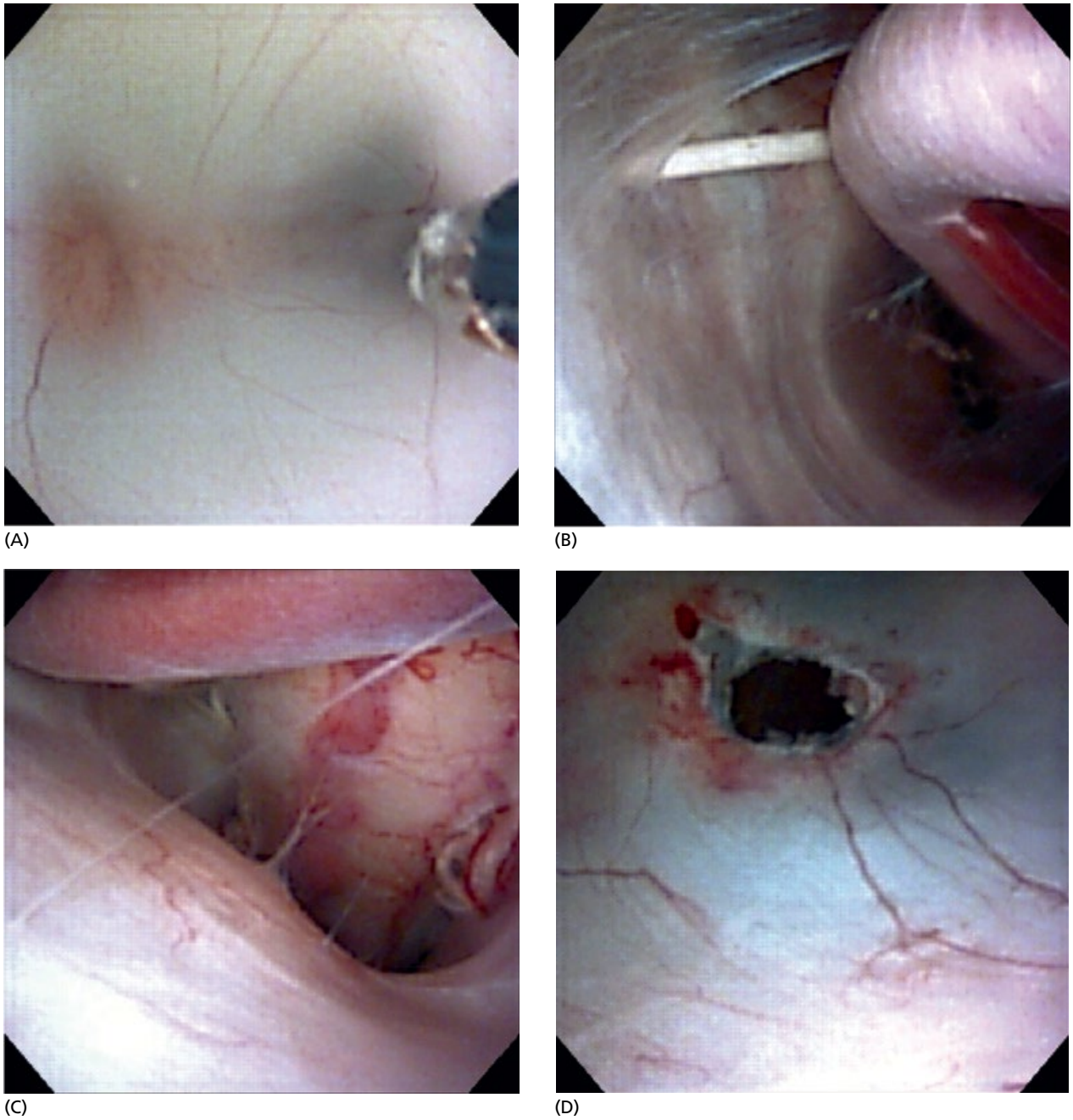


Figure 25.4 Digital flexible ventriculoscopic images of endoscopic third ventriculostomy procedure. (A) Endoscopic image of third ventricular floor with infundibular recess on left and tip of 1 mm Bugby wire poised to penetrate floor on right; anterior is left. (B) Endoscopic image of basilar artery on right and VIth cranial nerve entering cavernous sinus on left after passing endoscope through the third ventriculostomy into the prepontine cistern; clivus is anterior at left. (C) More caudal intracisternal endoscopic image showing right vertebral artery and junction of upper cervical spinal cord and lower medulla at the level of the foramen magnum; clivus is anterior at lower left. (D) Endoscopic image of endoscopic third ventriculostomy opening in floor of third ventricle after withdrawing scope from prepontine cistern back into third ventricle. *Source*: Reproduced from Kahle et al [155] with permission of Elsevier.

anesthesia is recommended. However, this does not guarantee that the patient will not vomit and aspirate gastric contents.

Induction and intubation

Many patients with hydrocephalus have undergone multiple surgical procedures. If there is no clinical evidence of elevated ICP, anesthesia can be induced by mask or with IV drugs; we usually allow children their preference. On the other hand, children with increased ICP and delayed gastric emptying usually have anesthesia induced with thiopental, atropine, lidocaine, a narcotic, and a non-depolarizing muscle relaxant after preoxygenation. Cricoid pressure is applied and the patient is hyperventilated at low peak inspiratory pressures. Since laryngoscopy is a potent stimulus for increasing ICP, an oral tracheal tube is placed as smoothly as possible.

Maintenance

Patients are placed in a supine position with the head turned, or in a slightly lateral position. Patients with increased ICP should be placed in a 30° head-up position with minimal neck rotation or flexion to improve cerebral venous drainage. Patients whose shunt tubing is placed posteriorly and those

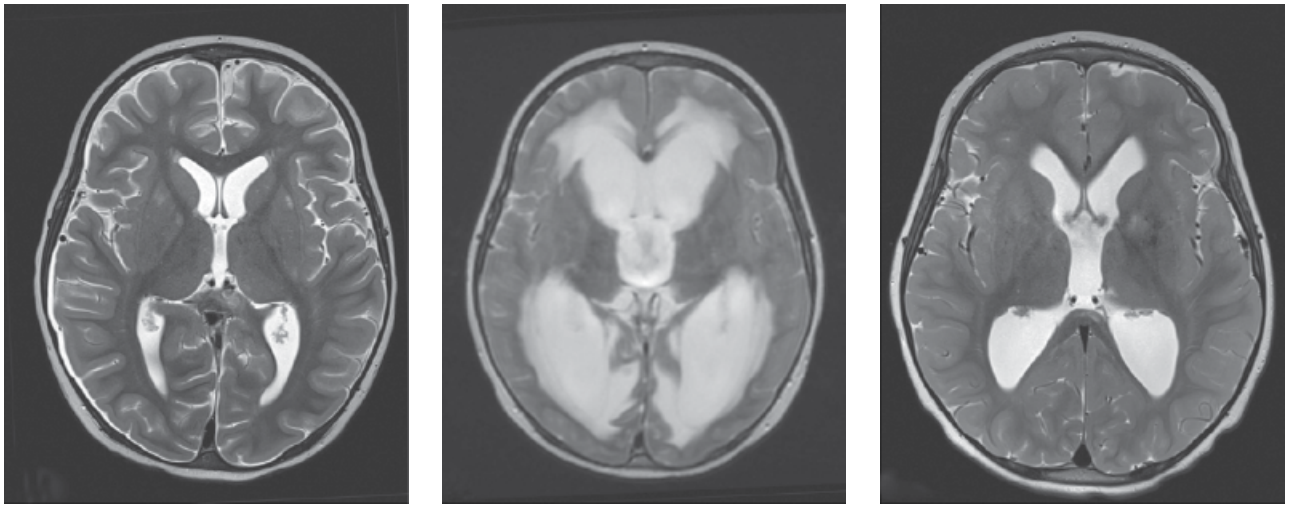


Figure 25.5 MRI of child with postmeningitic hydrocephalus before and after treatment. (A) Brain T2 MRI showing mild ventriculomegaly with very early stage hydrocephalus development in a child aged 22 months with meningitis. (B) Brain MRI of same child 2 weeks later showing severe hydrocephalus with severe ventriculomegaly and increased extracellular water in the periventricular white matter. (C) Brain MRI of same child 9 months after endoscopic third ventriculostomy and choroid plexus cauterization with resolution of hydrocephalus and clinical recovery. *Source*: Reproduced from Kahle et al [155] with permission of Elsevier.

who are placed in a lateral position should have an axillary roll placed and all extremities padded.

After the airway is secured, patients with increased ICP are hyperventilated to a $PaCO_2$ of between 25 and 30 mmHg. Patients with normal ICP are maintained at normocapnia. Spontaneous ventilation should be avoided in patients with ventriculopleural shunts to reduce the risk of pneumothorax, and in those with ventriculoatrial shunts to avoid air embolism. Also, spontaneous ventilation should be avoided when the cranium is opened. Patients with poor pulmonary compliance and those at risk for apnea should be mechanically ventilated during anesthesia.

Anesthesia is usually maintained with nitrous oxide in oxygen, low concentrations of isoflurane, and minimal narcotic supplementation. Although nitrous oxide increases CBF in anesthetized pediatric patients, increases in CBF and $CMRO_2$ are effectively blunted by hyperventilation and pretreatment with propofol. Halogenated anesthetics increase CBF, CBV, and ICP in a dose-dependent manner, with isoflurane having a less adverse effect than halothane. These agents are therefore either used in low concentrations in patients with elevated ICP or avoided entirely until the CSF is drained. Muscle relaxation is usually maintained with vecuronium or atracurium if the procedure is expected to last a short time.

Ventricular shunt procedures usually are not associated with significant blood loss or third-space losses, and fluid management centers around replacement of intravascular volume associated with emesis or drug-induced diuresis.

The body temperature may decrease during shunt procedures, despite their relatively short duration. Exposure of a large body surface area and cold preparation solution, particularly for ventriculoperitoneal shunting, may cause infants to cool rapidly.

Emergence

Adequate time for elimination of the anesthetic agents and adequate reversal of NMB should be ensured before extubation of the trachea. Although it does not provide absolute insurance against regurgitation, the stomach should be suctioned before extubation of the trachea in patients suspected of having increased gastric contents. The patient should be fully awake and have an appropriate gag reflex to protect the airway against emesis. Many patients coming for shunt procedures are severely neurologically impaired and have poor airway control.

Postoperative management

As with any postsurgical patient, supplemental oxygen should be given and the respiratory pattern and adequacy assessed. Neurosurgical patients in general, and preterm infants who are less than 50 weeks' postconceptual age in particular, are likely to have abnormal respiratory patterns or apnea after surgery. Hypothermic patients should be rewarmed before extubation of the trachea.

Analgesics should be used judiciously in neurologically impaired patients. Infiltration of the skin with local anesthetic at the time of surgery substantially reduces the requirement for postoperative analgesia. Patients without preoperative neurological impairment can be given routine postoperative opioids.

KEY POINTS: SPECIFIC ANESTHETIC CONSIDERATIONS FOR NEURORADIOLOGY, SKULL ABNORMALITIES, AND SHUNT PROCEDURES

- Neuroradiology studies are the cornerstone of pediatric neurosurgical procedures; challenges include delivering anesthetic care in remote locations for patients with unrepaired intracranial pathology
- Craniosynostosis surgery is usually a combined neurosurgery–plastic surgery procedure; large blood loss in small infants is a challenge although recent minimally invasive procedures often minimize this issue

- Hydrocephalus is one of the most common neurosurgical conditions; determination of the level of ICP and emergent nature of some hydrocephalus procedures is crucial to maximize outcomes
- CSF shunting procedures and endoscopic third ventriculostomy with choroid plexus cauterization are both now utilized in hydrocephalus

Intracranial tumors

Neoplasms of the CNS account for the major proportion of all solid tumors in children younger than 15 years of age and constitute the second most common cancer in childhood after leukemia. Primary brain tumors are responsible for 20% of all cancers in children and for 20% of childhood cancer deaths. For 2010–2014, the incidence of brain tumors in the USA was 5.54 per 100,000 children less than 15 years of age. An estimated 3560 new cases of childhood **primary malignant and non-malignant** brain and other CNS tumors are expected to be diagnosed in the USA in 2018 [158]. Unfortunately, treatment of primary malignant brain tumors has not resulted in the same dramatic increase in survival seen with childhood leukemia. However, the survival of children with tumors of the CNS has improved significantly over the last several decades. Despite this improvement, much remains to be accomplished, especially in children less than 2–3 years of age at the time of diagnosis. From the anesthesiologist's point of view, intracranial brain tumors are divided according to the site of the tumor. The following section describes an anesthetic approach for supratentorial and posterior fossa craniotomies and for surgical excision of craniopharyngiomas.

Supratentorial craniotomy

Supratentorial lesions account for about half of all pediatric brain neoplasms. For reasons related to embryogenesis, pediatric brain tumors often arise from midline structures, including the hypothalamus, epithalamus, thalamus, and the basal ganglia. These tumors tend to impinge on the ventricular system and cause obstructive hydrocephalus. Hemispheric masses are more common during the first year of life. Their frequency in infants is approximately twice as high as in children (i.e. 37% compared with 16–24%). The relative incidence of hemispheric tumors also increases after 8–10 years of age.

Anesthetic considerations

- *Increased intracranial pressure*. The ICP should be estimated. The CT and MRI images should be reviewed.
- *Full stomach*. Delayed gastric emptying occurs in the patient with raised ICP.
- *Electrolytes and fluid*. Hydration state and electrolyte balance may be altered in the child with intracranial pathology and SIADH.
- *Age-related pathophysiology*. Anesthetic considerations are identical to those discussed previously.
- *Positioning*. The head should be elevated not more than 10° from level. It should be confirmed that venous return is not obstructed.

Monitoring

To the routine monitoring previously described, we add an arterial line for hemodynamic monitoring and blood sampling. In patients in whom significant blood loss, hemodynamic instability, or air embolism, is expected we insert a central venous catheter. A urinary catheter is inserted because of the duration of the surgical procedure and the use of osmotic diuretics.

Preinduction

Detection of preoperative elevation of ICP in patients undergoing craniotomy is essential. Most patients with large mass lesions, significant tumor edema, or obstruction to CSF outflow require an anesthetic approach that aims to reduce ICP. Some children undergo external ventriculostomy drain (EVD) placement before their definitive surgical procedure. Preoperative neurological deficits should be detected and documented. Many patients with intracranial pathology present with SIADH. Such children have evidence of hyponatremia, low serum osmolality, high urine osmolality, and oliguria. Peripheral edema is rarely present. Preoperative treatment of SIADH usually includes fluid restriction.

Induction and intubation

Unlike children with normal ICP, rapid induction of anesthesia, followed by rapid securing of the airway and hyperventilation, is of paramount importance in patients with significantly elevated ICP. Induction of anesthesia generally proceeds as discussed for a modified rapid-sequence intubation. Cricoid pressure is applied and the patient hyperventilated with low peak inspiratory pressures to avoid inflation of the stomach. Laryngoscopy should proceed as smoothly as possible. Some anesthesiologists prefer nasotracheal intubation for patients in whom postoperative ventilation is expected or to better stabilize the ETT in small infants.

Maintenance

Patients with increased ICP are generally ventilated to a $PaCO_2$ of 25–30 mmHg. Occasionally, lower levels of $PaCO_2$ are required if the brain is very "tight" and there is uncontrollable intracranial hypertension. Caution must be exercised because extreme hyperventilation may decrease CPP and either induce cerebral ischemia or shift blood flow from areas of the brain with low flow to areas with impaired autoregulation and high flow (also called the "Robin Hood" phenomenon). Excessive PEEP (>8 cmH_2O) is generally avoided to facilitate cerebral venous drainage and avoid hemodynamic issues such as decreased arterial blood pressure. In patients with impaired oxygenation, low levels of PEEP (3–5 cmH_2O) may correct hypoxia without obstructing venous return.

Pediatric patients are usually placed supine for supratentorial procedures, with the head elevated slightly to facilitate venous drainage. Extremities should be well padded and the eyes protected from injury. Care must be taken to avoid undue flexion, extension, or rotation of the neck.

Fluid management can be a problem. Patients with increased ICP are usually dehydrated after receiving mannitol. This increases the potential for hypovolemia and hypotension, especially when there is significant blood loss. CVP monitoring allows early detection of hypovolemia and volume expansion with isotonic crystalloid and colloid solutions

(such as 5% albumin). Simple craniotomy in patients without significantly increased ICP and in procedures with little blood loss frequently requires crystalloid replacement only.

Emergence

The decision to extubate the trachea at the end of the procedure is made on the basis of the success of the surgical intervention, smoothness of the intraoperative course, normalization of ICP, age of the patient, degree of residual neurological deficit, and presence of factors that affect respiration and airway protection. Patients with inadequate respiratory efforts retain CO_2 and their ICP may therefore be increased. Those without a gag reflex cannot protect their airway. Children who remain sedated and who hyperventilate during the postoperative period should be suspected of having increased ICP. Neonates with poor pulmonary compliance or an immature respiratory drive may require postoperative mechanical ventilation. Barring any of these complications, a child's trachea can be extubated after awakening and after reversal of the NMB and elimination of anesthetic agents.

Postoperative management

As with any postsurgical patient, supplemental oxygen should be administered and the adequacy of respiration assessed. Patients who require postoperative ventilation also require sedation and possibly muscle relaxation to prevent agitation and increased ICP. Infiltration of local anesthetics into the wound intraoperatively or performance of a cervical superficial plexus block at the end of the procedure can reduce the requirement for postoperative analgesics. A balance between patient comfort and the ability to follow the patient's neurological status must be sought. An obtunded patient must be investigated for increased ICP or other surgically correctible pathology, such as intracranial bleeding. Body temperature should be maintained at a normal level.

The most common cause of increased ICP after surgery is uncontrolled systemic hypertension. When postoperative pain control has been achieved, blood pressure can be controlled with vasodilators. Beta-blocking drugs have been used successfully, particularly labetalol, which normally does not cross the BBB.

Seizures frequently occur during the immediate postoperative period. Therefore, many surgeons place their patients on anticonvulsants before surgery and continue these drugs postoperatively. Historically, phenobarbital was the most commonly used drug, with other medications (e.g. fosphenytoin and valproic acid) added if the seizures were refractory to treatment [159]. Nowadays, levetiracetam is more often used, with fewer side-effects than previous prophylactic regimens [160].

Craniopharyngioma

Craniopharyngioma is a benign encapsulated tumor of the hypophysis cerebri (Fig. 25.6). Children with this tumor often present with symptoms of endocrine failure, visual disturbances, or hydrocephalus, as the tumor grows beyond the sella turcica and compresses the optic chiasm or other midline structures. The trans-sphenoidal approach to this tumor is rarely used in pediatric patients, and most resections are therefore performed through a frontal craniotomy. Anesthesia for craniopharyngioma and hypothalamic tumor surgery is similar to that for supratentorial craniotomy.

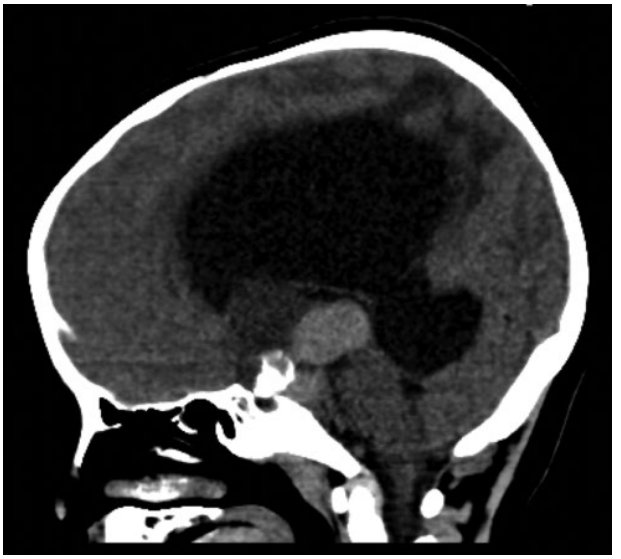


Figure 25.6 Sagittal gadolinium-enhanced T1-weighted MR image showing a 5-year-old girl with a large craniopharyngioma filing the suprasellar cistern and elevating and distorting the third ventricle. A heterogeneous mass is centered in the suprasellar cistern, most compatible with craniopharyngioma. There is obstruction at the third ventricle and cerebral aqueduct with resulting severe hydrocephalus and generalized mass effect/increased intracranial pressure.

Preoperative evaluation of the child with craniopharyngioma focuses on determining the presence of hydrocephalus and the types of endocrine dysfunction that could affect anesthetic management. Children may present with symptoms of hypothyroidism, growth hormone deficiency, adrenocorticotropic hormone (ACTH) deficiency, or diabetes insipidus (DI). Hormone replacement, including thyroid hormone and corticosteroids, may be necessary pre- and postoperatively.

DI is a complication of pituitary surgery and of head injury. It is caused by disruption of antidiuretic hormone (ADH)-secreting cells. It is rarely present preoperatively, but usually begins 4–6 h after surgery, although it occasionally becomes evident intraoperatively. Characteristically, patients produce a large quantity of dilute urine. Their serum osmolality increases, and their urine osmolality is low (less than 200 mOsm/L). The urine specific gravity is below 1.002. The patient becomes hypernatremic and hypovolemic. Treatment of DI requires careful determination of the patient's hourly urine output and administration of maintenance fluids plus 75% of the previous hour's urine output. The type of fluid to be administered is determined by the patient's serum electrolyte concentrations. Urine is low in sodium content and should be replaced with hypotonic solutions, such as 5% dextrose in 0.5 normal saline. Hyperglycemia and osmotic diuresis may occur if a large volume of D5W is used. Vasopressin or one of its analogs, such as DDAVP (1-deamino-8-D-arginine vasopressin), should be administered at an early stage of DI. When administered intraoperatively, aqueous DDAVP occasionally produces hypertension. Postoperatively, DDAVP is divided into two doses (5–30 μg/day) and given transnasally. If DDAVP is given IV, the dose is one-tenth the intranasal dose, divided into two doses. Alternatively, vasopressin can

be administered by constant infusion at 0.5 mU/kg/h. The rate must be adjusted to achieve the desired degree of antidiuresis, typically with monitoring of serum sodium and reduction of urine output to under 2 mL/kg/h.

Postoperative management should include administration of steroids, thyroid, mineralocorticoid, and sex hormone supplements. Insulin-dependent diabetic patients may have reduced insulin requirements after surgery. Therefore, the amount of glucose in their blood must be closely monitored and their insulin regimens altered as necessary.

Other problems that arise postoperatively include seizures and hyperthermia. Surgical exposure often requires significant retraction of the frontal lobes. Consequently, anticonvulsant prophylaxis may be necessary intraoperatively and should be continued postoperatively. Injury to the hypothalamic thermoregulatory mechanisms may result in hyperthermia. Efforts should be made to maintain normothermia and reduce the risk of hypermetabolic cell injury.

Posterior fossa tumor surgery

Posterior fossa tumors (Fig. 25.7) are more frequent in children than in adults and account for about half of all pediatric brain tumors. The four most common tumors are medulloblastoma (30%), cerebellar astrocytoma (30%), brainstem glioma (30%), and ependymoma (7%). The remaining 3% include acoustic neuroma, meningioma, ganglioglioma, and other much rarer tumors. Cerebellar astrocytomas have no gender predilection, but medulloblastomas occur more frequently in males. Hydrocephalus occurs in 90% of children with medulloblastoma and in virtually all children with cerebellar astrocytoma [161].

The most frequent posterior fossa neurosurgical procedure, other than for tumors, is decompression for Arnold–Chiari malformation. The Arnold–Chiari malformation is a complex developmental anomaly that characteristically presents with downward displacement of the inferior cerebellar vermis into the upper cervical spinal canal and elongation of the medulla oblongata and the fourth ventricle. Preoperatively, the anesthesiologist should pay particular attention to the neurological symptoms, such as cerebellar dysfunction, upper airway obstruction (inspiratory stridor), cardiovascular instability, and increased intracranial pressure.

Anesthetic considerations

- *Age-related pathophysiology*.
- *Intracranial pressure*. Symptomatic hydrocephalus may require placement of an EVD after induction of anesthesia. Maintenance of cerebral perfusion is essential. Mannitol, furosemide, and corticosteroids may be required.
- *Full stomach*. Pathology in the posterior fossa decreases gastric emptying in children and makes them prone to regurgitation and aspiration of gastric contents with induction of anesthesia.
- *Associated pre-existing problems:*
  - cardiovascular: some patients may be hypertensive in response to brainstem compression
  - pulmonary: recurrent aspiration pneumonia is a common occurrence
  - nervous system: central sleep apnea occurs and may persist postoperatively.
- *Air embolism*. See previous sections.
- *Airway management*. Arnold–Chiari malformation or brainstem compression may cause upper airway dysfunction and inspiratory stridor.
- *Fluid and electrolytes*. Preoperative attempts to reduce ICP may cause electrolyte imbalance and contraction of the intravascular volume.
- *Premedication*.

Preoperative evaluation and induction of anesthesia

Preoperative assessment of these patients is similar to that described previously.

During the induction of anesthesia, attempts must be made to preserve CPP, to avoid ICP elevations, and to provide an appropriate depth of anesthesia. The choice of anesthetic is not as crucial as the manner in which it is administered. A combination of propofol, atropine, and a non-depolarizing muscle relaxant associated with an opioid, such as fentanyl, is common. Succinylcholine can be used safely unless the patient

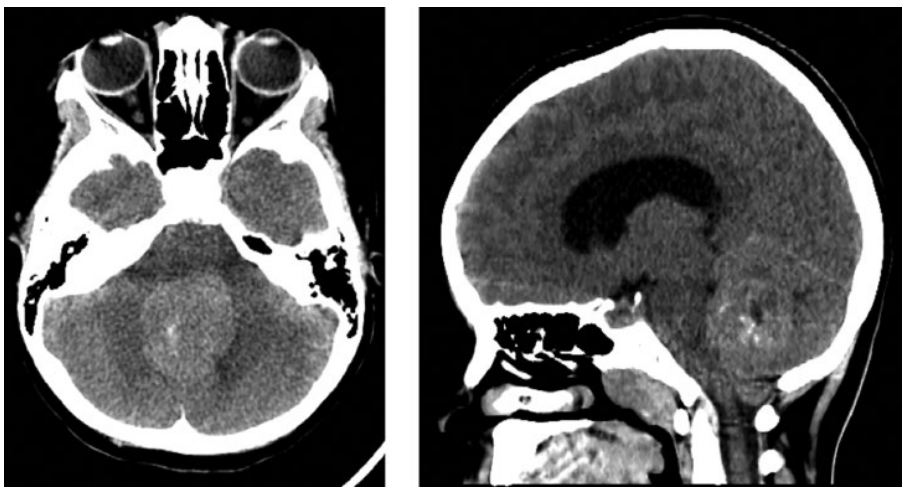


Figure 25.7 Axial and sagittal unenhanced T1-weighted MR image of a 9-year-old boy who presented with ataxia, headache, and morning vomiting showing probable medulloblastoma within the fourth ventricle resulting in brainstem compression, mild obstructive hydrocephalus, tonsillar herniation, and increased intracranial pressure.

shows signs of severe increased ICP with hemodynamic instability. To minimize the possibility of kinking and obstructing the ETT during positioning, a wire-reinforced armored orotracheal tube can be used. Many neuroanesthesiologists, however, prefer to use a nasotracheal tube for better stability and fixation. Use of an oral tracheal tube with a soft bite block reduces epistaxis and avoids possible nasal mucosal injury and infection.

Maintenance

As with induction of anesthesia, no single anesthetic technique has been shown to be superior, and the maintenance regimen must be tailored to the needs of the patient and the requirements of the surgical procedure. After skin preparation, local anesthetic (bupivacaine 0.125% with epinephrine 1:200,000) should be infiltrated along the incision line and anesthesia depth should be increased with fentanyl and/or isoflurane. The aim is to provide a "slack brain," which will reduce the amount of pressure caused by retractors and allow adequate cerebral perfusion. Muscle paralysis is provided by a non-depolarizing muscle relaxant, and the ICP is reduced by mannitol and furosemide. The intermittent positive pressure ventilation is adjusted to maintain the $PaCO_2$ between 25 and 28 mmHg.

Patient positioning

Three patient positions are commonly used for posterior fossa tumor operations. Older literature reported that the prone position is used in 55% of cases, the sitting position in 30%, and the lateral position in 15% [162,163]. In recent years, the sitting position has rarely been used in pediatrics because of the increased risk of VAE. It is the anesthesiologist's responsibility to ensure that during positioning the ETT is not advanced into or withdrawn from the trachea, that ventilation is adequate, that pressure points are well padded, and that the neck is not flexed enough to occlude jugular venous drainage. The method of head fixation depends on the age of the patient, the skull thickness, and the surgeon's needs. Horseshoe head rests are useful, but the patient's face must be padded carefully and the eyes must be free of compression. After 3 years of age, the multipin head-holder is preferable. Infiltration of the pin sites with local anesthetic reduces nociceptive responses.

Monitoring

Monitoring for posterior fossa surgery is basically the same as for supratentorial craniotomy, with one important exception. The precordial Doppler should be used to detect air embolism). Occasionally, sensory-evoked potentials should be obtained during resection of intramedullary or brainstem tumors.

Emergence and recovery

Prompt awakening is mandatory, but it is important to keep the patient hemodynamically stable and unstimulated during tracheal extubation. The pathological process often dictates the appropriate postoperative airway management (e.g. postoperative tracheal intubation is essential after resection of intramedullary tumor). When early tracheal extubation is appropriate, intraoperative administration of opioids plus lidocaine 0.5–1 mg/kg to infants and children will allow emergence from anesthesia without coughing and straining, which might otherwise lead to a hypertensive episode and intracerebral bleeding. Postoperative pain can usually be managed with morphine 50 μg/kg, with or without acetaminophen. Avoidance of medications that affect the sensorium or the pupils is important.

Intraoperative magnetic resonance imaging

Postoperative imaging for intracranial tumors by MRI or CT, either immediately after surgery or within 12–24 h of the end of surgery, has become common practice to assess the extent of resection and residual tumor, and complications such as intracranial bleeding. With the advent of MRI scanners within the operating room suite, a number of institutions are now performing an intraoperative MRI scan before the end of surgery to determine whether additional resection is indicated, and to rule out complications before the craniotomy is closed [164,165]. In addition, traditional stereotactic planning methods rely on imaging obtained preoperatively, or at the beginning of the procedure with images obtained on a remote scanner. This approach does not account for the brain shift that occurs intraoperatively during open craniotomy. Intraoperative MRI allows the stereotactic planning process to occur after the craniotomy begins, saving time and also potentially increasing the accuracy of the surgical plan.

There are two basic configurations for intraoperative MRI (iMRI) scanning: (1) mobile iMRI scanner, fixed OR table and patient position; and (2) fixed iMRI scanner, and mobile OR table and patient. The first configuration is displayed in Figures 25.8 and 25.9, and the second in Figure 25.10. MRI safety is an integral consideration for the planning of iMRI suites, and obviously any equipment that is near or in the iMRI field must be MRI compatible. Extensive planning for MRI compatible anesthesia machines, monitors, laryngoscopes, infusion pumps, OR tables, instruments, and other equipment must occur. In addition, there are certain patients with implanted devices, i.e. pacemaker–defibrillators, in whom iMRI is contraindicated unless the device itself is certified to be MRI safe. Thorough MRI safety training for all personnel, including support personnel such as anesthesia technicians and housekeeping staff, must occur. Detailed preoperative planning, and safety checklists before the procedure, and before and after intraoperative MRI scanning, are important considerations in the implementation of iMRI programs. Additional discussion of MRI safety is presented in Chapter 41.

Myelodysplasia

Because myelomeningocele is usually diagnosed prenatally with ultrasound, selected patients are eligible for fetal surgery for this disorder. Results have been encouraging in major series; i.e. avoidance of CSF shunting and improved functional outcomes [166]. Chapter 21 presents a detailed discussion of this approach.

Anesthetic considerations

- *Coexisting disease*. Additional pathology may accompany myelodysplasia (Arnold–Chiari, hydrocephalus, congenital heart disease, prematurity).

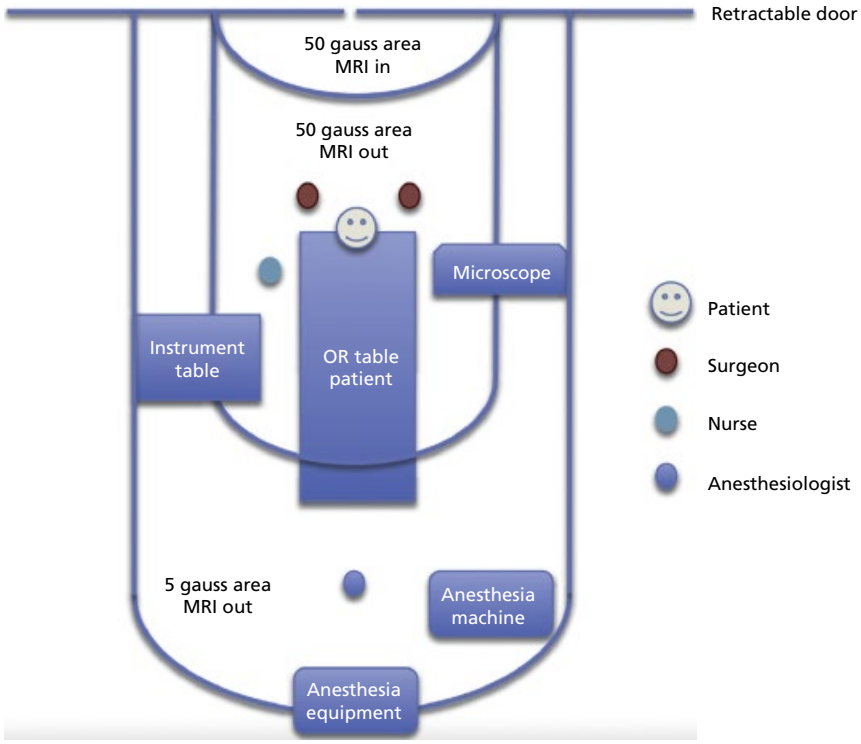


Figure 25.8 A common iMRI setup. This system uses a movable magnet and stationary patient. *Source*: Reproduced from McClain and Landrigan-Ossar [165] with permission of Elsevier.

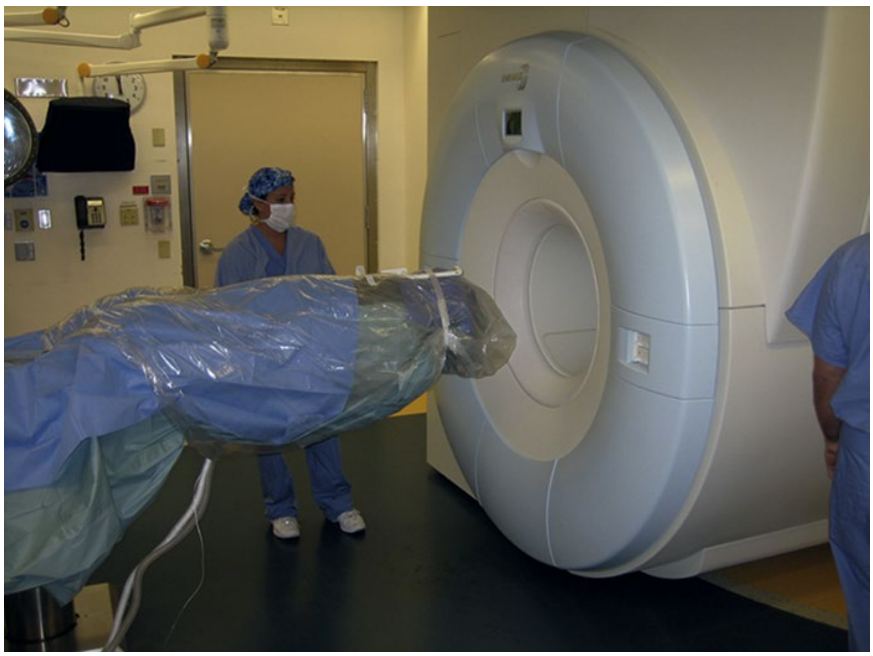


Figure 25.9 Patient being placed into movable 1.5-T iMRI. Note the degree of draping to pad and protect the patient as well as maintain sterility. *Source*: Reproduced from McClain and Landrigan-Ossar [165] with permission of Elsevier.

- *Age-related pathophysiology*.
- *Airway management*. Encephaloceles may be associated with difficulty in control of the airway.
- *Positioning*. Protection of the neuroplaque.
- *Volume status*. High third-space losses from the skin defect.
- *Potential for hypothermia*. Exposure of large body surface area and loss of third-space fluid.

Monitoring

Routine monitoring is necessary. Blood loss can be insidious, especially if the sac is large and significant undermining of skin, relaxing incisions, or skin grafting is required for closure of the defect. Blood transfusion may be necessary. Patients with encephaloceles who must undergo craniotomy for repair should have an arterial line placed for blood pressure and

hemoglobin measurement. A central venous line may be indicated for repair of a nasal encephalocele when the repair is done in a semi-sitting position.

Preinduction

Infants presenting for repair of meningomyeloceles rarely exhibit increased ICP. The majority of myelodysplastic patients have an associated Arnold–Chiari malformation, and most have hydrocephalus, which usually requires ventricular shunt placement. Preoperative assessment of these children reveals a variety of neurological deficits, depending on the level of the lesion. Seventy-five percent of all lesions occur in the lumbosacral region. Lesions above the level of T4 usually result in paraplegia, whereas lesions below S1 allow ambulation. The legs are severely affected by lesions between L4 and S1. Before induction of anesthesia, the patient's volume status should be assessed. These patients have the potential for large third-space losses from the exposed myelomeningocele. These patients will be receiving preoperative antibiotics, and subsequent doses must be maintained on schedule to reduce the risk of infection, which can be a devastating complication.

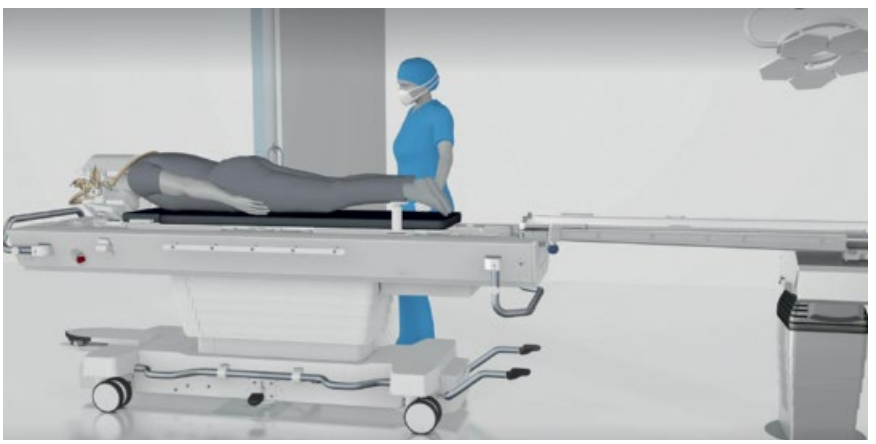
Induction and intubation

Anesthesia for patients with lumbosacral or thoracic myelomeningoceles can be induced either in the left lateral position or supine with the sac protected by a cushioned ring. Anesthesia can be induced in a majority of patients with propofol, atropine, and a muscle relaxant. Either a non-depolarizing muscle relaxant or succinylcholine can be used safely [167]. Patients with nasal encephalocele commonly have airway obstruction, and it may be difficult to obtain a good mask fit.

Maintenance

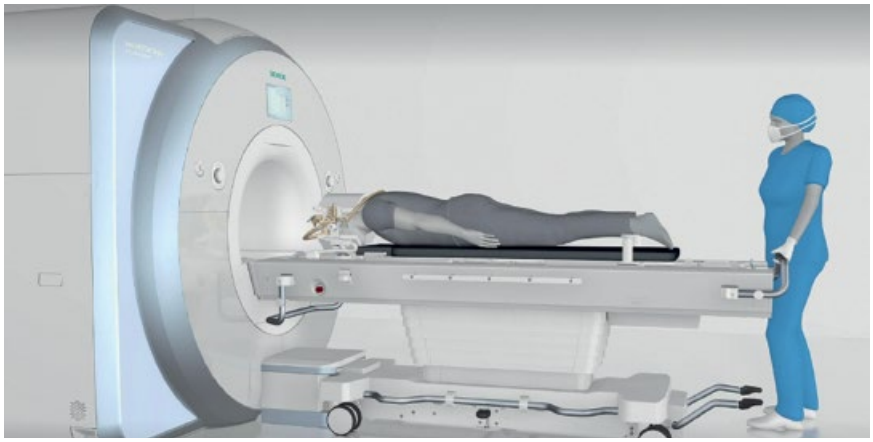
After tracheal intubation the patient is turned to the prone position. Injury to the exposed neural tissue must be prevented. Chest and hip rolls are placed to ensure that the abdomen is free, to facilitate ventilation, and to reduce intra-abdominal pressure and decrease bleeding from the epidural plexus. Since most of these children have an Arnold–Chiari malformation, excessive rotation of the neck should be avoided. The extremities should lie in a relaxed position and be well padded. The lungs are mechanically ventilated. Barotrauma in the immature lung must be prevented. Premature infants (especially those of less than 32 weeks' gestation) are at increased risk for retinopathy of prematurity [168] and lung injury from prolonged exposure to high oxygen concentrations. Anesthesia can be maintained with a variety of agents, but higher-dose opioids and ketamine may cause postoperative apnea. Muscle relaxants are contraindicated during maintenance of anesthesia because nerve stimulation is often required to identify neural structures. The large area of exposed tissue and the liberal use of cold surgical

(A)

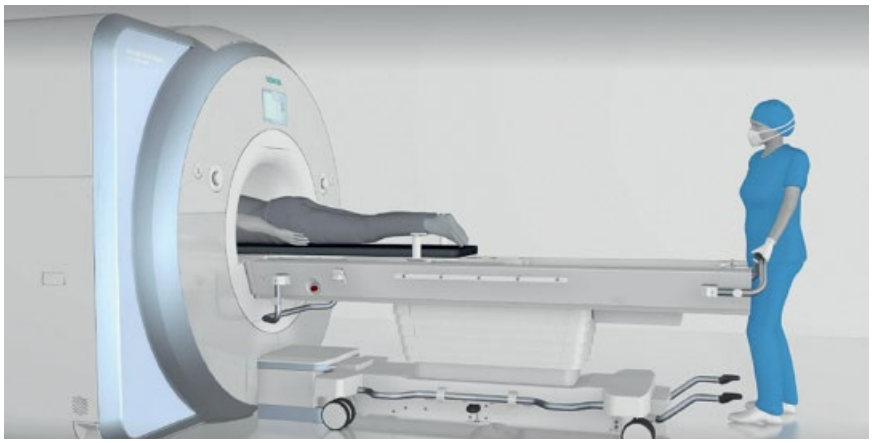


(B)

Figure 25.10 Workflow for iMRI with stationary MRI. (A) iMRI room doors have opened and dockable MRI table is moved into position with patient positioned prone on OR table. (B) iMRI table docked and patient moved on track system connecting tables. (C) iMRI table docked in place to bore of 3T iMRI scanner. (D) Patient in bore of iMRI during scan. *Source*: Photos courtesy of Siemens Medical Solutions USA Inc., Washington DC.



(C)



(D)

Figure 25.10 (*Continued*)

preparation solutions increase the risk of hypothermia in these patients. Care must be taken to prevent drying or thermal injury to the exposed neural tissue by radiant heat lamps. Myelomeningocele repair is often accomplished with the aid of the surgical microscope, and some surgeons will request that NMB not be used during the repair so that motor response in the lower extremities can be detected.

Emergence

Neonates at risk for apnea after anesthesia, patients with severe central neurological deficits, and those undergoing craniotomy for encephalocele repair should be extubated fully awake. Patients with nasal encephalocele repairs may have residual airway obstruction or blood in the oropharynx, and may require postoperative tracheal intubation.

Basic anesthetic considerations for the postoperative period have been discussed previously.

Spinal cord surgery

Common diseases of the spinal cord that require surgery include herniated disks, spondylosis, syringomyelia, primary or metastatic tumors, hematomas or abscesses, and trauma (Fig. 25.11). In all cases, compression of the spinal cord may produce ischemia, interstitial edema, and venous congestion, and may interfere with nerve transmission. Maintaining spinal cord perfusion pressure and reducing

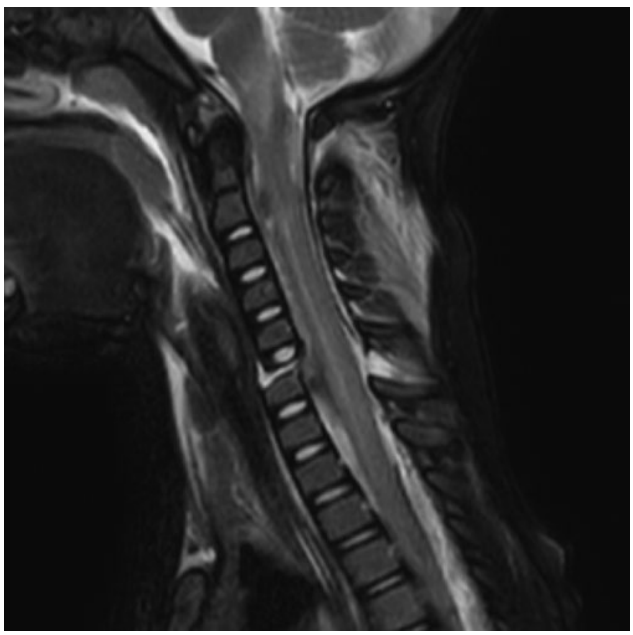


Figure 25.11 MRI of cervical spine demonstrates a large extradural hematoma. Sagittal T2 fat-saturated image of the cervical spine again demonstrating oblique, comminuted C6 vertebral body synchondroses fractures with mild distraction and retrolisthesis of the superior fracture fragment. Disruption of the anterior and posterior longitudinal ligaments and interspinous ligament. Epidural hemorrhage is present with subsequent mass effect on the cord. Diffusely increased signal of the cord consistent with long segment cord injury from the medulla oblongata down to the level of C7.

spinal cord compression are crucial. Despite apparently optimal surgical and anesthetic management, devastating neurological complications still occur with spinal surgery. Intraoperative monitoring of spinal cord function includes the wake-up test, somatosensory-evoked potentials (SSEP), and motor-evoked potentials (MEP). The wake-up test remains the traditional method for assessing spinal cord well-being during corrective procedures on the spinal column. Its main advantage is that it assesses anterior spinal cord (i.e. motor) function, but it does so only at one time. Evoked potential monitors (e.g. SSEP monitoring) generate an electrical potential by stimulation of peripheral nerves (e.g. the median nerve at the wrist or the posterior tibial nerve at the ankle). If nerve transmission is intact, a signal is recorded from the scalp or at various sites along the neural pathway. The electrical signals arise from axonal action potentials and graded postsynaptic potentials as the impulse is propagated from the periphery to the brain. The technique measures only the response of the sensory nervous system. This limitation can be overcome by use of MEPs, in which the motor cortex is stimulated by a transcranial electric current or a pulsed magnetic field generated by a coil placed over the scalp. See Chapter 29 for a more detailed discussion of spinal cord monitoring and scoliosis surgery.

Head injury

Head trauma is a major cause of morbidity and mortality in the pediatric population. Skull fractures (Fig. 25.12) are found in more than 25% of all children who present at hospitals with head injuries and in more than 50% of fatal cases of childhood head trauma. The incidence of post-traumatic intracranial hematomas varies considerably, but some children with head injuries do require surgical treatment. Failure to recognize the presence of a hematoma may transform an otherwise mild head injury into a fatal or permanently disabling one.

Head injury causes several different pathophysiological events, including intracranial hematomas (epidural, subdural, intracerebral, and brain contusion), brain edema, and systemic effects. Adults suffer more hematomas than children, and children have diffuse cerebral edema more frequently [169].

Epidural hematoma

This lesion is frequently caused by laceration of a middle meningeal artery during a deceleration injury. Children do not necessarily have an overlying skull fracture (Fig. 25.13). Epidural hematomas comprise 25% of all intracranial hematomas in pediatric patients and are a true neurosurgical emergency. In adults there is a lucid interval between the initial loss of consciousness and later neurological deterioration. Children often do not have the initial alteration in the state of consciousness observed in adults. The child who is old enough to talk complains of an increasing headache and then becomes confused or lethargic. Rapid development of hemiparesis, posturing, and pupillary dilation occurs frequently and may confuse the diagnosis. Rapid expansion of the hematoma causes herniation of the temporal lobe downward through the tentoria incisura. Anisocoria is an early sign. Herniation eventually leads to rostrocaudal deterioration and is associated with bradycardia, slowed and irregular breathing, and widened pulse pressure (Cushing triad). The relationship between the degree of brain shift and the level of consciousness has been confirmed; the role of uncal herniation in the syndrome has been questioned.

Subdural hematoma

Subdural hematomas are associated with parenchymal contusion, blood vessel laceration, and cortical damage (Fig. 25.14). The mass effect of the contused and edematous brain may prompt surgical removal of the hematoma if the brain region involved is not functionally important. Studies using positron emission tomography have demonstrated that cerebral metabolism and blood flow are reduced by 50% with brain contusion [170]. Severe edema and elevated ICP often lead to persistent neurological deficits.

Intracerebral hematoma

Intracerebral hematomas are rare but carry a poor prognosis. Surgery is usually avoided for fear of damaging viable brain tissue (Fig. 25.15).

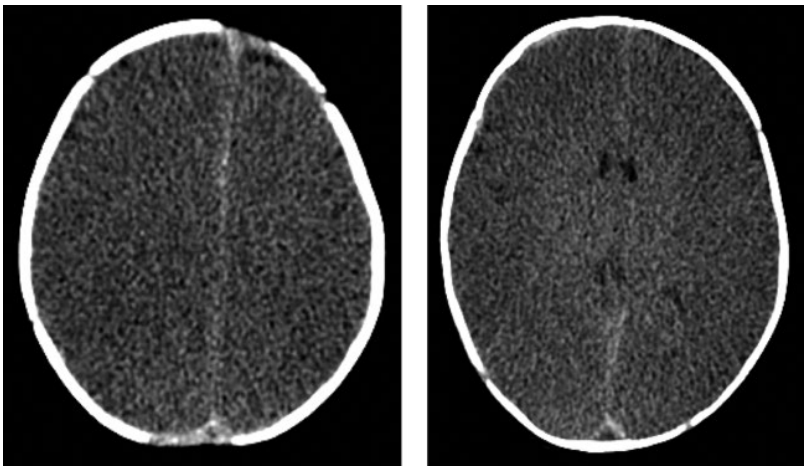


Figure 25.12 Axial non-contrast CT showing loss of gray/white differentiation in a 2-year-old boy with traumatic brain injury after non-accidental trauma. Note bilateral frontal skull fractures. The cerebral parenchyma is diffusely hypodense, with loss of the normal gray-white differentiation and global sulcal effacement. Also note small extra-axial hyperdensity within the interhemispheric fissure, compatible with hemorrhage.

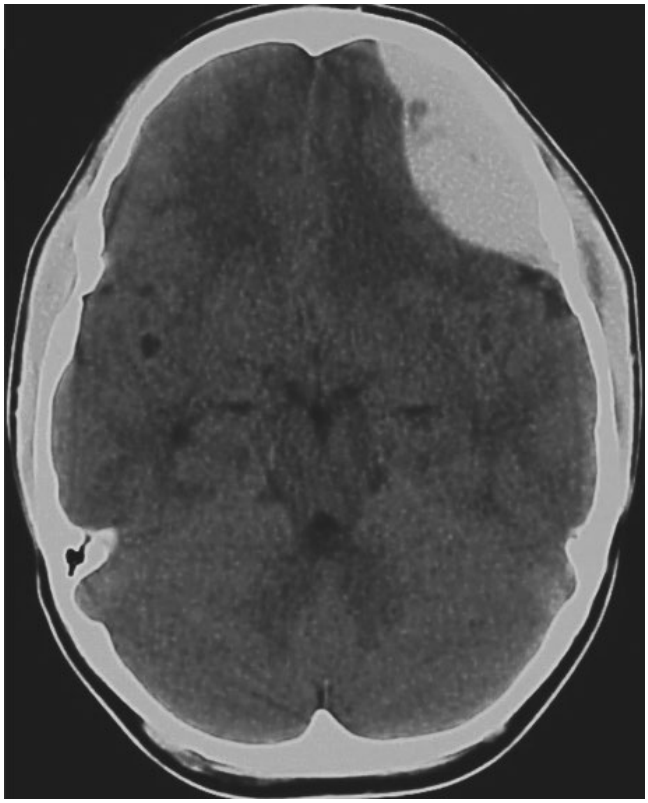


Figure 25.13 This non-enhanced axial CT reveals a typical lens-shaped epidural hematoma. Although the patient presented with a Glasgow coma score (GCS) of 14, he quickly became very lethargic.

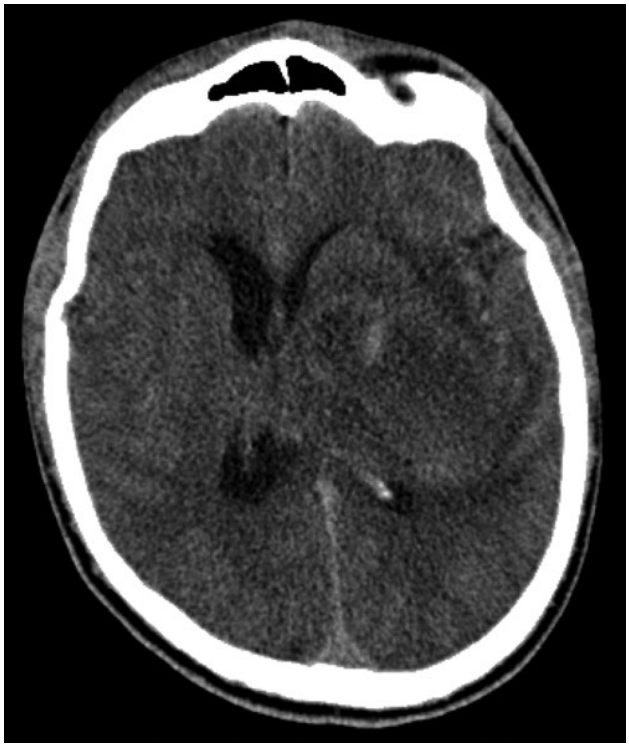


Figure 25.15 Non-enhanced axial CT in a 20-year-old with history of congenital heart disease. Although the patient presented with a GCS of 14, he quickly became very lethargic. Imaging found a large left basal ganglia hemorrhage resulting in 10 mm left to right midline shift/subfalcine herniation.

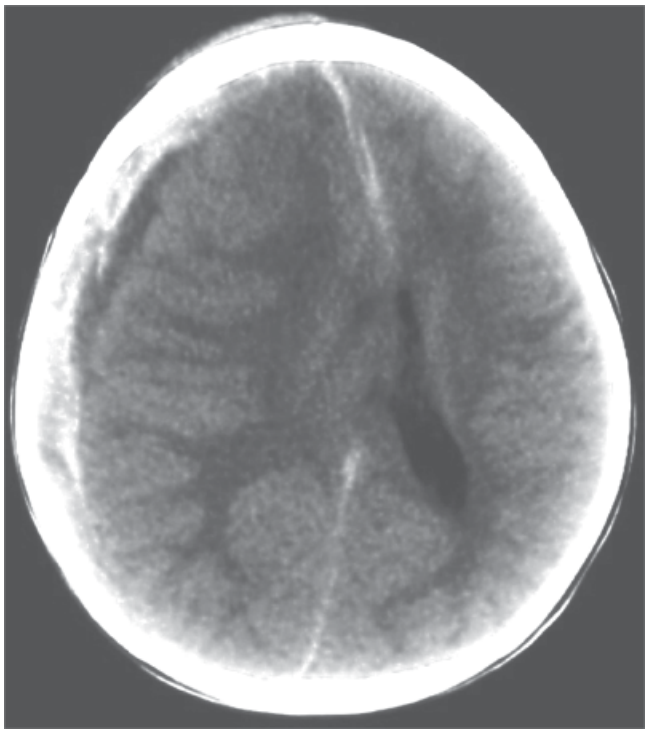


Figure 25.14 Non-contrast axial CT in a 2-year-old comatose boy shows a large right acute subdural hematoma. It is important to notice the tremendous shift of the midline to the left.

Anesthetic considerations

- *Resuscitation and stabilization*. Airway, breathing, and circulation are essential components of the initial clinical assessment. Traumatized patients often have a variety of physiological disturbances, including acid–base and electrolyte imbalances and abnormalities of glucose homeostasis and body temperature control.
- *Neurological status*. The Glasgow Coma Scale provides a means of detecting changes in the patient's condition. Symptoms of raised ICP must be evaluated.
- *Associated injuries*. Pediatric trauma often occurs from high-velocity energy transfer, which leads to injuries to the neck, chest, and abdominal organs.
- *Full stomach*. Vomiting leads to pulmonary aspiration and respiratory complications.
- *Age-related pathophysiology*.

Monitoring

Arterial catheter and central venous line placement are indicated. A urinary catheter should be inserted unless contraindicated by an associated bladder neck injury. Central body temperature should be monitored at all times.

Preinduction

CT is the procedure of choice for evaluation of head injury during the first 72 h after the accident. Management of an elevated ICP is essential to provide a safe anesthetic. Adequate hemodynamic resuscitation and stabilization must be achieved to maintain a normal CPP and brain tissue oxygenation.

Induction and intubation

Providing a patent airway is an essential part of the management of patients with head injury. Although the airway of an unconscious patient may not be compromised by the injury, tracheal intubation will protect the lungs against aspiration of stomach contents or secretions and allow ventilatory support of patients with increased ICP. The association of head injury and neck injury occurs so often in infants and children that tracheal intubation must be accomplished with minimal manipulation of the neck. The neck should be stabilized by an assistant who applies axial traction. Since a cervical spine fracture is always considered present, until proven otherwise, in patients with head injury, use of the Sellick maneuver is contraindicated. Patients should be hemodynamically stable before anesthesia is induced. After airway injury has been ruled out, anesthesia should be induced rapidly with atropine, propofol, lidocaine, and either succinylcholine or a non-depolarizing muscle relaxant such as vecuronium. Ketamine is contraindicated. If the patient is suspected to have a difficult airway, a two-person technique may be required for tracheal intubation. Depending on the age of the patient, the use of a volatile anesthetic and assisted ventilation or the use of neuroleptanesthesia with topicalization of the larynx is recommended.

Maintenance

Anesthetic considerations for maintenance of anesthesia are similar to those previously described for supratentorial surgery. Evacuation of an intracranial hematoma usually requires a craniotomy, which can commonly be done without opening the dura mater. Evacuation of a large hematoma may suddenly decrease ICP and allow upward movement of the brainstem through the tentoria incisura. This may result in transient hemodynamic instability and cardiac arrhythmias.

Emergence and postoperative management

Patients with severe head injury remain intubated after surgery to provide ventilatory support and to control elevated ICP. Transfer to an ICU is indicated for continued care.

Cervical spinal cord injury

Isolated cervical spine injury is uncommon in the pediatric population. However, all children with severe head injury should be treated as though they have a cervical spine injury, until proven otherwise. Injury to the high cervical cord is usually caused by high-velocity injuries to the cranium (Fig. 25.16). Children with cord injury or disruption of the cord often present without respiratory efforts, often in cardiac arrest or with profound hypotension. They frequently die from hypoxic-ischemic encephalopathy and may have serious traumatic brain injury. In one study, all patients with absent vital signs had high cervical cord luxation on a lateral view radiograph of the neck [171]. Physicians caring for such patients might think that the hypotension is related to blood loss from intra-abdominal, pelvic, or thoracic injury, or even from devastating cerebral injury and loss of brainstem function.

Anesthetic considerations and management

Some cervical spine injury victims have signs of brain shift and elevated ICP. The anesthetic considerations for these patients include:

- Resuscitation and stabilization of cardiopulmonary function, i.e. spinal shock.
- Decreasing ICP and improving cerebral perfusion.
- Stabilization of the cervical spine.
- Correction of metabolic disturbances.
- Treatment of adult respiratory distress syndrome (ARDS).
- Identification of the central rostrocaudal deterioration and uncal herniation.

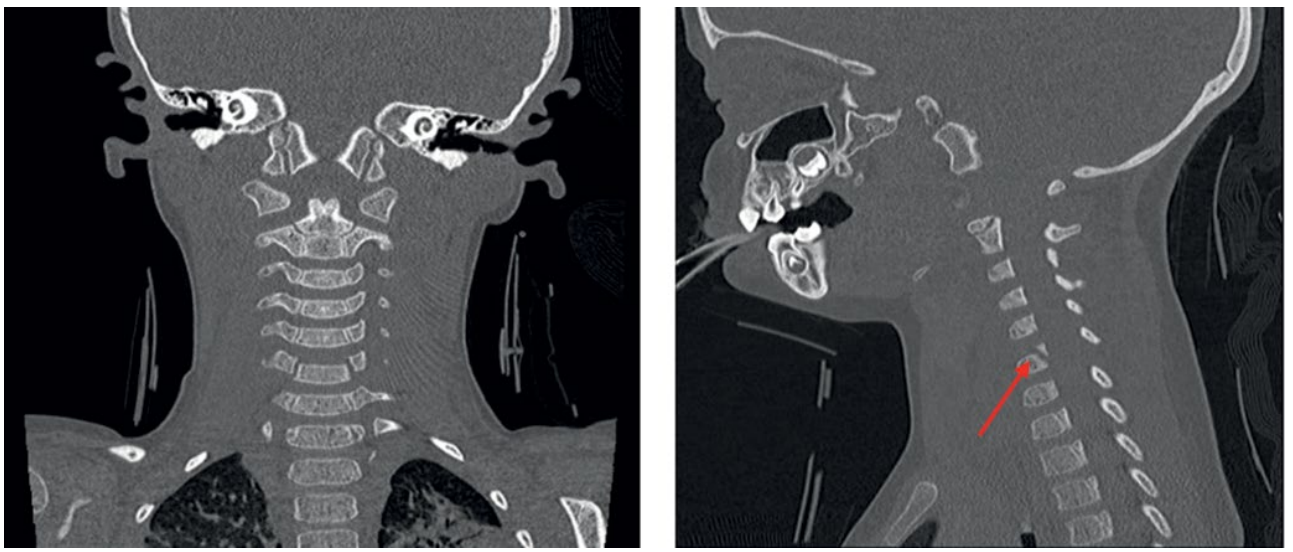


Figure 25.16 Lateral CT scan of the cervical spine of a 3-year-old girl following motor vehicle accident presents intubated in field with GCS of 3 and no spontaneous respiration. CT scan demonstrates a distraction injury, with abnormal widening of the joint space between the right occipital condyle and C1 lateral mass and between the right C1 and C2 lateral masses. Fracture through bilateral C6 vertebral body synchondroses (red arrow). There is associated paraspinal soft tissue swelling and focal hemorrhage in the C5–C6 disk.

- Meeting the fluid requirements for trauma victims with isoosmolar solutions such as normal saline.
- Monitoring arterial pressure, CVP, and urine output.
- Correcting the coagulopathy often caused by brain tissue thromboplastin release.
- Treatment of DI (see section "Craniopharyngioma").
- Treatment of SIADH.
- Controlling the hyperglycemia that frequently occurs in head-injured patients, which is thought to be a good indicator of the severity of the injury and a predictor of outcome. It is advisable to prevent the increase in glucose associated with head injury [172].
- Maintaining corticosteroid dosing for spinal cord injury: although controversial, this approach is still used in many institutions.

Chapter 39 presents further discussion of the approach to the neurotrauma patient.

KEY POINTS: MYELODYSPLASIA, SPINAL CORD SURGERY, AND NEUROTRAUMA

- Myelomeningocele is a neonatal emergency, and induction and intubation must be accomplished while protecting the sac and neural placode from damage or infection
- Spinal cord monitoring with sensory and motor evoked potentials is essential for spinal cord surgery; anesthetic regimens to maximize accurate monitoring must be planned

Anesthesia for pediatric epilepsy and movement disorders

Anesthesia for brain mapping during epilepsy surgery

Introduction to epilepsy and brain mapping

Advances in pediatric neurosurgery have offered many new treatment options for patients with medically intractable seizures. With the advent of intraoperative brain mapping and electrocorticography (ECoG), precise anatomical targets can be obtained and planned for resection. Intraoperative brain mapping is an essential tool for neurosurgical procedures that involve lesions near functional or "eloquent" cortex. Eloquent areas include primary motor cortex, primary somatosensory cortex, language areas such as Broca's and Wernicke's, primary visual areas, angular gyrus, and mesial temporal regions for memory. When tumors or epileptic foci are located adjacent to these areas of functional cortex, both intraoperative electrophysiological monitoring and neurocognitive testing aid in aggressive resection of the pathological lesion while attempting to minimize neurological deficits.

The demands of electrophysiological monitoring have a profound effect on the anesthetic technique and agents that can be used during the procedure. In some instances the patient must be awake, such as when language testing is being performed. ECoG and motor mapping can be performed under general anesthesia. Anesthetic goals include providing adequate surgical conditions, minimizing interference with intraoperative brain mapping, and maintaining patient comfort and safety throughout the procedure [173].

Any procedure involving brain mapping requires constant communication between the anesthesia team and surgeon. Preoperatively, this ensures that the entire team understands the surgical and anesthetic plan; intraoperatively, neurophysiological monitoring may require adjustments of anesthetic depth and anesthetic agents.

Adding to the difficulty of providing anesthesia to these patients is the lack of prospective, randomized trials comparing anesthetic techniques. Most evidence involves case series or retrospective analysis. These studies can be confusing to an anesthesiologist naïve to the technical neurophysiology language, and the available studies form conclusions that are sometimes contradictory and inconsistent. This has resulted in protocols that vary by institution, and there is no consensus as to the optimal anesthetic technique for mapping procedures.

Brain mapping techniques and anesthetic concerns

Electrocorticography

ECoG is utilized during epilepsy surgeries to help identify abnormal EEG patterns that result from epileptogenic foci. ECoG can be obtained via the placement of dural grids (Fig. 25.17) or via the placement of depth electrodes while under anesthesia. Spike waves identify the seizure focus and allow precise resection. After resection, ECoG recordings can be performed again to ensure there is no further spike activity.

Most anesthetics affect intraoperative ECoG recordings, yet ECoG has successfully been performed with local anesthetic only, monitored anesthetic care, and general anesthesia. The commonly used agents, including volatile anesthetics, nitrous oxide, propofol, dexmedetomidine, and opioids, will be discussed in greater detail.

Volatile agents

Volatile agents are commonly used for maintenance of general anesthesia when patients are not candidates for an awake

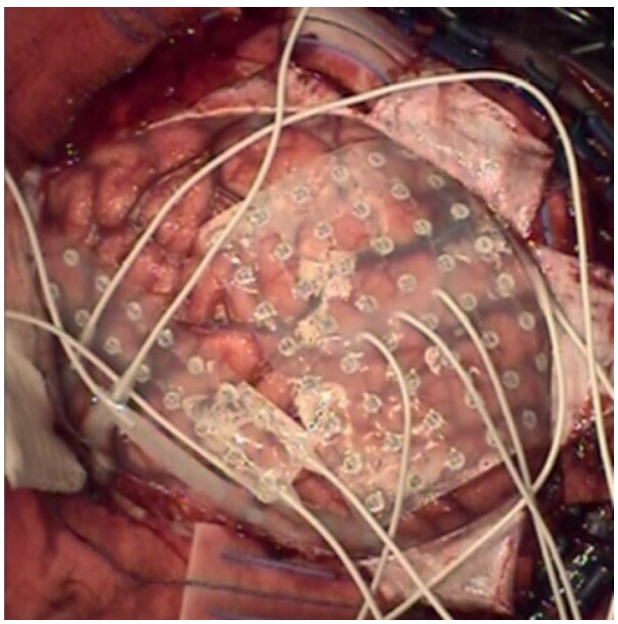


Figure 25.17 Intraoperative electrode grid placement. *Source*: Photo courtesy of Daniel J. Curry, MD.

craniotomy. However, their use still varies between institutions. For instance, sevoflurane has been shown to significantly reduce spike activity in epileptic patients at 1.5 MAC [174]. However, this study was performed with patients under the effects of a fentanyl-based anesthetic. Fentanyl, like many opioids, has been shown to induce spike wave activity, especially at high doses, and may have increased spike activity at the baseline recordings for this study [175]. Other studies have shown that sevoflurane can increase spike activity at higher concentrations, just prior to causing burst suppression [176–178]. One can see the confusion as one agent, sevoflurane, has both epileptic and antiepileptic properties. Indeed, some institutions' protocols avoid volatile agents altogether for fear that they may make reliable ECoG impossible, while others have attempted to use the epileptogenic properties of higher-dose sevoflurane to localize seizure foci.

As shown by Kurita et al [179], sevoflurane's ability to increase epileptiform activity may help in accurate resection of seizure foci. This study showed that ECoG recordings at 0.5 MAC sevoflurane were similar to those at ictal onset in the awake state, whereas at 1.5 MAC the ECoG recordings were more similar to those in the interictal period in the awake state. These interictal spikes correspond to "irritative" zones, whereas the ictal onset zone is the area where a seizure originates, and is the gold standard for localizing the epileptogenic zone, the smallest area needed to be resected to prevent further seizures. Higher sevoflurane levels may increase the "volume" of the recordings; however, they may not increase the specificity of recordings to allow for resection of the smallest area necessary. Isoflurane, like sevoflurane, does appear to have some epileptogenic potential, but not to the same degree [178]. When used to maintain general anesthesia during ECoG monitoring, low levels of volatile anesthetic combined with higher-dose opioid administration should not interfere with ECoG [179,180]. A dexmedetomidine infusion is commonly added to further lower the volatile agent dose needed to maintain an adequate level of anesthesia.

Nitrous oxide

Nitrous oxide is often used in neurosurgical procedures. It has been shown to attenuate spike activity on ECoG, especially when combined with volatile anesthetics [181,182]. Despite this, nitrous oxide is a key component of many successful anesthetic protocols for epilepsy surgery. If used, it should not be combined with additional volatile agent, but rather with liberal opioid administration. Opioid and nitrous oxide alone should not interfere with ECoG [164].

Of note, when patients already have an ECoG grid in place and are returning for resection, one should avoid using nitrous oxide until the dura is open to prevent pneumocephalus [183].

Propofol

As with sevoflurane, propofol has been shown to have both epileptic and antiepileptic properties that appear to be dose dependent. In low doses, propofol causes activation of EEG activity [184,185]. It may even cause background activity, which may resemble epileptiform spiking [186]. Larger doses lead to slowing and attenuation of spike activity, and at sufficient doses may lead to burst suppression and isoelectricity.

Both Herrick et al [186] and Soriano et al [187] reported that propofol did not affect the ability to obtain ECoG recordings if terminated at least 20 min prior to the start of ECoG. In light of the evidence, propofol should be discontinued before the start of ECoG.

Dexmedetomidine

Dexmedetomidine has minimal effect on ECoG and can be continued during recordings at low infusion rates [188]. Because of its minimal respiratory depression, titratability, and ability to provide a cooperative, relaxed patient, dexmedetomidine is an excellent anesthetic for procedures that require a patient to be awake during a portion of the procedure. In addition, dexmedetomidine has been shown to provide hemodynamic stability during neurosurgical procedures [189]. Modest reductions in blood pressure and heart rate are secondary to α_2-mediated adrenoreceptor activity. Reductions in circulating catecholamines result in a decreased incidence of tachycardia and hypertension during the perioperative period [190].

When used for maintenance of general anesthesia in combination with sufentanil, dexmedetomidine did suppress epileptiform activity [191]. However, at this author's institution, high infusion rates of dexmedetomidine are typically used throughout brain mapping procedures requiring ECoG with minimal to no effect on intraoperative recordings.

Opioids

Opioids are a mainstay of neuroanesthesia, and this is particular true with brain mapping procedures performed under general anesthesia. Because both volatile agents and propofol are discontinued or used in very low doses during brain mapping, there is potential for patient awareness, discomfort, and movement. Using large doses of short-acting opioids, one can maintain patient comfort, minimize the chance of patient movement, and not affect brain mapping. During awake craniotomies, opioids help manage pain and discomfort that may occur despite an adequate scalp block with local anesthesia.

Opioids do not alter seizure threshold or interictal spike activity. Moderate doses may result in muscle rigidity without EEG spiking, and extremely high doses will induce seizures [192–194]. Patients with partial complex epilepsy given moderate doses of fentanyl may experience increases in interictal spikes (IIS) that are not confined to the previously identified seizure foci [195]. Alfentanil, an opioid with a shorter terminal half-life than fentanyl, has been used in bolus dosage to increase IIS activity for mapping foci [196]. Remifentanil has a similar effect on IIS but its duration of action is much shorter than fentanyl, making it a better choice during awake craniotomy when ventilation cannot be mechanically supported [197].

Direct cortical stimulation

Direct cortical stimulation is the process of applying direct electrical stimulation to the cortex to help map eloquent areas responsible for motor function, language, vision, or sensation. Only motor mapping may be performed under general anesthesia, as all other forms of mapping inherently require the patient to be awake to participate in testing and provide feedback while testing is being performed.

There are few limitations on anesthetic agents for motor mapping, the main one being that cortical motor evoked potential (cMEPs), just like transcranial motor evoked potentials, are especially sensitive to volatile agents. Concentrations as low as 0.2–0.4 MAC have been shown to interfere with the ability to obtain adequate recordings. Intravenous agents and an awake anesthetic technique have less interference with motor mapping than the use of volatile agents and general anesthesia [198,199].

Motor mapping may be performed by the surgeon stimulating the cortex, and either the anesthesiologist or another member of the operating team assessing whether there is a visually observed motor response to a particular area, such as hand, foot, or face. This allows for mapping of the functional motor cortex during the operation so that it may be spared during resection. For motor mapping to be performed, the patient cannot receive neuromuscular blocking agents.

Protocols for brain mapping procedures

Awake or asleep

The decision to perform either a general anesthetic or an awake craniotomy is complex and depends on patient factors, institutional culture, surgeon preference, and the anesthesia provider's familiarity and comfort with various techniques. Some basic rules are evident that may simplify the decision process.

- Language/sensory testing can only be performed in an awake patient.
- General anesthesia can be performed during ECoG and motor mapping.
- Less anesthetic equals less interference with neurophysiological monitoring; if a patient is a candidate for an awake craniotomy, one should strongly consider it.
- Do not perform an awake anesthetic on a patient who cannot be expected to cooperate.

This puts the anesthesiologist in a unique situation. What might be best for the surgical excision of the lesion (awake patient minimizing the chance of interference with neuromonitoring or neurological deficit) might not be best for the patient (traumatic experience from awake craniotomy or risks from lack of cooperation/movement).

While these rules are helpful, they ignore the complexity of the challenges involved in patient selection and the risk/benefit ratio inherent to the decision to perform an awake craniotomy or general anesthetic.

Patient selection

Some institutions have absolute age cut-offs for performing an awake craniotomy. Ideally, the decision involves many team members including surgeon, patient and parents, anesthesiologist, neurologist, and if possible someone with expertise in helping ascertain whether a patient is mature and capable of dealing with the procedure, such as a child psychiatrist. The importance of a thorough preoperative assessment and communication with the child cannot be overemphasized. The patient should have a clear understanding of what will be done, what he/she will experience, and be reassured that they will be kept comfortable and safe. Other issues that can make the decision more clear-cut include comorbidities such as anxiety disorder, developmental delay, obesity, obstructive sleep apnea, and anything that would make conversion to general anesthesia challenging (difficult airway). Such co-morbidities are strong contraindications to performing an awake craniotomy.

Adding to the difficult decision as to whether an awake or general anesthetic is more appropriate are the opposing risks and benefits of both techniques. To simplify, an awake anesthetic will benefit aggressive surgical excision of the tumor or seizure focus and allow for neurocognitive assessment to look for neurological deficits during resection. However, inherent to this technique is a certain loss of control of parameters that as anesthesiologists we are accustomed to maintaining. These include the ability to precisely control hemodynamics and ventilatory status (blood pressure control, secure airway, adjustment of CO_2). These parameters not only allow us to feel more comfortable, they benefit surgical conditions by preventing a "tight brain" and ensuring patient cooperation. By performing a general anesthetic, the risk of interference with mapping techniques and neural deficits postoperatively may be increased. As one can see, the decision as to anesthetic choice can be quite complex, and requires communication between surgeon, anesthesiologist, and patient.

General anesthesia

The following are some examples of protocols for epilepsy surgery involving brain mapping with ECoG and cortical mapping under general anesthesia. The basic premise is to minimize anesthetic agents that may interfere with mapping procedures (volatile agents, propofol, benzodiazepines), yet still ensure patient safety and comfort. To do this, one should consider opioid administration as the mainstay of the anesthetic technique.

Protocol

1. Minimal or no benzodiazepines for premedication.
2. Opioid infusion: sufentanil 0.3–1 μg/kg/h or remifentanil 0.1–0.5 μg/kg/min.
3. Volatile agent <0.5 MAC.
   - N_2O may be substituted for volatile agent.
   - Propofol infusion 100–250 μg/kg/min (discontinued 20–30 min prior to ECoG).
4. Motor mapping: no NMB, low volatile agent (0.2–0.4 MAC) but may still attenuate cortical MEPs.
5. *Consider adding dexmedetomidine 0.2–0.7 μg/kg/h* for all variations of this protocol. This has minimal effect on ECoG recordings while helping deepen the anesthetic while other agents are discontinued.
6. Local anesthetic: as general anesthesia during ECoG is a time when the patient may be "light," one should consider the scalp block just as important as it is for an awake craniotomy. This may lower the chance of patient discomfort or movement during this time.

Methods to improve electrocorticography

Despite strict attention to anesthetic technique, poor signals are still sometimes present. Drugs that have been used to increase epileptiform activity include:

- methohexital 0.3–0.5 mg/kg [200]
- etomidate 0.1–0.2 mg/kg [201]
- alfentanil 50 μg/kg [202,203]
- remifentanil 2.5 μg/kg [204].

Awake craniotomy

Two common methods for "awake craniotomy" are local anesthesia with conscious sedation and the asleep/awake/asleep (AAA) technique whereby general anesthesia is induced and then completely stopped during mapping. The benefits of the AAA technique include shortened time needed for patient cooperation, increased depth of anesthesia during stimulating portions of the procedure (craniotomy), and more control of ventilation if an airway is in place. The disadvantages include the need to remove an airway during the procedure with limited access to reacquire it and the chance of patient bucking or delirium on awakening.

All combinations of anesthetic agents have been used successfully for all anesthetic techniques during awake craniotomy. The most popular agents for sedation include propofol and dexmedetomidine. These agents have been used alone or in combination with an opioid, with fentanyl and remifentanil being the most commonly used. Volatile agents have also been used during the asleep portion of AAA techniques. When deciding on which agents to choose the following should be considered:

- *Dexmedetomidine* causes minimal respiratory depression and has been shown to provide stable hemodynamics during craniotomy [189]. It also allows for smooth emergence from anesthesia and provides a cooperative patient who is easily arousable. Typical infusion rates during the asleep portion range from 0.5 to 1 μg/kg/h and during the awake portion from 0.1 to 0.5 μg/kg/h [188].
- *Propofol* is widely used during awake craniotomies because of its easy titratability. Its antiemetic properties are also beneficial for an awake patient. It does cause dose-dependent ventilatory depression, and should be terminated 20–30 min prior to ECoG to prevent attenuation of spike activity [187].
- *Remifentanil* is easily titratable, allowing for rapid emergence from anesthesia. These characteristics make it an ideal opioid for an AAA technique.

Tips for awake craniotomy

The success or failure of an awake craniotomy is dependent on many variables. However, with attention to detail and proper planning, most patients tolerate the procedure very well.

- Local anesthetic for scalp block is essential for patient comfort.
- Antiemetic: nausea may occur from opioids, hypotension, hypovolemia, or pulling on the dura.
- Laryngeal mask airway for less straining/bucking on emergence.
- If endotracheal intubation is chosen, local anesthetic to the trachea may prevent bucking/straining.
- A processed EEG monitor may help with timing of removal of airway.
- Patient padding and positioning are crucial to patient comfort while awake.

Hemispherectomy

Children with severe seizure disorders, unresponsive to medical management, may be candidates to undergo resection of the affected cerebral hemisphere, or hemispherectomy [205]. The criteria for surgery typically demand that the child has had a generalizable seizure that comes from a focus in a single hemisphere. Localization may require prior grid placement with mapping, functional MRI, or other imaging prior to the grid removal and hemisphere resection. Hemispherectomy is an extensive procedure with potential for massive blood loss, and planning for this is essential when approaching these patients.

Vagal nerve stimulator

Vagal nerve stimulators were first implanted in humans in 1988 and have proved an effective method of reducing seizure burden for many patients. The procedure has the benefit of avoiding any intracranial intervention, and may reduce the seizure burden up to 50% in some patients. The stimulator is attached to the vagus nerve, usually on the left side of the patient's neck, to avoid any cardiac efferent nerves whose stimulation may result in bradyarrhythmias or asystole. The generator is then placed under the left pectoralis fascia similar to a pacemaker. There are minimal anesthetic concerns for this procedure, however general endotracheal intubation is usually desired because of the surgical site and proximity to major vascular structures including the internal jugular vein and internal carotid artery.

MRI-guided laser interstitial thermal therapy for epilepsy

MRI-guided laser interstitial thermal therapy (LITT) is a new minimally invasive technique in which a small laser fiber is stereotactically placed into a seizure focus in the brain via occipital, parietal, or frontal entry, and the focus is thermally ablated while monitoring tissue temperatures via MRI thermography [206]. This approach has been employed for focal and generalized pediatric epilepsy, and can be utilized instead of traditional epilepsy surgery when open surgery poses an unacceptably high risk of morbidity or patient and family preference precludes craniotomy. The workflow for LITT procedures is complex and institution-dependent; all involve stereotactic systems that operate with or without stereotactic head frame placement, and intraoperative MRI to guide placement of the laser and monitoring of the ablation and tissue temperature (Figs 25.18, 25.19). An MRI scanner within the operating room is ideal for this procedure, but other protocols involve induction of anesthesia in the operating room and transport to an MRI scanner, or the entire procedure can be performed in an MRI suite. Adequate endotracheal anesthesia with muscle relaxation is required to prevent dislodgement or movement of the laser. ECoG or other means to identify ablation targets will normally have been performed prior to the procedure, but occasionally ECoG is performed immediately prior to the laser ablation procedure during the same anesthetic. Extensive multidisciplinary planning is an essential component when approaching MRI–LITT procedures.

Deep brain stimulation

The most common indications for deep brain stimulation (DBS) in the pediatric population include movement disorders such as dystonia and Tourette syndrome. The challenge with DBS procedures concerns balancing the desire for an awake patient with a patient population that, because of the

disease process, can be difficult to manage with an awake technique. Additionally, microelectrode recordings place many limitations on anesthetic agents.

Surgical procedure

DBS involves the placement of electrodes into deep nuclei of the brain, with common targets being the globus pallidus internus (GP_i) and subthalamic nuclei (STN). The procedure has two parts: the insertion of electrodes, and subsequent internalization of the connecting wires and pacemaker. These can be done on the same day of surgery and are separated into a two-part procedure [207].

The first step is placement of the head frame, which in pediatric patients is usually done after induction of anesthesia. MRI or CT is then performed, and for the initial surgery burr hole(s) are placed. If DBS insertion is bilateral, then bilateral burr holes are made. After that, electrode placement begins. There are three steps by which proper electrode placement in the target nuclei is achieved. The first is frame-based imaging, which calculates depth and trajectory to get electrodes close to the target nuclei. Second, neurophysiological monitoring via microelectrode recordings (MER) further guides electrodes to the proper placement, and third, macrostimulation takes place [208]. MER details the electrical activity of individual neurons and can distinguish between such tissues as the globus pallidus externa and interna, and even the border between the two. MER is started about 10 mm away from the target, and then the probe is inserted millimeter by millimeter as recordings are taken. This is a painstaking process, and may take hours. After this, macrostimulation of the awake patient occurs. The patient needs to be awake in order to express if there is alleviation of his/her symptoms and if there are any side-effects during stimulation of the electrodes.

After the electrode is in place, the rest of the procedure involves placement of the wires and pacemaker (usually subclavicular); this portion can be performed under any anesthetic technique.

With newer technology, some DBS insertions are being performed with only MRI-based imaging. This eliminates the need for MER and an awake patient, and relieves many of the limitations on anesthetic agents.

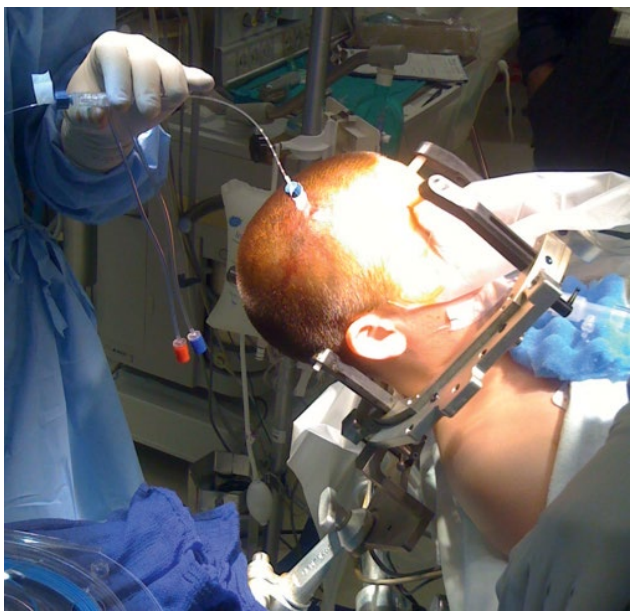


Figure 25.18 MRI-guided laser interstitial thermal therapy for epilepsy. The patient is positioned in a stereotactic head frame and right fronto-lateral approach of minimally invasive laser fiber is demonstrated. *Source*: Photo courtesy of Daniel J. Curry, MD.

Anesthetic agents and microelectrode recording

Anesthetic agents have a profound effect on MER, although the mechanisms by which this occurs are not completely understood. The effects appear to depend on both the target nuclei (GPi versus STN) and disease process [208–210]. MER is less affected in dystonia than in Parkinson disease, and the GP_i is more sensitive to anesthetic agents than the STN. This may be due in part to higher GABA input to the GP_i.

All GABA agents affect MER; despite this, propofol is the most widely used agent for these procedures. Agents with the least effect include the opioids remifentanil and fentanyl, as well as dexmedetomidine and ketamine, likely due to their non-GABAergic action [211,212].

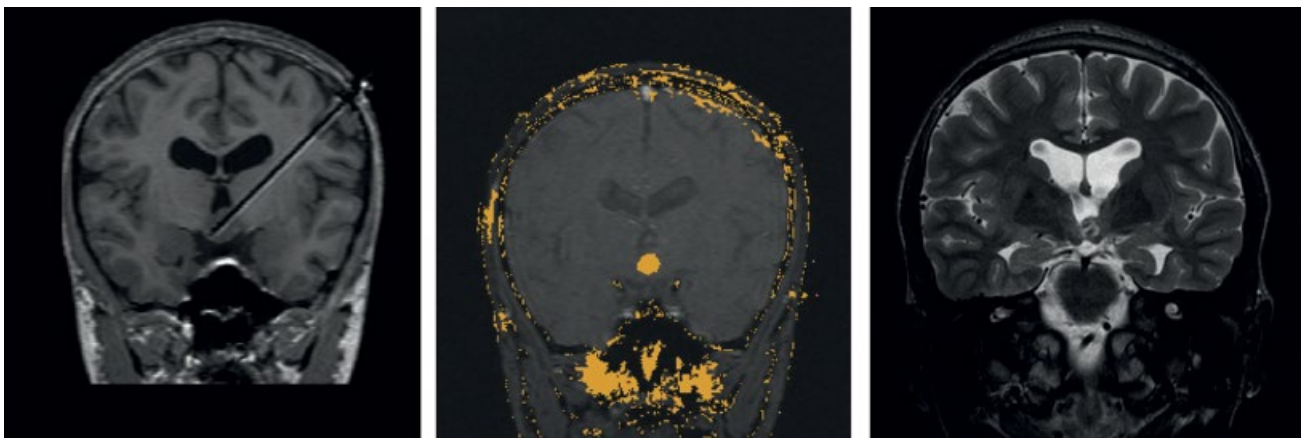


Figure 25.19 MRI of stereotactic laser ablation of hypothalamic hamartoma using laser interstitial thermal therapy for epilepsy. (A) Coronal MRI showing cannula placement before ablation on T1-weighted imaging (left). (B) The irreversible damage map (orange) superimposed upon a phase scan (middle). (C) A 3-month follow-up T2-weighted MRI showing ablated hamartoma. *Source*: Reproduced from North et al [206] with permission of Elsevier.

Volatile agents have also been used for DBS, but most success has been shown in procedures where the STN was the target [213–215]. Unfortunately for the pediatric anesthesiologist, the primary target in dystonia patients is the GP_i. Information as to acceptable concentrations of volatile agents, or whether one agent is preferable over another, is lacking.

MER has been successfully performed with commonly used anesthetic agents such as propofol, volatile agents, opioids, ketamine, and dexmedetomidine. However, any agent with GABA agonism may attenuate MER. Benzodiazepines have been shown to abolish MER, and propofol may attenuate MER. As such, our protocol for DBS relies heavily on combinations of dexmedetomidine, remifentanil, and ketamine. In our experience, these agents cause minimal interference with MER, and allow for an awake and comfortable patient during macrostimulation.

Macrostimulation

Macrostimulation requires an awake and cooperative patient. The benefit of performing macrostimulation is that it allows for confirmation of correct placement of electrodes by relief of symptoms and assessment of side-effects such as rigidity, nausea, pain, and paresthesia.

DBS can be a long, tedious procedure, with a lengthy period during which the patient must be awake if macrostimulation must be performed. An AAA technique is employed at this author's institutions, but DBS has been performed under conscious sedation in pediatric patients with success using combinations of dexmedetomidine and propofol [216].

KEY POINTS: ANESTHESIA FOR PEDIATRIC EPILEPSY AND MOVEMENT DISORDERS

- Electrocorticography (ECoG) can be accomplished via dural grids or depth electrodes; although most anesthetics affect ECoG, it can be performed with local anesthetic only, sedation, or general anesthesia
- Language or sensory testing can only be performed in an awake/lightly sedated patient; careful patient selection (age, maturity, ability to cooperate) and patient preparation are essential
- General anesthesia without benzodiazepines, with sufentanil or remifentanil infusion, volatile agent <0.5 MAC, and adding dexmedetomidine and local scalp anesthesia is a successful approach for ECoG
- "Awake" craniotomy with dexmedetomidine and remifentanil, adding propofol as needed, is a successful approach

Cerebrovascular anomalies

Patients with intracranial vascular malformations such as AVMs or cerebral aneurysms are commonly co-managed by the pediatric anesthesiologist in conjunction with neurologist, neurosurgeons, and interventional neuroradiology [217]. This may require that one or more anesthetics be provided to facilitate the diagnosis and/or intervention for the lesion. Since congenital and acquired forms of AVM can prove to be one of the greatest anesthetic challenges throughout life, we will focus on their general management in infants and children. AVMs and arterial aneurysms can be acquired, but the majority arise from abnormal development of the arteriolar–capillary network that connects the arterial and venous systems. These vascular malformations often consist of large arterial feeding vessels that lead to dilated connecting vessels and then to the venous system. Flow of blood through this low-resistance connection results in progressive distention of the venous structures and increased venous mixed oxygen content from the shunting of blood. Specific AVM scenarios that occur in infants and children involve the posterior cerebral artery and the great vein of Galen (Fig. 25.20). These anomalies often present in the neonatal period with congestive heart failure. Alternatively, the patients can present with obstructive hydrocephalus from saccular enlargement or dilatation of the vein of Galen that directly compresses the aqueduct and prevents drainage of the CSF.

Outside the neonatal period, many AVMs go undetected until the fourth or fifth decade of life, with only 18% reported in patients under 15 years of age. Although the incidence is low, when intracranial AVMs occur, neurological injury can result from one or more causes:

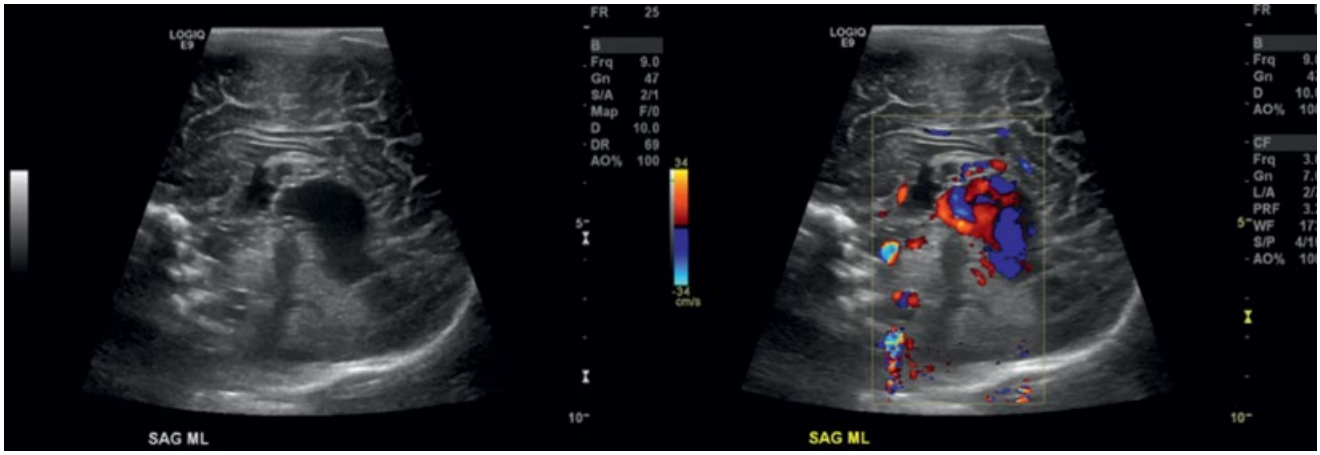
- hemorrhage with thrombosis or acute infarction
- compression of adjacent brain tissue or intracranial structures
- parenchymal ischemia created by "steal" of blood flow through the AVM
- congestive heart failure from the shunt
- surgical or interventional injury resulting in disruption or diversion of blood flow from viable brain tissue supplied by the AVM during treatment.

Families and physicians must therefore balance these potential outcomes when deciding between surgical versus interventional treatment options. Regardless, patients with complex AVM lesions may undergo interventional or stereotactic radiosurgical procedures to control blood flow as definitive or adjunctive therapy. In addition, surgical clipping of feeding vessels or removal of aneurysmal tissue may need to be done as either a single or staged procedure. Again, clear communication between the anesthesiologist and the various treatment teams is necessary to facilitate optimal care.

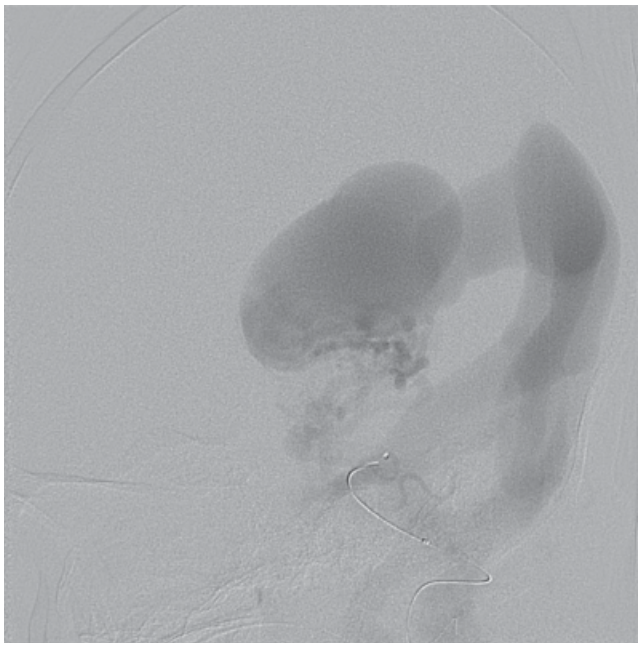
Anesthetic considerations

Considerations for patients undergoing AVM resection or embolization include the following:

- *Assessment for pre-existing pathophysiology*. Does the patient present with increased ICP or congestive heart failure? Does the patient have additional congenital defects?
- *Age-related pathophysiology*. Will organ system maturity impact on the anesthetic technique?
- *Blood loss*. The possibility of massive blood loss is high, especially if pre-resection therapies for embolization were limited.
- *Ventilation pattern*. Hyperventilation to control cerebrovascular tone and reduce inflow is a therapeutic consideration for most AVM treatment.



(A)



(B)

Figure 25.20 (A) Head ultrasound – grayscale and color Doppler sagittal image of the brain demonstrates a large aneurysmal vascular structure within the midline just above the tentorium with multiple adjacent dilated vessels, compatible with vein of Galen malformation. (B) Fluoroscopic image during intervention – lateral view of an aneurysm of the great vein of Galen. The main arterial contribution is from the anterior cerebral artery. The dilated vein of Galen empties directly into an enlarged straight sinus.

Monitoring

Routine monitoring is as previously described. Patients undergoing AVM resection should have vascular access via two large-bore peripheral IV catheters that are capable of delivering blood products should hemorrhage occur. Intravenous solutions should be warmed throughout the procedure. Invasive hemodynamic monitoring with an arterial line is essential. CVP monitoring is useful to determine intravascular status and to facilitate administration of medications. A urinary catheter is essential and should be placed after induction of anesthesia.

Preinduction

Symptoms can vary depending on the age of the patient and the size of the AVM [218]. Older children often present with evidence of subarachnoid hemorrhage (SAH) or intraventricular hemorrhage (IVH). Up to 50% of children who present with spontaneous SAH have an AVM as the etiology [219]. In 24% of children, seizure is a common presenting feature. However, the neonatal presentation of AVMs is often associated with congestive heart failure and deserves special attention.

The low-resistance pathway of the AVM creates a situation of volume overload and high-output heart failure. The symptoms of congestive heart failure rarely manifest *in utero* because the patency of the ductus arteriosus provides for increased systemic flow through the AVM and reduces the work of the ventricles. However, after birth, with closure of the ductus, the left ventricle alone must meet the demands of increased arterial to venous flow. The degree of the arterial to venous shunt will affect the demand on the left ventricle. In addition, with the low resistance of a cerebral AVM, a low systemic diastolic pressure results. This low intra-aortic pressure during diastole, combined with increased left end-diastolic

pressure and heart rate from the ventricular failure, results in reduced coronary perfusion and worsening myocardial function from ischemia [220]. The cycle of ventricular failure and decreased oxygen delivery to the systemic tissues results in the cascade of adaptive mechanisms that results in decreased urine output and increased fluid retention [218,221]. Physical examination of the infant shows signs such as tachypnea, pulmonary edema, tachycardia, hepatomegaly, and ECG changes. Echocardiography will often confirm the hyperdynamic nature of the congestive heart failure, and evidence of functional failure of one or both ventricles. Laboratory studies may provide evidence of electrolyte abnormalities from aggressive diuretic management. Some infants may require endotracheal intubation and mechanical ventilation support, and inotropic support, all of which may help reduce the workload of the failing myocardium.

Induction and intubation

Prevention of hypertension during induction is desirable, given the possible association between AVM bleeding and hypertension. Inhalation or IV induction of anesthesia can be performed if there is no evidence of increased ICP. This can be accomplished with a variety of anesthetic agents. In the patient with AVM and elevated ICP, an IV induction is preferable with attention to avoiding hypotension and low cerebral perfusion pressure. In the neonate with AVM and congestive heart failure, special consideration should be taken when inducing anesthesia to maintain cardiac output. Extreme caution should be maintained as many anesthetic agents are myocardial depressants and could precipitate cardiac arrest. To this end, placement of an IV and an arterial line is useful prior to induction. Either oral or nasal tracheal intubation is reasonable after induction of anesthesia.

Maintenance

Considerations for maintenance of anesthesia include the following:

- positioning
- ventilation
- anesthetic agents
- blood loss and fluid management
- temperature maintenance.

Positioning for the procedure will be dictated by the site of the AVM. Typically, AVMs receive their blood supply from the middle cerebral artery, and the majority are approached by a supratentorial craniotomy.

All patients should undergo mechanical ventilation with intended maintenance of normocapnia. Patients with evidence of elevated ICP may require transient hyperventilation to control ICP, and ongoing ICP monitoring may be a consideration. In general, normocarbia is preferable and hypocarbia should be avoided, as the resultant cerebrovascular vasoconstriction may result in more shunting of blood flow away from normal tissues and into the AVM, potentially contributing to increased cerebral ischemia and increased bleeding from the AVM.

The anesthetic agents used for maintenance are similar to those for any intracranial procedure. If congestive heart failure is absent, then permissive or controlled hypotension can be applied to facilitate control of bleeding from the AVM during ligation. This can be accomplished with infused antihypertensive agents such as nicardipine, nitroprusside, or fenoldopam. Neonates with congestive heart failure undergoing AVM ligation or treatment require inotropic support and are not candidates for permissive hypotensive strategies. For these infants, vasoactive drugs should be readily available and administered through a central venous catheter.

Fluid management in these patients is challenging. Neonates may not tolerate large volume shifts or drops in hemoglobin concentration, especially if they have elements of cardiac dysfunction. Early efforts to maintain normal intravascular volume and stable hemoglobin content should be the goal. This may necessitate early blood replacement and judicious supplementation with inotropic support.

Maintaining a normal body temperature is important and can be difficult given the fluid losses and sometimes massive transfusion requirements. This usually requires the use of both fluid and convective warming devices that should be adjusted to avoid profound hypothermia and coagulopathy. Although the merits of hypothermia (temperature < 35°C) for neuroprotection in neurosurgical procedures are debated, hyperthermia (temperature >38°C) should be avoided as this can propagate ischemic injury by increasing metabolic demands of the brain and the body.

Emergence

Considerations for emergence from anesthesia after AVM treatment include:

- elimination of anesthetic agents
- reversal of NMB
- assessment of respiratory effort and airway patency
- assessment of neurological function.

Patients without a history of congestive heart failure can be extubated at the end of surgery if they are neurologically appropriate and hemodynamically stable. However, those patients with a history of significant congestive heart failure or at risk for significant neurological deficits (i.e. required brain resection, significant brain retraction, or obvious cerebral edema) should remain sedated and be transitioned to the ICU with an endotracheal tube in place.

Postoperative management

The basic anesthetic considerations for postoperative care of patients following AVM treatment include:

- cerebral edema
- congestive heart failure
- hypertension
- vasospasm.

Cerebral edema can arise from either the AVM itself or from the therapeutic approach – be it surgical or interventional. Certainly, the interventional procedures for embolization or radiosurgery incur less injury to the tissues getting to the AVM, however they can still result in significant edema [222]. In those situations where the edema is anticipated or recognized, leaving the patient intubated and monitoring in the ICU is indicated. Following resection of a large AVM, it may take several days for the cerebral edema to resolve and the patient's neurological examination and level of consciousness to become appropriate. During this period, supportive care and careful neurological monitoring are of greatest importance.

Despite removal or reduction of the extracardiac shunting of blood, patients with preoperative myocardial dysfunction remain critical in the days following recovery from the surgery and require ICU care. In addition to maintaining an adequate cerebral perfusion pressure, the care team must balance the needs of the myocardium to reduce afterload. Aggressive analgesic and antihypertensive management may be required to prevent sudden increases in arterial blood pressure, which not only stress the heart but increase the risk for acute intracranial bleeding.

Vasospasm is not a common postoperative complication but must be a consideration if the patient's neurological status deteriorates or if SAH was present in the perioperative period. The pathogenesis of vasospasm is not completely understood, but early diagnosis and intervention can be beneficial. Transcranial Doppler sonography has been used to guide therapy in adults, but its role in children remains limited. Certainly, Doppler ultrasonography can detect increased blood flow velocities and allow for diagnosis of vasospasm as well as provide a means of guiding therapy. Treatment is typically with adequate hydration, stable/generous blood pressure, and use of calcium channel blockers [223].

Interventional neuroradiology

Over the past three decades, neuroradiological techniques and expertise in the diagnosis and treatment of diseases of the CNS have undergone significant advances. Interventional neuroradiology (INR), or endovascular neurosurgery, has evolved as a hybrid of traditional neurosurgery and neuroradiology. Although practice varies between institutions, INR has developed a clear role in the management of a variety of neurosurgical conditions, particularly neurovascular diseases (see section "Arteriovenous malformations"). INR, like interventional cardiology, can be broadly defined as treatment by endovascular access for the purpose of diagnosis and/or treatment by delivering therapeutic drugs and devices. The number, variety, and complexity of conditions treated using this route are increasing, and this creates challenges for the pediatric anesthesiologist [224]. The pediatric anesthesiologist has a crucial role in facilitating neuroradiological procedures, and this requires an understanding of the indication and purpose of the procedures, their potential complications, and the management goals of the involved neurologist, neurosurgeons, and neurointerventionalist, which will vary depending on the individual child.

Although most diagnostic neurological imaging can be accomplished with MRI and CT techniques, the power to both diagnose and intervene makes interventional techniques appealing, though they are often not the first line for diagnosis [225]. INR procedures can be broadly classified on the basis of treatment goals:

- *Closing or occluding procedures*. Common examples include: embolization of aneurysms, AVMs, and fistulae of the brain and spine; preoperative embolization of vascular tumors such as meningiomas; and temporary or permanent occlusion of intra- or extracranial arteries.
- *Opening procedures*. Common examples include: treatment of vasospasm or stenosis by angioplasty and stenting; and chemical and mechanical thrombolysis in stroke.

The most common INR procedures in children are endovascular treatment of aneurysms, AVMs, and preoperative embolization of tumors.

Although specific procedures will have different neurological complications, INR procedures are at higher risk for the following:

- *Hemorrhage*. This can result from vascular injury or dissection of an arterial vessel and/or aneurysmal perforation.
- *Ischemia*. This can result from malpositioning of a catheter or absence of collateral blood flow to a region, thromboembolic complication, displacement of a coil or stent that results in occlusion, and/or vasospasm of the vessel.

Non-neurological complications can also occur and are typical of other interventional procedures. They involve contrast reactions, contrast nephropathy, and hematoma/bleeding/hemorrhage at the femoral puncture site.

Anesthetic considerations

At many institutions, the interventional suites are situated remotely from the operating rooms. Because this not only involves multiple floors and distance, but sometimes multiple anesthetic locations (i.e. pre-/post-procedure CT angiography in one location and the INR procedure in a different location), technical support must be coordinated for the anesthesia team, patient transport, and potentially remote patient recovery. Other potential problems typical of interventional radiological locations include working in reduced light, limited or poor access to the patient and equipment during the procedure, and concerns about ionizing radiation. Anesthetic considerations when caring for patients undergoing INR procedures include maintenance of patient immobility and physiological stability, manipulating systemic and regional blood flow, managing anticoagulation, and treating sudden unexpected complications during the procedure. The medical management of critically ill patients during transport to and from radiology suites and smooth and rapid recovery from anesthesia to facilitate neurological examination are equally important [226,227].

There are no studies demonstrating a clear benefit of one anesthetic management technique over another in the INR suite. Multiple approaches have been reported including general anesthesia, MAC, and even sedation and/or awake techniques [195]. Because of the need for immobility in many of these procedures, we favor a general anesthetic with endotracheal intubation. Routine anesthetic monitoring is applied, and arterial blood pressure monitoring can often be obtained from the femoral arterial sheath. If postoperative ICU admission is anticipated with continued hemodynamic control (i.e. permissive normotension) then a radial arterial catheter should be placed. Vascular access should include two good peripheral IV catheters for fluid and blood product administration. A Foley catheter should be placed to monitor urine output. If vasoactive drugs are to be administered as part of the procedure, a central venous catheter is desirable.

Postoperative considerations

Postanesthetic management of children following diagnostic or mapping neuroradiographic procedures is similar to other interventional cardiology and radiology procedures. Monitored transport to the postanesthetic care unit, with

careful monitoring of bleeding complications from the femoral vein and arterial sheath sites, is necessary. In addition, careful neurological monitoring should be performed to assure return to the patient's baseline examination. Any new deficits or decline in neurological status should prompt aggressive assessment and management by the anesthesiologist and neuroradiologist, as bleeding complications may necessitate imaging, repeat intervention, and/or surgery.

Patients with anticipated swelling, neurological deficit, or continued need for hemodynamic monitoring following the procedure should be transferred directly to an ICU with or without tracheal extubation. Management goals should be discussed carefully between the neuroradiologist, neurosurgeons, anesthesiologist and intensivist, so that patient care can be optimized and the risk of ongoing neurological injury minimized. We will often transport a patient with anticipated swelling and/or deficits, to the ICU sedated, intubated, and monitored, and then facilitate extubation in the ICU where all concerned parties can examine the patient and agree with the postprocedural neurological examination. This approach can also facilitate any additional neuroimaging, such as CT or MRI, that might be planned or unplanned, prior to admission to the ICU. Chapter 41 presents additional discussion of neuroradiology procedures.

KEY POINTS: CEREBROVASCULAR ANOMALIES AND INTERVENTIONAL NEURORADIOLOGY

- Arteriovenous malformations and other cerebrovascular anomalies may be found in critically ill neonates with severe congestive heart failure and pulmonary hypertension, patients who have suffered subarachnoid or intracranial hemorrhage, or relatively asymptomatic older children with smaller lesions
- Tracheal intubation with controlled ventilation, blood pressure control, and preparation for lengthy procedures are often necessary for interventional neuroradiology procedures
- Rapid and smooth emergence from anesthesia, and early neurological assessment are important after interventional neuroradiology procedures; emergent neuroimaging should occur if emergence is delayed or new neurological examination findings occur

CEREBRAL PROTECTION, RESUSCITATION, AND OUTCOME

A comprehensive discussion of these topics is beyond the scope of this chapter. See Chapter 8 for a presentation of the physiology of the central nervous system. General principles are presented here for completeness [228].

Cerebral protection

After ischemic injury, the CNS has limited regenerative ability. *Brain protection* has been defined as the "prevention or amelioration of neuronal damage evidenced by abnormalities in cerebral metabolism, histopathology, or neurological function occurring after an hypoxic or ischemic event" (i.e. treatment that is instituted before and often sustained throughout the insult) [227]. Brain resuscitation refers to the treatment of the secondary brain injury or simply to therapy given after the primary insult. The secondary consequences of ischemia are those that occur after the cerebral circulation is restored and are usually termed postischemic injury or reperfusion injury. Cell vulnerability differs, depending on the type of neuron. For example, the limbic system, especially the pyramidal cells of the CA1 layer of the hippocampus, Purkinje cells of the cerebellum, and layers three, four, and six of the cortex, are extremely vulnerable to ischemia; spinal cord cells, on the other hand, seem to tolerate a longer period of oxygen deprivation before they are injured.

Cerebral protection either increases oxygen delivery, reduces its demands, or ameliorates the pathological process by free radical scavenging or by reducing the effects of excitatory amino acids (glutamate, aspartate) and ionic fluxes. The difficulty with cerebral protection is that these strategies must be instituted before the onset of ischemia. With complete global ischemia, the brain tolerates 4–6 min of oxygen deprivation. The goal of cerebral protection is to delay the onset of irreversible CNS damage. There are no proven methods of cerebral protection except for mild hypothermia in animal models of neurotrauma [229–231]. However, recent human trials using hypothermia following neonatal birth asphyxia, cardiac arrest, or trauma, have demonstrated an unclear benefit to neurological outcome or survival. Whether this variable result is due to differences in the method and degree of hypothermia administration, variability in clinical practice with the initiation and maintenance of a cooling method, variation in the patient population with co-morbid factors (i.e. renal failure or lung injury), or heterogeneity of the secondary brain injury remains unclear [232]. Therefore, maintaining adequate cerebral perfusion and oxygen delivery, avoiding hyperglycemia, and aggressively managing hyperthermia are, at this time, the only means we have to reduce CNS injury.

Cerebral resuscitation

Intracellular events that occur during ischemia or after restoration of circulation and oxygenation contribute to the ultimate neurological damage. Ischemia depolarizes neurons and allows ionic fluxes (Na^+ and Ca^{2+}) into the cells, probably owing to release of glutamate and aspartate and activation of the NMDA receptors. Depletion of ATP stores leads to the energy-dependent ion pump's failure to eject Na^+ and Ca^{2+} from the cells. This leads to formation of prostaglandins and oxygen free radicals, to mitochondrial respiratory chain paralysis, to acidosis, and finally to membrane destruction.

Cerebral outcome

The future of cerebral well-being depends on our level of understanding of the pathophysiology of hypoxic-ischemic injury and our broad-based medical and pharmacological knowledge. Future therapy depends on development of a better understanding of the molecular and cellular processes that cause CNS injury and the development of specific treatments to salvage or protect injured tissue. Ultimately, the goal is to provide effective therapeutic measures that reverse the cascades of cellular events leading to injury. Table 25.7 is a summary of neuroprotective strategies.

Table 25.7 General neuroprotective principles for elevated intracranial pressure (ICP)

Goals	Clinical management/treatment
Avoid edema formation	Corticosteroid to reduce vasogenic edema from tumors Maintain normal sodium >140 mg/dL Maintain serum osmolality >300 mOsm/L
Avoid cerebral hypoxia	Controlled ventilation, maintain $ETCO_2$ <40 mmHg Avoid seizure activity
Avoid cerebral hypoperfusion	Early insertion and monitoring of ICP and CPP Avoid elevations in ICP >20 mmHg Avoid hypotension Maintain CPP >50 mmHg Maintain head of the bed at 30° to promote venous drainage
Avoid cerebral hypermetabolism	Avoid hyperthermia (>38°C) May require paralysis to prevent shivering and increased ICP Use antipyretics Use cooling blankets

CPP, cerebral perfusion pressure; $ETCO_2$, end-tidal CO_2.

CASE STUDY

A 2-year-old girl chases a ladybug to her open second-story bedroom window. The window screen is unable to support her weight and she falls two flights, plus an additional half-flight into the basement stairwell, striking the side of her head on a concrete step. Paramedics transport the child from the scene to a prearranged Medivac flight waiting at a nearby school parking lot. She arrives at the trauma bay with generalized tonic-clonic seizure activity, cyanotic lips, pulse oximeter registering a heart rate of 80 bpm, and 88% arterial saturation. Her left antecubital region is swollen around the insertion site of an IV that does not run freely, and her last blood pressure recorded on the transport monitor is "timed out."

The trauma team consists of a general pediatric surgeon, pediatric anesthesiologist, pediatric emergency room physician, and three nurses: one from the trauma service, one from the pediatric ICU, and one from the pediatric emergency department. Prior to the arrival of the child, the anesthesiologist has chosen from a shelf of prepackaged, age-dependent trauma supplies, a kit labeled "toddler: 1–3 years; 8–14 kg." The package is unwrapped on the trauma table to reveal the following supplies: size 3 airway mask, laryngoscope handle with Miller 1 and Mac 2 blades and spare bulbs, uncuffed 3.5, 4.0 and 4.5 tracheal tubes and a cuffed 4.5 tracheal tube, sizes 6 and 14 French stylets, sizes 2 and 2.5 laryngeal mask airways, 8 French suction catheters, 60 mm oral airway, sizes 18 and 20 nasal trumpet with lidocaine jelly, tongue blades, an IV start kit with 20 and 22 gauge IV catheters and a 15 gauge interosseous needle.

A pediatric respiratory therapist and a pharmacist have also been paged to the room per rapid response protocol. The pharmacist has a tackle box filled with syringes predrawn and sealed in a sterile hood, including: atropine 0.1 mg/mL, epinephrine 100 µg/mL, lidocaine 20 mg/mL, phenylephrine 100 µg/mL, rocuronium 10 mg/mL, succinylcholine 20 mg/mL, pancuronium 1 mg/mL, etomidate 2 mg/mL, fentanyl 50 µg/mL, ketamine 100 mg/mL, midazolam 1 mg/mL, and thiopental 25 mg/mL. The cover of the tackle box is a table of weights and standard doses (in mL) for each of the predrawn medications included.

According to roles predetermined and practiced in a simulator setting, the pediatric anesthesiologist commences with the management and stabilization of the airway and hemodynamics of the patient while the surgeon and ER physician perform the trauma survey. Initial concerns for securing the airway are overridden by the more pressing concern for impending herniation, which might be hastened by an uncontrolled and unmedicated laryngoscopy. Bag mask ventilation is applied to the child with 100% oxygen and jaw thrust while the respiratory therapist holds in-line traction, stabilizing the neck, and cricoid pressure is held while supporting the back of the neck to avoid posterior displacement in case of C-spine fracture. The anesthesiologist confirms that the lungs of the child are easily ventilated with a mask, whereas the trauma surgeon reports a large, minimally responsive left pupil, and the ED physician reports a left hemotympanum. Neurosurgery is called. The ED nurse has transferred the patient monitoring to the overhead monitor, visible to all members of the team, with audible pulse oximeter tone and a blood pressure cuff cycling every minute. The child is still unresponsive with a Glasgow Coma Score of 5, no eye opening, no verbal response, and abnormal flexor posturing with stimulation.

The immediate benefit of CO_2 reduction and restoration of normoxia is a reduction in cerebral blood volume, and the heart rate rises to 120 bpm. The pulse oximeter reads 100% but the mean blood pressure reads only 45 mmHg. The PICU and trauma nurses are attempting IV placement, which is difficult because of the tonic-clonic seizure activity. The anesthesiologist requests the ED nurse to prepare the interosseous needle, estimates the patient weight at 12 kg, and requests the intramuscular administration of 0.2 mg/kg

midazolam to abort the seizure activity. Seizure activity stops within a minute of injection and 2 IVs are quickly placed. An IV bolus of 20 mL/kg of acetate-balanced 2% saline, which is part of the pharmacist tackle kit, is administered. After hypertonic saline administration, the arterial blood pressure is 105/45, mean 65 mmHg, and the heart rate is 105 bpm. Both pupils are now responsive. The anesthesiologist requests drugs for laryngoscopy and intubation. Lidocaine 1 mg/kg and atropine 0.15 mg are given. After 1 min, and an additional 20 mL/kg of normal saline, the arterial blood pressure is 100/45, mean 60 mmHg, and the heart rate is now 120 bpm. Thiopental 2 mg/kg (half of the usual induction dose) and rocuronium 1.2 mg/kg are given. The child is easily intubated with in-line traction and cricoid pressure still in place. The 4.5 cuffed ETT is secured after confirming placement, and ventilation is initiated and titrated to keep the end-tidal CO_2 between 30 and 35 mmHg.

The arterial blood pressure after intubation is now 65/25 with a mean of 35 mmHg. Phenylephrine 5 μg/kg is given and the repeat blood pressure is 90/45, mean 55 mmHg. The dose is repeated, along with an additional 10 mL/kg of 2% saline. Repeat blood pressure is 105/55, mean 65 mmHg. The trauma survey is completed and the child is taken to the CT scanner which reveals a large epidural hematoma with midline shift, effacement of cortical sulci and the ipsilateral ventricle, as well as imperceptible basal cisterns.

The child is taken immediately to the operating room for decompression. The anesthesiologists prepare for incision. O-positive trauma release blood is requested to the room. An arterial line is started and a second IV is placed. Anesthesia is maintained with IV remifentanil and propofol. The child is ventilated without positive end-expiratory pressure (PEEP) to an end-tidal CO_2 of 30 mmHg and an arterial blood gas is sent, but the result is not available until the procedure is well underway. Blood pressure is stabilized with phenylephrine infusion titrated to keep systolic blood pressure greater than 90 mmHg and mean arterial blood pressure between 60 and 65 mmHg. Temperature is maintained between 36° and 36.5°C without the need for a warming blanket. Mannitol 25 mg/kg is given and a Foley catheter is placed.

Incision is made 50 min after the initial trauma, and the hematoma is evacuated through a craniotomy within 5 min. After evacuation of the hematoma, the heart rate falls to 65 bpm and the arterial blood pressure falls to 65/25. Phenylephrine and 10 mL/kg of trauma release blood are immediately given and the pressure responds. An additional 10 mL/kg of saline is required to replace the brisk urine output following mannitol administration.

A parenchymal fiberoptic ICP monitor is placed upon closure of the dura and skull, reading 12 mmHg with a normal waveform. The child is taken to the ICU with only the remifentanil infusion, as cerebral perfusion pressure is 55 mmHg without phenylephrine. In the ICU, the remifentanil is stopped hourly for neurological checks and within 6 h of admission the child is opening her eyes and reaching purposefully for the tracheal tube, which is removed. After a night without ICP elevations at a serum sodium of 145 mg/dL, she is interacting appropriately with her parents at the bedside and her ICP monitor is removed.

This case illustrates the main anesthetic considerations presented in this chapter in critically ill patients with neurotrauma and increased ICP undergoing emergent procedures, with choices for airway, drug, and hemodynamic management to facilitate successful outcomes.

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A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 26
Anesthesia for Thoracic Surgery

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Introduction

Thoracic surgery and thoracic anesthesia in the pediatric population have changed significantly over the last two decades with the advent of video-assisted thoracoscopic surgery (VATS) and robotic surgery, and evolution of anesthetic practice to facilitate this type of surgery. While the less invasive approach of VATS has undoubtedly changed certain aspects of the perioperative and particularly the postoperative management of the pediatric thoracic patient, thoracotomy remains a relatively frequent surgical procedure, particularly in the very small infant where thoracoscopic equipment can be too large and cumbersome to perform complex procedures. Hence, the pediatric anesthesiologist needs to have the capacity to manage both approaches to surgery within the thoracic cavity.

Certain aspects of anesthetic practice remain common to both thoracoscopic and open procedures, namely the requirement for one-lung ventilation (OLV). Indeed, due to the initial access to the thoracic cavity by trocar in VATS, the goal of OLV is even more sought after than in open thoracotomy, where the surgical team can use a combination of retraction and packing to facilitate surgical access and visualization without damaging the underlying lung parenchyma. This requirement in the younger child has led to the development of a multitude of devices to allow lung isolation in children for whom the smallest size of traditional double-lumen tube (26 Fr) is too large.

VATS has significantly decreased the requirement for neuraxial blockade during the intraoperative and postoperative period due to its less invasive and hence less painful nature. This has radically decreased the number of inpatient days following complex thoracic procedures [1]; however, due to the ongoing requirement for thoracotomy within the pediatric population, the pediatric anesthesiologist is still required to maintain within their armamentarium the ability to provide adequate postoperative analgesia when necessary.

The relatively recent development of rapid-onset and -offset anesthetic agents, specifically the highly insoluble desflurane and rapidly metabolized remifentanil [2], has had a huge impact on the ability of the anesthesiologist to provide the rapid-onset and profoundly deep anesthesia that is necessary for thoracic surgery. These agents are so rapidly reversed at the end of thoracic cases that fast operating room turnover with alert, awake, compliant postoperative patients has become a reality.

This chapter reviews the pathophysiology of OLV, discusses the anesthetic practice and tools necessary to facilitate the perioperative management of the pediatric thoracic surgery patient, discusses analgesia for thoracic surgery, and finally describes in a little more detail some of the finer nuances of certain specific thoracic surgical challenges within the pediatric population, namely lobectomy, pneumonectomy, congenital cystic lung disease, anterior mediastinal mass, pectus excavatum, and empyema.

Pathophysiology of one-lung ventilation

During thoracic surgery, several factors have profound effects on ventilation/perfusion (V/Q) matching. General anesthesia, neuromuscular blockade, mechanical ventilation, the open hemithorax, and surgical retraction all affect normal

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

V/Q matching, primarily because of their effects on lung compliance [3]. OLV uncouples V/Q matching to the operative lung, which may result in significant hypoxemia if not properly managed [3]. These factors apply equally to children and adults.

The lateral decubitus position

When awake, spontaneously breathing adults with unilateral lung disease are placed in the lateral decubitus position, oxygenation is optimal when the healthy lung is dependent ("down") and the diseased lung is non-dependent ("up") [4,5]. Because of the hydrostatic pressure gradient between the two lungs, there is greater perfusion of the dependent, healthy lung than the non-dependent, diseased lung, improving V/Q matching.

Studies suggest that infants, both those breathing spontaneously and those receiving positive pressure ventilation, demonstrate the opposite effect to that seen in adults. Oxygenation is improved with the healthy lung "up" and the diseased lung "down" [6,7]. Ventilation may be distributed differently in infants and adults because the soft, more compliant ribcage in infants cannot fully support the underlying lung. This results in a lower functional residual capacity (FRC), which is closer to residual volume, making airway closure more likely to occur in the dependent lung, even during tidal breathing [8]. In smaller children there is less cephalad displacement of the dependent hemidiaphragm by abdominal organs than in larger subjects, thus in accordance with Starling's law, contraction is less forceful in the dependent hemidiaphragm than in the upper hemidiaphragm, limiting the efficiency of ventilation of the dependent lung. Ventilation is therefore distributed preferentially to the non-dependent lung in infants.

The infant's small size reduces the hydrostatic pressure gradient between the dependent and non-dependent lungs that is seen in the adult. Consequently, the favorable increase in perfusion to the dependent, ventilated lung that is seen during OLV in adults is attenuated in infants. It is not known at what age the adult pattern appears. It is suggested that during the postoperative period the child with unilateral lung disease should be nursed in both lateral decubitus positions, as well as supine, to determine the position of optimal gas exchange.

Pulmonary perfusion during one-lung ventilation

Current lung separation techniques have made it easier to deliver the entire tidal volume to the dependent lung. When OLV is initiated, residual oxygen will gradually be absorbed from the unventilated alveoli until complete absorption atelectasis results. Continued perfusion of the unventilated lung leads to a large increase in V/Q mismatch or shunt fraction in addition to positional effects. This right-to-left shunt through the unventilated lung should result in an overall shunt fraction in excess of 50%. Observed shunt fractions are fortunately much lower. The operation of passive (mechanical) and active (biological) forces accounts for the lower than expected shunt fraction. Surgical manipulation, the effects of the open or artificial pneumothorax, and physical kinking of pulmonary vessels with lung deflation reduce blood flow to the operative lung. In addition, hypoxic pulmonary vasoconstriction (HPV) increases vascular resistance in the unventilated lung, resulting in a gradual decrease in blood flow and shunt fraction. The true clinical importance of HPV has been questioned [9].

Ventilation during one-lung ventilation

Ventilatory management of patients undergoing OLV has long focused on the issue of hypoxia avoidance. Hypoxia, however, has become less frequent because of more effective lung isolation, particularly with the use of fiberoptic bronchoscopy for confirmation of bronchial blocker or double-lumen tube position, and the use of anesthetic agents with fewer or no detrimental effects on HPV. Recent publications have focused on prevention of acute lung injury (ALI) associated with OLV. ALI has been found in 2.45% of lung resections in adults, with a peak incidence of 7.9% after pneumonectomies. It is associated with significant morbidity and a mortality rate around 40% in adults [10]. Similar outcome data are not available in children. Recommendations for protective lung ventilation (PLV) during OLV include: reducing tidal volume to 6 mL/kg with acceptance of mild hypercapnia, limiting the plateau airway pressure to <20 cmH_2O, and 5–10 cmH_2O positive end-expiratory pressure (PEEP) to preserve dependent lung unit aeration, prevent atelectasis, and reduce injury from mechanical stress [11]. Continuous positive airway pressure (CPAP) or oxygen insufflation may need to be added to the operative lung to treat hypoxemia. Resumption of two-lung ventilation with 100% oxygen during surgery may be required to treat severe or refractory hypoxemia. If this is not possible, the surgeon should consider placing a pulmonary artery clamp on the operative side during pneumonectomy or lung transplant.

KEY POINTS: PATHOPHYSIOLOGY OF ONE-LUNG VENTILATION

- In the lateral decubitus position, infants have improved oxygenation with the healthy lung "up" and diseased lung "down" – opposite from adults
- During one-lung ventilation, V/Q mismatch and shunt fraction are less than expected in children due to reduced perfusion of the "up" lung from mechanical factors and probably hypoxic pulmonary vasoconstriction
- During one-lung ventilation, tidal volumes of 6 mL/kg, limiting peak pressure, applying 5–10 cmH_2O PEEP, and oxygen insufflation to the operative lung are recommended

Anesthetic requirements for thoracic anesthesia

One-lung ventilation

There are three principal indications for OLV [12]:

1. To control the distribution of ventilation: bronchopleural (cutaneous) fistulas, gigantic unilateral lung cysts or bullae, and differential lung ventilation.
2. To avoid spillage or contamination: infection, hemorrhage, and unilateral pulmonary lavage.
3. To provide a quiet operative field: thoracoscopy, thoracotomy, and thoracic non-pulmonary surgery.

To facilitate this, there are three basic techniques or devices that are currently widely available to help isolate one lung from the other in the pediatric patient:

1. Selective endobronchial intubation with a conventional single-lumen endotracheal tube.
2. A bronchial blocker.
3. A double-lumen tube (DLT).

In the modern era and with widespread availability of the fiberoptic bronchoscope (FOB), the authors feel that clinicians should strive to directly visualize and verify device placement where possible. The choice of device is dependent upon patient age and size and device availability (Table 26.1, Fig. 26.1).

Endobronchial intubation

The simplest method of isolating one lung involves advancing a standard endotracheal tube (ETT) past the carina and into the desired main bronchus. When passed blindly, the ETT will almost always pass into the right main bronchus.

Table 26.1 Device selection for one-lung ventilation (OLV) in children

Age	OLV airway device
Less than 2 years	Selective endobronchial intubation
	Fogarty catheter (4 Fr) as a bronchial blocker
	Extraluminal wire-guided endobronchial blocker (5 Fr)
2–6 years	Fogarty catheter (4 Fr or larger) as a bronchial blocker
	Wire-guided endobronchial blocker (5 Fr)
6–10 years	Wire-guided endobronchial blocker (5 Fr or larger)
	Univent tube (3.5 ID)
Over 10 years	Wire-guided endobronchial blocker
	Univent tube
	Double-lumen tube (26 Fr or larger)

ID, internal diameter.
Source: Reproduced from Choudhry [15] with permission of Elsevier.

In order to selectively intubate the left main bronchus, the ETT must be rotated so that the bevel faces the right, the patient's head is rotated to the right, and the ETT is advanced [13]. Placement should be confirmed with a FOB, which requires a good working knowledge of the anatomy of the bronchial tree distal to the carina.

An alternative is to place the ETT in the trachea and pass the FOB into the left or right main bronchus before advancing the ETT over it. Note that the smallest size of FOB available is 2.2 mm in diameter and is not rigid enough to withstand aggressive advancement of a rigid ETT without the potential of significant damage to the FOB fibers, so care should be taken when using this scope to guide intubation.

Bronchial blockers

Embolectomy catheter/blocker

Embolectomy catheters are effective in achieving lung isolation in the smallest of patients [14]. The blocker can be positioned either within or alongside the ETT. Fogarty catheters have a central stylet that can be bent to facilitate the catheter being placed in either bronchus whilst being observed with a FOB through the ETT (Fig. 26.2). The open tip of the catheter

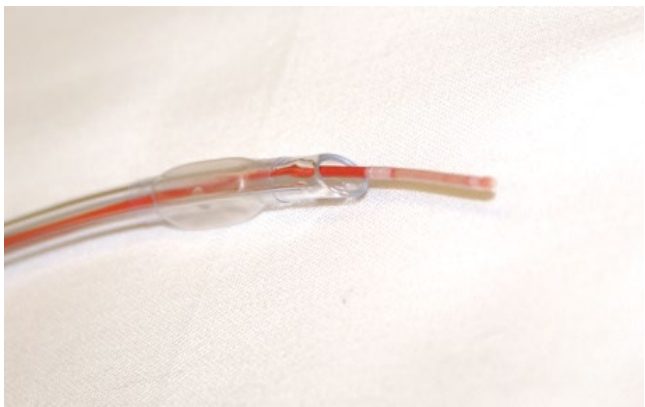

Figure 26.2 4 Fr Fogarty catheter within a standard 3.5 endotracheal tube.

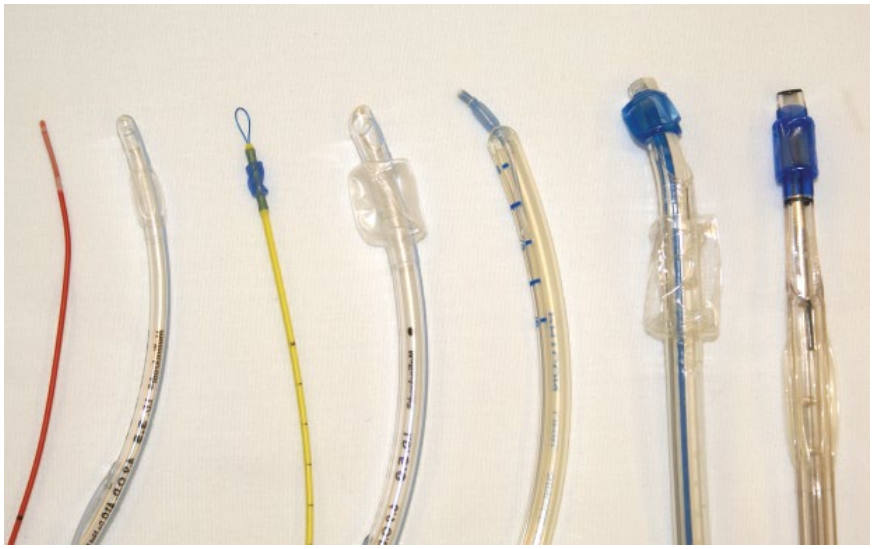

Figure 26.1 The devices available for facilitation of one-lung ventilation in children. Left to right (smallest to largest): 4 Fr Fogarty catheter, endotracheal tube (standard), 5 Fr wire-guided endobronchial blocker, 5.0 endotracheal tube (standard), 3.5 internal diameter Univent tube, 26 Fr (Rusch, Buluth, GA, USA) double-lumen tube (DLT), 28 Fr (Mallinckrodt Medical, St Louis, MO, USA) DLT.

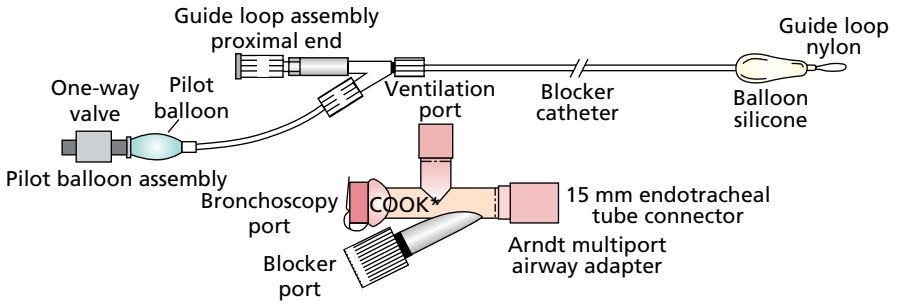

Figure 26.3 The components of the wire-guided endobronchial blocker (WEB).

allows for lung collapse following isolation and insufflation with oxygen if necessary.

Wire-guided endobronchial blocker

Wire-guided endobronchial blockers (WEBs) are available in a "pediatric" size – 5 Fr. The blocker is designed to be placed within a standard ETT, and a guidewire loop attached around the end of a FOB allows direct visualization and placement of the blocker. This device has the benefit of three ports, allowing ventilation while the blocker is manipulated into place (Fig. 26.3). The smallest ETT that can be used with the smallest 5 Fr WEB is a 5.0 mm ETT, hence this device is generally limited to children over 2 years of age (Fig. 26.4).

Bronchial blockers may alternatively be placed alongside (rather than within) an ETT for children under 2 years old. The WEB is prepared with a 35–45° bend just proximal to the occlusive cuff to facilitate maneuvering into the correct position. The WEB may then be placed either nasally or orally into the larynx and the ETT placed alongside the WEB. Employing an ETT 0.5 mm internal diameter (ID) smaller than standard size for the patient facilitates free movement of the WEB. Under fiberoptic visualization through the ETT, the WEB can then be manually directed into the appropriate bronchus. This technique allows use of bronchial blockers in children as young as 3 months old (Figs 26.5–26.8) [15,16].

Univent™ tube and blocker

The Univent tube (Fuji Systems Corporation, Tokyo, Japan) has a second lumen containing a separate bronchial blocker that is styletted and can be bent to facilitate positioning (Fig. 26.9). The smallest size Univent tube is 3.5 mm ID; however, the total external diameter is 8 mm, making it comparable in size to a 6.0 mm ID uncuffed ETT and limiting its use to older children (approximately 8 years of age). There are two main disadvantages to Univent tubes that should be noted: (1) Univent tubes, unlike double-lumen tubes, have a low-volume, high-pressure cuff that may contribute to mucosal injury; and (2) the blocker channel occupies a significant cross-sectional area, leaving a smaller lumen available for ventilation of the patient [17,18].

Double-lumen endotracheal tube

DLTs are considered the gold standard for lung isolation in the adult population; however, the smallest sizes available are a 26 Fr (Rusch, Duluth, GA, USA) and a 28 Fr (Mallinckrodt Medical, St Louis, MO, USA) (Fig. 26.10). These devices can only be realistically utilized in older children (8–10 years of age) and are positioned in the same manner as in adults. Due

Figure 26.4 A standard 5.0 endotracheal tube with fiberoptic bronchoscope and 5 Fr wire-guided endobronchial blocker *in situ*.

Figure 26.5 A 5 Fr wire-guided endobronchial blocker placed alongside a standard 3.5 endotracheal tube (ETT) with the fiberoptic bronchoscope within the ETT.

to the wide variation in the size of pediatric patients, there are no designated depth measurements for the placement of the DLT, hence its location should be confirmed with a FOB.

Anesthetic techniques

Preoperative evaluation and preparation is important and should be thorough and complete, as in all pediatric operative candidates. Some children will be otherwise completely fit and healthy; others may have significant concurrent and severe systemic illness. Premedication and induction technique is at the discretion of the anesthetic provider and needs to be tailored to the individual [19].

Lung isolation, if required, and analgesic technique should be planned well in advance. The authors advocate arterial line placement for thoracotomy and consideration in VATS, particularly in small infants and babies where the potential for accidental overinflation of the pleural cavity and iatrogenic tension pneumothorax is significant. Lung isolation and deflation should be initiated early, particularly in VATS patients, to allow adequate time for the lung to collapse

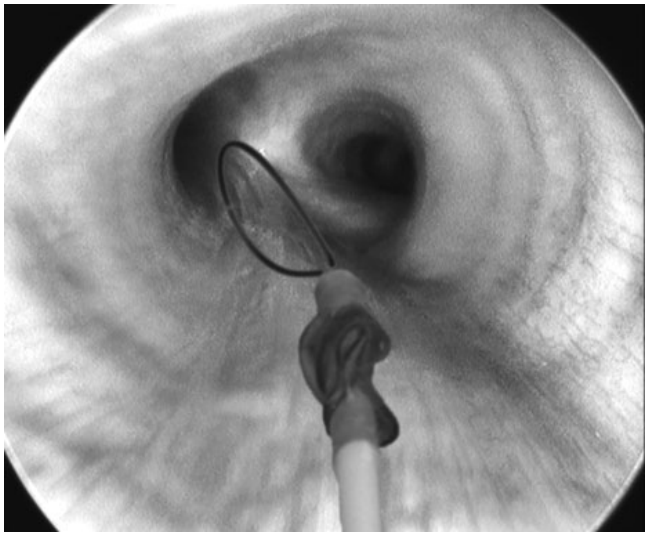

Figure 26.8 Visualization of wire-guided endobronchial blocker position.

Figure 26.6 Wire-guided endobronchial blocker with bend to facilitate manual positioning.

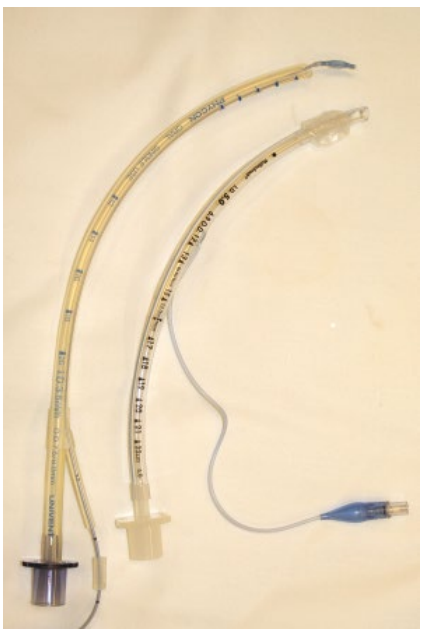

Figure 26.9 The smallest 3.5 internal diameter Univent tube available next to a standard 5.0 endotracheal tube.

(A) (B)

Figure 26.7 (A, B) Placement of extraluminal wire-guided endobronchial blocker.

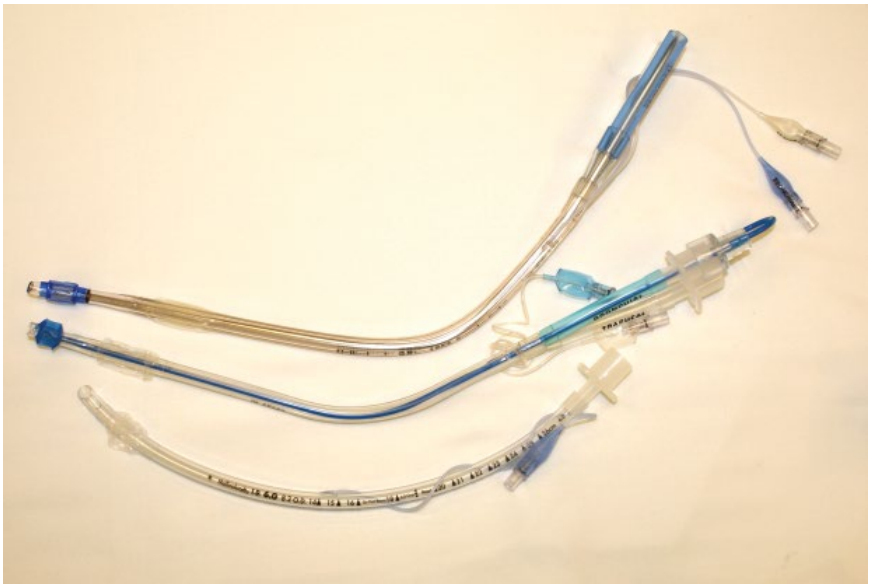

Figure 26.10 Smallest double-lumen tubes available. Top to bottom: 28 Fr (Mallinckrodt Medical, St Louis, MO), 26 Fr (Rusch, Duluth, GA, USA), 6.0 endotracheal tube (standard).

KEY POINTS: ANESTHETIC REQUIREMENTS FOR THORACIC ANESTHESIA

- One-lung ventilation (OLV) is indicated to control distribution of ventilation, avoid contamination, and provide a quiet operative field
- OLV can be provided even in small infants, but in these patients the technical difficulty may outweigh any benefits, and a pack and retract technique can be used
- Embolectomy catheters or wire-guided endobronchial blockers may be employed inside or outside the ETT, with fiberoptic guidance, to provide OLV in smaller patients
- Univent ETT and double-lumen tubes can provide OLV in larger patients, with fiberoptic guidance

(up to 20 min) and minimize the need for lung retraction [15]. Once OLV is instituted, the patient should be ventilated with as high a concentration of oxygen as is necessary to achieve adequate oxygen saturation. Nitrous oxide should be avoided to prevent overinflation of tracheal and bronchial balloons leading to airway trauma [20].

There is a perception that isoflurane may be beneficial in decreasing V/Q mismatch during OLV because it is thought to have less impact on HPV than other volatile agents [21]; however these data are limited to older anesthetic vapors, and isoflurane's slow offset time makes it less appealing as a primary anesthetic agent. The rapid offsets of the more recently developed volatile agents, such as desflurane, particularly after a long protracted case, make them very appealing agents for thoracic anesthesia. However, in order to minimize inhibition of HPV, the authors advocate using a maximum of 1 minimum alveolar concentration (MAC) of the chosen volatile anesthetic. In order to ensure that awareness is not encountered, a balanced anesthetic approach is therefore necessary using an adjunct intravenous agent such as propofol that will not impact HPV [22] and/or opiates.

When a short-acting volatile agent such as desflurane is coupled with the profound μ agonism of remifentanil, regional anesthesia, a non-steroidal anti-inflammatory drug (NSAID) and, where available, intravenous acetaminophen/paracetamol at the end of the case, the anesthesia practitioner has a number of tools that can facilitate rapid emergence with a coherent and interactive patient at the end of a major surgical procedure.

Analgesic requirements for thoracic surgery

Thoracic surgery, especially open thoracotomy and minimally invasive pectus excavatum repair, may result in significant postoperative pain. Thoracotomy results in severe chest wall trauma, including fractured ribs and damage to peripheral nerves. The chest wall cannot be immobilized to control this pain. It must remain in constant motion for effective gas transfer to take place, and vigorous motion is required for effective clearing of secretions. Shallow respirations and a poor cough predispose the child to atelectasis, sputum retention, and postoperative pneumonia. Sensitization to painful stimuli can cause chronic pain and/or higher pain levels during subsequent surgical procedures. Recent studies suggest that around one-third of adult patients suffer from chronic pain after thoracic surgery, with similar incidence for thoracotomy or VATS [23–26]. The incidence is likely somewhat lower in children [27].

Some surgical literature suggests that children should understand "that they are going to have to learn to be comfortable with being uncomfortable" [28]. The authors would contest this statement and contend that it is the anesthesiologist's responsibility to offer his or her patients optimal pain relief. The authors agree with Suresh, who asked the question: "If placing a thoracic epidural catheter in adults is considered the 'standard of care' in many institutions across the country, why is the child deprived of the same privilege?" [29].

Various pain treatment modalities have been described to treat post-thoracotomy pain, but when the factors influencing the generation of post-thoracotomy pain are considered,

regional analgesia is the most logical approach [30]. This is because neurogenic pain, which results from intercostal nerve damage as well as chest wall trauma, and central nervous system hyperexcitability are both known to be poorly sensitive to opioids [31,32]. Reliance on these drugs may have detrimental effects on respiration and oxygenation [33,34]. In order to achieve the optimal effect, it is logical to start the regional analgesic regimen preoperatively [35]. A multimodal analgesic approach combining an effective afferent nerve block with a NSAID, acetaminophen/paracetamol, and low doses of opioids is expected to achieve an optimal level of postoperative analgesia. Although regional anesthesia is addressed in Chapter 20, several regional techniques deserve emphasis in a discussion of anesthesia for thoracic surgery.

Epidural analgesia

In contrast to older children and adults, epidural and subarachnoid blockade in infants and children under the age of about 6 years is characterized by hemodynamic stability, even when the level of the block reaches the upper thoracic dermatomes [36]. Although heart rate variability is lower, heart rate is preserved, because the parasympathetic activity modulating heart rate appears to be attenuated in infants [37]. This attenuated vagal tone allows the heart rate to compensate for peripheral vasodilation. Other factors playing a role in the preservation of hemodynamic stability are the relatively small venous capacitance in the lower extremities of infants, and the relative lack of resting sympathetic peripheral vascular tone [38].

Thoracic epidural blockade has been shown to improve several measures of respiratory function [39–41]. There is evidence to suggest that improved postoperative tidal volume and diaphragmatic shortening after thoracic epidural blockade may be due to changes of chest wall conformation and diaphragmatic resting length, and a shift of the workload of breathing from the ribcage to the diaphragm, caused by motor block of intercostal muscles [42].

In infants, thoracic catheter placement can be achieved via the caudal space with cephalad threading of a styletted catheter [43]. Although successful application of this technique has been described in children up to 10 years of age [44], in children over the age of 1 year there is an increased chance of the catheter exiting a dural sleeve or becoming knotted or tangled [45,46]. Epidurograms [47], epidural electrocardiography [48], and electrical stimulation [49] have been used to confirm catheter tip positioning at the desired level. As clinicians gain confidence in the use of ultrasound for regional anesthesia, it is becoming the modality of choice for the visualization of the epidural catheter tip [50–53]. Ultrasound localization is non-invasive, avoids exposure to radiation and contrast medium, and is not affected by the use of neuromuscular blocking drugs or epidural local anesthetics.

Epidural placement near the dermatomal level of the surgical incision(s) allows the safest and most effective application of local anesthetics. A thoracic epidural catheter has less risk of contamination by stool and urine than a caudally placed catheter. Thoracic epidural catheters may be safely placed in anesthetized infants and children by experienced anesthesiologists [54]. A prospective study from the French-Language Society of Pediatric Anesthesiologists found no lasting complications in over 10,000 epidural blocks [55]. Another recent study from the Pediatric Regional Anesthesia Network (PRAN) demonstrated no deaths or sequelae lasting longer than 3 months in nearly 3000 epidural catheters [56].

Paravertebral analgesia

The paravertebral space is wedge shaped. Its boundaries are: posteriorly, the superior costotransverse ligament; laterally, the posterior intercostal membrane; anteriorly, the parietal pleura; and medially, the posterolateral aspect of the vertebrae, intervertebral disks, and intervertebral foramen. The space contains spinal nerves and dorsal rami, rami communicantes, and anteriorly, the sympathetic chain. Injection of local anesthetic into the paravertebral space avoids possible complications of central neuraxial blockade.

Paravertebral block (PVB) has been employed in children since 1992, when two different techniques were described: Lönnqvist's modification of the original Eason–Wyatt percutaneous catheter technique [57] and Eng and Sabanathan's surgical catheter placement during thoracotomy [58]. More recently, ultrasound-guided techniques have been described and are becoming increasingly popular [59]. The main indication for thoracic PVB is unilateral thoracic surgery. Continuous infusion is possible via a catheter placed transcutaneously or surgically via thoracotomy. A rate of 0.25 mL/kg/h is recommended [57,60–62]. The advantage of a PVB is that deposition of local anesthetic into the paravertebral space will lead to a unilateral block of one or more adjacent dermatomes. Because all the effects of PVB are unilateral, hypotension, which limits the dosage of local anesthetic used in epidural analgesia in children over the age of 6 years, is rarely a problem. Relatively large doses of drug can therefore be used with a consequent improvement in efficacy of the unilateral blockade. The sympathetic chain that is known to be important in pain transmission is reliably blocked by PVB, whereas the central sympathetic blockade produced by epidural and spinal anesthesia leaves this pathway unaffected, thereby allowing central relaying of information (bypassing the blockade) [63]. Confirmation of the lack of provision of high-quality afferent blockade with epidural analgesia is shown by its failure of inhibition of somatosensory-evoked potentials and the failure of stress inhibition for any surgery more rostral than gynecological, or more distal surgery [64,65]. There are far fewer PVB data for comparison, but thoracic somatosensory-evoked potentials have been shown to be abolished [66] and some parameters of the stress response have been inhibited [35,67].

Intercostal analgesia

Intercostal blocks after thoracotomy and in children with rib fractures can reduce opioid requirements and improve respiratory function [68–70]. The disadvantage of single-shot blocks is their limited duration of action. The development of degradable bupivacaine microspheres, which produce dramatically prolonged duration of action, may increase the usefulness of these blocks in the future [71,72]. Plasma concentrations of local anesthetics after intercostal blocks are greater than after any other regional block. Plasma concentrations rise faster in children than in adults [73,74].

A continuous infusion of local anesthetic via an extrapleural catheter, placed during thoracotomy wound closure by the

surgeon, can prolong the analgesic effect [69]. The infusion may have an analgesic effect by delivering local anesthetic to the paravertebral space [75].

Summary

How can clinicians decide which regional analgesic technique to use in thoracic surgery in children? A meta-analysis of 10 trials that had enrolled 520 adult patients concluded that PVB and epidural analgesia provide comparable pain relief after thoracic surgery, but PVB has a better side-effect profile and is associated with a reduction in pulmonary complications [76].

For adult thoracic surgery, the Procedure-Specific Postoperative Pain Management (PROSPECT) Working Group evaluated the available literature comparing various regional analgesic techniques for the management of post-thoracotomy pain [77]. Seventy-four randomized studies in thoracotomy were identified that compared regional analgesic techniques with systemic opioid analgesia or with each other. The Working Group concluded that evidence supported the use of thoracic paravertebral block as an effective alternative to thoracic epidural local anesthetic (LA) alone, and showed that PVB reduced the incidence of postoperative pulmonary complications compared with systemic analgesia. They suggested that further studies were required to determine whether thoracic PVB is equivalent to thoracic epidural combining LA plus opioid in terms of pain relief and morbidity. Apart from thoracic PVB, all other regional analgesic techniques were inferior to thoracic epidural analgesia. In particular, interpleural techniques do not provide adequate analgesia. However, when thoracic epidural or paravertebral techniques are not possible or are contraindicated, intercostal nerve block or preoperative intrathecal opioid is recommended.

KEY POINTS: ANALGESIC REQUIREMENTS FOR THORACIC SURGERY

- Chronic pain is common after thoracotomy; a multimodal approach to analgesia may be preventative
- Epidural, paravertebral, or intercostal analgesia can be provided for thoracotomy pain
- A caudal approach with the catheter threaded to the thoracic regions is effective in small infants, with epidurogram, electrocardiogram, electrical stimulation, and ultrasound useful for proper placement

Thoracoscopy

The field of minimally invasive surgery (MIS) is the fastest growing area of surgical innovation. Each year, as new techniques and tools are developed, more patients benefit from surgical procedures previously associated with a significantly more invasive approach. Thoracoscopy has several potential advantages over thoracotomy for resection or repair of intrathoracic abnormalities in children. Scoliosis develops in up to 30% of neonates after thoracotomy [78]. In addition, thoracoscopy appears to be associated with decreased pain and better pulmonary mechanics postoperatively and improved cosmesis when compared to thoracotomy. Shorter hospital stays, a faster return to normal activity, and a shorter recovery period are just a few of the advantages that MIS offers to pediatric patients.

Box 26.1: Thoracoscopic procedures in infants and children

- Diagnostic thoracoscopy
- Lung biopsy
- Pectus repair
- Empyema drainage
- Lung decortication
- Bronchopulmonary sequestration resection
- Congenital pulmonary airway malformation resection
- Lobar emphysema resection
- Bronchogenic cyst excision
- Esophageal duplication resection
- Congenital diaphragmatic hernia repair
- Esophageal atresia and tracheo-esophageal fistula repair
- Thymectomy
- Aortopexy
- Vascular ring division
- Patent ductus arteriosus (PDA) ligation
- Thoracic duct ligation
- Sympathectomy
- Mediastinal mass excision
- Anterior spinal fusion

Originally, VATS was developed to provide biopsy specimens of thoracic structures in immunocompromised patients when a definitive diagnosis otherwise could not be obtained [79]. Although VATS continues to be used widely for this indication in pediatric patients, an increasing number of pediatric surgical conditions also are being addressed using a thoracoscopic approach (Box 26.1).

With the advances in thoracoscopic equipment, including the availability of smaller scopes and improvements in fiberoptics and the quality of digital video signals and screen resolution, these techniques are being applied to younger and younger children, and even to neonates and infants.

Blood loss during thoracoscopic surgery is generally minimal; however, adequate venous access should be secured prior to the start of these procedures because of the possibility of inadvertent injury to intrathoracic vascular structures by one of the trocars or endoscopic instruments. Because these procedures are routinely performed in the lateral decubitus position, access to the extremities to obtain additional venous access during the procedure can be limited. Standard perioperative monitoring includes pulse oximetry, electrocardiogram, end-tidal CO_2 and inhaled volatile agent concentration, non-invasive blood pressure measurement, and temperature.

In patients with normal cardiovascular function, routine monitoring of central venous pressure offers little additional information to improve or influence anesthetic care. Central venous access generally is reserved for cases in which adequate peripheral intravenous access is unavailable. Invasive monitoring of arterial blood pressure is not routinely used but is guided by the clinical status of the patient.

OLV is highly desirable during thoracoscopy because lung deflation improves visualization of thoracic contents and may reduce the risk of lung injury caused by the use of retractors. If OLV cannot be achieved, thoracoscopy can be performed

during two-lung ventilation using CO_2 insufflation and placement of a retractor to displace lung tissue from the operative field [80]. This technique also can be used to improve visualization if there is an inadequate separation of the two lungs with overflow ventilation into the operative side. Cardiopulmonary function should be monitored during the creation of the artificial pneumothorax because the displacement of intrathoracic contents and creation of an excessive pneumothorax related either to excessive volume or pressure can lead to significant cardiovascular compromise resulting from decreased venous return or increased left ventricular afterload. The effects of the artificial pneumothorax can be minimized by slowly adding the CO_2 (flow rate 1 L/min), limiting the inflating pressure to 4–6 mmHg, and optimizing cardiovascular function, including the optimization of myocardial contractility (if required) and restoration of intravascular status [81]. The other significant risk during the creation of the artificial pneumothorax is inadvertent CO_2 embolism [82]. CO_2 embolism can occur from the entry of the insufflating gas into the circulation either from direct injection during insufflation into the vasculature or from the entry of the gas, which is under pressure in the hemithorax, into an internal vessel that has been damaged during the procedure [83].

Comparative analysis of outcomes of VATS versus open thoracotomy has been limited to retrospective comparative studies [84]. A systematic analysis of 21 studies found that five scenarios had been studied: repair of congenital diaphragmatic hernia (CDH), esophageal atresia/tracheo-esophageal fistula (EA/TEF) repair, lung resection, treatment of pneumothorax, and resection of neuroblastoma. The level of evidence was 3 on the Oxford Center for Evidence Based Medicine Scale of 1–5. Advantages of VATS included less postoperative pain for CDH, EA/TEF, and pneumothorax; shorter hospital stay for all conditions except neuroblastoma; shorter ventilation time and lower $PaCO_2$ for CDH; shorter chest drain duration for lung resection; and less blood loss for neuroblastoma. However there were some disadvantages to VATS, including higher recurrence rates for CDH, higher $PaCO_2$ for EA/TEF, and longer operative times for CDH and EA/TEF.

Robotic surgery

The field of robotic surgery continues to progress, and robotic instruments increasingly are considered for implementation in pediatric surgery because of their ability to articulate, increasing surgeon dexterity while working in small spaces. Although robotic thoracic surgery use in children is infrequent, there are a few literature reports demonstrating feasibility and safety for some conditions, including thymectomy, EA, cyst resection, and diaphragmatic hernia. Small patients, including neonates, are included in case series [85,86]. Articulated tools and a three-dimensional optical stereoscopic view make the procedure more similar to an open procedure for the surgeon, using all the advantages of traditional thoracoscopy. Good preoperative communication with the surgeon is essential to plan for positioning of the operating room table within the operating room, positioning of the operating robot to allow the anesthesia providers to gain good access to the child's airway, and positioning of the child on the operating table. It is of enormous benefit to perform robotic surgery in a dedicated operating room with staff who are experienced in the management of robotic surgery cases [87].

KEY POINTS: THORACOSCOPY AND ROBOTIC SURGERY

- Video-assisted thoracoscopy (VATS) can be utilized for essentially any thoracic operation for which open thoracotomy would be used
- OLV is desirable for VATS; however CO_2 insufflation with lung retraction can be used if OLV is not feasible
- VATS results in less postoperative pain and shorter hospital stay than thoracotomy
- Robotic thoracic surgery may be used increasingly in pediatric patients in the future

Lung resection

In developed countries, the age of children undergoing pulmonary resection has steadily decreased over the last decades, reflecting a decline in such procedures performed for infectious etiologies and a rise in resections performed for congenital malformations. An understanding of normal lung growth in the postnatal period is essential to predict pulmonary function after lung resection in children. It is well established that alveoli multiply after birth [88]. The number of alveoli rises from approximately 20×10^6 at birth to approximately 300×10^6 by the age of 8. The most rapid increase in the number of alveoli occurs during the first 3 years of life. After 8 years of age, the number of alveoli remains constant. The lung volume doubles between the ages of 8 and 25, which can be accounted for by the increase in the volume of individual alveoli [89].

Lobectomy

Pulmonary resection in an adult leads to a proportional decrease in lung volume; however, case series evaluating pulmonary function after lung resection performed during infancy point out that these patients develop normally, live normal lives, and have no physical impairment at rest. McBride et al [90] evaluated pulmonary function of 15 patients who had undergone lobectomies for congenital lobar emphysema as infants between 1 week and 3 years of age. They found the vital capacity and total lung capacities to be within the normal range in the vast majority of these patients after a follow-up period of 8–30 years. However, they observed an association between the resected anatomical portion and the extent of compensatory growth. The most vigorous compensatory growth was seen after upper lobectomies. This could be related to elevation of the hemidiaphragm after lower and middle lobectomies. In addition, normal residual volumes in these patients are a further indication that the compensatory growth was consistent with multiplication of alveoli.

Pneumonectomy

Early studies described preserved pulmonary function after pneumonectomies performed during childhood. In 1947, Cournard [91] reported outcomes of four patients who had

undergone left pneumonectomies for pulmonary infections between the ages of 6 and 16 years. It was observed that the total lung capacity for the remaining lung was greater than would have been predicted for the right lung of an individual without a history of pulmonary resection. In three of the four patients, the vital capacity was greater than the predicted value for a right lung.

Laros and Westermann [92] stratified a population of 130 pneumonectomy patients by age at the time of their operation. Preservation of total lung capacities decreased with increasing age at the time of the pneumonectomy. The total lung capacity was 96% of the predicted value in patients who were younger than 5 years at the time of their pneumonectomy, and 85% of predicted in patients between 6 and 20 years of age, but only 70% of predicted in patients between 31 and 40 years of age.

Postpneumonectomy syndrome

The postpneumonectomy syndrome is associated with progressive hyperinflation of the remaining lung and typically leads to progressive dyspnea. It can also lead to the development of bronchomalacia and can predispose to pulmonary infections. Postpneumonectomy syndrome is most commonly seen after a right pneumonectomy [93]. It is associated with counterclockwise rotation of the mediastinal structures, which leads to compression of the left mainstem bronchus or left lower lobe bronchus between the aorta and spine posteriorly and the pulmonary artery anteriorly. Postpneumonectomy syndrome can also be encountered after a left pneumonectomy when a right-sided aortic arch is present, and the airway is compressed between ascending and descending aorta [94]. However, this complication has also been reported after a left pneumonectomy in patients who have a left-sided aortic arch [95]. In this case, the bronchus intermedius is thought to be compressed between the right pulmonary artery anteriorly and the thoracic spine posteriorly after clockwise rotation of the mediastinal structures into the right pleural cavity.

Early attempts to prevent mediastinal shifts after pneumonectomies in children included thoracoplasties, which were eventually abandoned because of resulting crippling deformities. Other attempts to prevent mediastinal shifts in the past included instillation of inert substances such as oil into the pleural cavity. The principles of treating this syndrome today include a combination of anterior pexy of mediastinal structures such as pericardium and pulmonary artery, and an intervention in the postresection pleural cavity to prevent future shifting [96]. For many years, rigid prostheses such as Silastic testicular or breast prostheses were placed in the pleural cavities to stabilize the mediastinum [97]. One shortcoming of this method is the inability to adjust the size of the prosthesis in a growing child. In 1992, Kosloke and Williamson [98] first reported the use of expandable tissue-expander prostheses in an effort to address this problem. Finally, placement of endobronchial stents has been reported, mostly in adults.

Thoracic surgical lesions

Thoracic surgery in neonates is primarily performed to treat congenital pulmonary anomalies such as congenital cystic lesions, CDH, and TEF. These anomalies often present *in utero* or in the newborn period. Others, such as neoplasms, infectious diseases, and musculoskeletal deformities are found in later childhood. CDH and TEF are described in Chapter 23, but the remainder of the surgical lesions affecting infants and children are reviewed here, along with specific anesthetic considerations (Table 26.2).

Congenital cystic lung disease

Of the many types of congenital cystic lesions, the overwhelming majority can be categorized into four groups: congenital cystic adenomatoid malformation (CCAM), bronchopulmonary sequestration (BPS), congenital lobar emphysema (CLE), and bronchogenic cyst (BC). These malformations have distinct features but there is significant overlap, suggesting there may be a single pathological mechanism for their development [99]. Of note, CCAM is more correctly termed CPAM (congenital pulmonary airway malformation) since many are neither cystic nor have adenoid tissue [100], and will henceforth be referred to as CPAM in this text.

Cystic lung lesions are often identified around 20 weeks' gestation, when they are found on routine fetal ultrasound [101]. Management in a fetus depends on the lesion itself as well as the status of the fetus and mother. Large lesions may cause compression of the esophagus, lung, or vena cava, resulting in polyhydramnios, pulmonary hypoplasia, or low-output cardiac failure and fetal hydrops, respectively. With evidence of fetal hydrops, intervention options include thoracocentesis, thoracoamniotic shunting, open fetal surgery and resection, *ex utero* intrapartum therapy and resection (EXIT procedure), or early delivery with postnatal resection. For a fetus greater than 32 weeks' gestation, resection during EXIT procedure is recommended, while in those less than 32 weeks' gestation there is an option for intrauterine surgery [102]. Anesthesia for fetal surgery and EXIT procedure is discussed in Chapter 21.

Small lesions may be asymptomatic or cause respiratory distress in the newborn period. Initially asymptomatic lesions may lead to infection, pneumothorax, or malignant degeneration later in life. Serial imaging has revealed, however, that many large lesions may actually decrease in size [103,104]. Postnatal presentation depends on the size, location, and type of lesion as well as any communication with the gastrointestinal tract or bronchopulmonary tree. Pulmonary hypoplasia can lead to pulmonary hypertension and respiratory failure and may need extracorporeal membrane oxygenation (ECMO). Many lesions can remain asymptomatic and undiagnosed for many years. Almost all patients will eventually develop complications, most often presenting as pneumonia unresponsive to medical management.

Patients with prenatally diagnosed lesions should have a computed tomography (CT) scan of the chest after birth. In a patient not identified prenatally who presents in respiratory distress after birth, chest radiography is the first diagnostic test, with confirmatory studies such as CT to follow (Figs 26.11, 26.12). Occasionally, magnetic resonance imaging (MRI) and bronchoscopy may be necessary. CPAM, CLE, and extralobar BPS are occasionally associated with other congenital anomalies and may necessitate additional preoperative work-up, including echocardiography [99].

Table 26.2 Pediatric thoracic lesions

Lesion	Evaluation	Treatment	Anesthetic considerations
Tracheal stenosis			
Acquired	Laryngoscopy/ bronchoscopy	Cricoid split	TIVA
Congenital	Laryngoscopy/ bronchoscopy	Laryngotracheoplasty	TIVA, postoperative ventilation
Congenital cystic lung disease			
Congenital pulmonary airway malformation	CT	VATS versus thoracotomy	Minimize inflating pressure, avoid N_2O
Bronchopulmonary sequestration	CT, MRI	VATS versus thoracotomy	Minimize inflating pressure, avoid N_2O
Congenital lobar emphysema	CT	VATS versus thoracotomy	Spontaneous ventilation, N_2O contraindicated
Bronchogenic cyst	CT	VATS versus thoracotomy	Minimize inflating pressure, avoid N_2O
Congenital diaphragmatic hernia	CXR	Replace abdominal contents Repair defect	Decrease PVR, minimize inflating pressure, avoid N_2O, may need nitric oxide, HFOV, ECMO
Tracheo-esophageal fistula	CXR	Repair defect	Minimize inflating pressure, occlude fistula with ETT or blocker
Neoplasms			
Mediastinal	CT, MRI, PFTs	Needle or open biopsy, resection	Respiratory and/or cardiovascular collapse, possible OLV
Thoracic	CT, MRI	VATS versus thoracotomy	OLV, effects of chemotherapy and/or radiation therapy
Pectus excavatum	CXR, CT, PFTs, echocardiogram	Nuss versus Ravitch	Postoperative analgesia
Scoliosis	CXR, PFTs	Spinal fusion	Possible OLV with anterior fusion
Empyema	CXR, CT, pleurocentesis	Thoracostomy versus VATS or thoracotomy	Possible OLV

CT, computed tomography; CXR, chest X-ray; ECMO, extracorporeal membrane oxygenation; ETT, endotracheal tube; HFOV, high-frequency oscillatory ventilation; MRI, magnetic resonance imaging; OLV, one-lung ventilation; PFTs, pulmonary function tests; PVR, pulmonary vascular resistance; TIVA, total intravenous anesthesia; VATS, video-assisted thoracic endoscopy.
Source: Reproduced from Hammer [19] with permission of Elsevier.

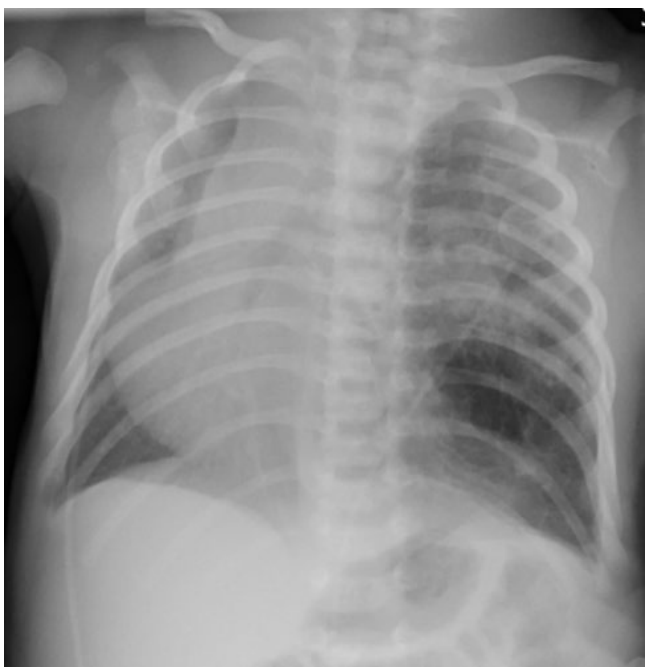

Figure 26.11 Chest radiograph of a newborn with congenital pulmonary airway malformation (CPAM).

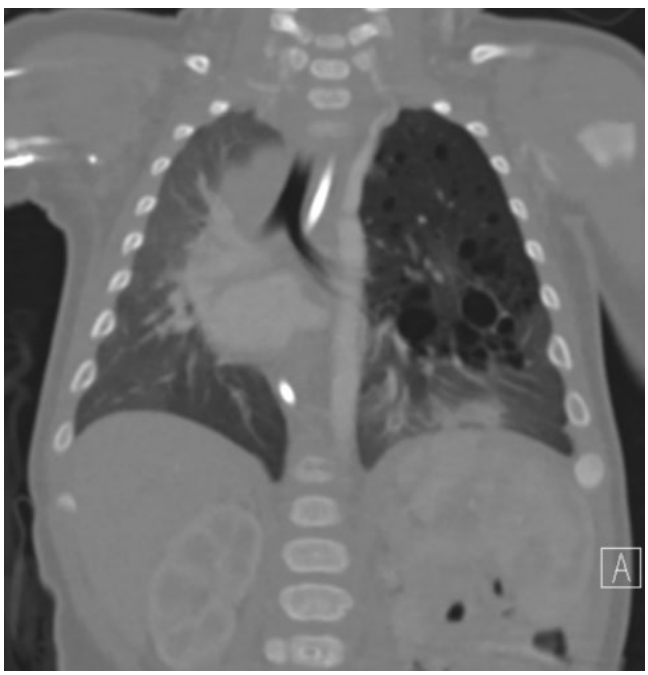

Figure 26.12 Chest CT of a newborn with congenital pulmonary airway malformation (CPAM).

Although there is consensus that all symptomatic lesions should be resected, there is some debate whether asymptomatic lesions should merely be observed. CPAMs and BPS sometimes resolve spontaneously on fetal ultrasound, but there is no evidence that this occurs after birth.

Pulmonary lesions that become undetectable by fetal US and postnatal radiograph may be visible postnatally on CT Asymptomatic CPAMs that were followed conservatively had complication rates of 10% requiring surgery [103]. It is therefore still recommended that CPAM, intralobar BPS, and

BC are resected between 3 and 6 months of age. Extralobar BPS can remain asymptomatic for life but can also result in complications. A period of observation has been advocated [101]. Asymptomatic CLE may resolve spontaneously and should be observed. The preferred surgical approach in recent years has been thoracoscopic lobectomy for most lesions, with repeat CT imaging just before the time of elective resection at age 6 months for asymptomatic lesions [105].

When anesthetizing neonates with congenital lung lesions, it is important to determine if positive pressure ventilation (PPV) will be tolerated. PPV in lesions that contain a bronchial connection to abnormal lung parenchyma could result in overdistension of the abnormal lobe with compression of normal lung tissue due to a ball-valve effect. This can lead to compromised ventilation, mediastinal shift, compression of the great vessels, and decreased cardiac output. If there is doubt as to the bronchial connections of the thoracic lesion, spontaneous ventilation during induction and maintenance of anesthesia is indicated. If OLV is planned, once the affected lung is isolated, PPV and neuromuscular blockade can be safely used. Postoperative analgesia can be in the form of intravenous opioids or, preferably, a thoracic epidural catheter, either placed directly at the desired level or threaded from the caudal canal. Recently, more congenital lung lesions have been resected using VATS. While this technique is challenging in the infant population and results in significantly longer operative time, it is safe and may reduce hospital stay [106].

Congenital pulmonary airway malformation

A CPAM is a discrete intrapulmonary mass that may be solid or contain cysts, and is typically characterized by increased adenomatous respiratory bronchioles (see Chapter 21). Cysts can be of various sizes, from 1 mm to over 10 cm. Although the lesion is non-functional, it does communicate with the normal tracheobronchial tree and can lead to air trapping during PPV [102]. CPAM is usually found only in one lobe; it occurs in all lobes with equal frequency. When it does involve more than one lobe it may require pneumonectomy. Associated anomalies are uncommon.

CPAMs are usually detected *in utero* by ultrasound (see Chapter 21). They can rarely result in pulmonary hypoplasia, hydrops fetalis, or fetal demise. Most CPAMs are asymptomatic and are resected electively in the neonatal period. Those that cause cardiac or respiratory distress may necessitate emergency resection either in the immediate postnatal period or by EXIT procedure [102].

Although there is a communication between the lesion and the tracheobronchial tree, CPAMs are usually solid or have small cysts, acting more like solid lesions and allowing for safe use of PPV. Most lesions can be resected without lung isolation, but if necessary OLV can be accomplished by mainstem intubation. Intraoperative and postoperative pain management can be accomplished with good results using an epidural catheter [107].

Bronchopulmonary sequestration

A BPS is a portion of non-functioning lung tissue without a bronchial connection. It typically has an anomalous blood supply, arising from bronchial or aortic vessels, and has systemic, bronchial, or azygous venous drainage. BPS is usually found in the lower lobes with the majority being intralobar (inside lobe pleura) while the rest are extralobar (with their own pleura). BPS can be confused with CPAM, and some lesions are considered "hybrid," having features of both BPS and CPAM.

BPS is often diagnosed *in utero*. Detection of a systemic artery from the aorta to fetal lung tissue by color flow Doppler is pathognomonic for BPS [103]. At birth, most BPS are asymptomatic and present later in life as pneumonia resistant to antibiotic therapy. Sometimes, when a BPS is large, it can compress the lungs and lead to respiratory distress. If it has a large blood supply it can also lead to high-output heart failure. BPS can be diagnosed using CT, but MRI can be helpful to map the blood supply and drainage before surgical resection.

There are few unique anesthesia concerns. OLV is helpful for surgical resection, but because there is no connection between a BPS and the bronchial tree, PPV is safe. However, nitrous oxide can cause expansion and should be avoided.

Congenital lobar emphysema

CLE is an abnormally emphysematous pulmonary lobe that communicates with the bronchial tree. It is most common in the left upper lobe, followed by the right middle lobe and the left lower lobe, and can be distinguished from other cystic lesions by ultrasound. It often enlarges before 28 weeks' gestation because of fetal lung fluid trapping, similar to air trapping found postnatally. After this time, it may regress and may look like normal lung tissue at birth [102].

Even though they are usually asymptomatic, it is important that patients with CLE are carefully evaluated at birth because they are at risk of air trapping of the emphysematous lobe. Overinflation may ultimately lead to "tension emphysema" and compression of the contralateral lung [108]. At this stage CLE can be confused with tension pneumothorax and a chest tube may be inappropriately placed, leading to further respiratory distress. Large lesions may lead to decreased cardiac output and eventually cardiac collapse. These patients need emergent thoracotomy and rapid lobe exteriorization.

The primary anesthetic concern is to avoid overdistension of the affected lung tissue (Fig. 26.13). PPV can lead to rapid expansion of the lesion due to a ball-valve effect, so an effort to maintain spontaneous ventilation should be made. If PPV is necessary, low inflating pressures should be used. OLV is typically necessary for isolation of the affected area, and once initiated it is also safe to switch to PPV. Nitrous oxide should be avoided throughout the case. At the end of the procedure two-lung ventilation is instituted to check for air leaks at the resection site. Patients should be extubated early or, if they remain intubated, allowed to breathe spontaneously to avoid air leak. VATS has been described for resection of cystic lesions, but is more challenging with CLE [104]. As with other congenital cystic lesions requiring thoracotomy, pain is well controlled with a thoracic epidural.

Bronchogenic cyst

BCs are usually mediastinal, solitary, unilocular cysts filled with air, fluid, or mucus. They do not communicate with the bronchopulmonary tree and therefore, like BPS, pose few additional anesthetic concerns. PPV can be used, and some authors have even reported the safe use of nitrous oxide [109].

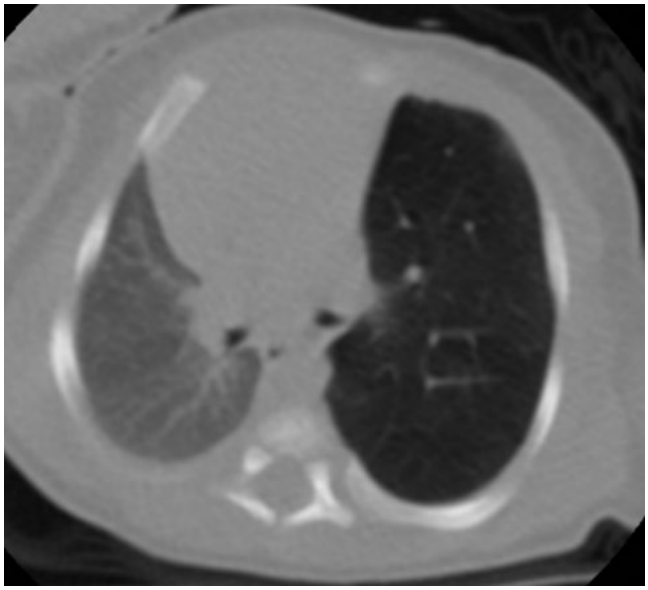

Figure 26.13 Chest CT of an infant with congenital lobar emphysema complicated by hyperinflation and mediastinal shift.

KEY POINTS: LUNG RESECTION AND THORACIC SURGICAL LESIONS

- Because of ongoing lung growth, lobectomy in infants and young children often results in normal lung function
- Congenital pulmonary airway malformation, bronchopulmonary sequestration, congenital lobar emphysema, and bronchogenic cyst comprise the majority of cystic lesions in children
- All symptomatic lesions are resected; asymptomatic lesions may be observed for 3–6 months; most are resected by age 6 months

Anterior mediastinal mass

Anesthetizing children with anterior mediastinal mass can be associated with a high risk of morbidity and even mortality [110–113] as a result of cardiovascular and/or respiratory collapse. Fortunately, over the past several decades as anesthesiologists have become more aware of these risks and perioperative management has improved, the reported morbidity and number of fatalities have decreased [114].

Mediastinal masses can be located in the anterior, middle, or posterior mediastinum. While this designation is somewhat arbitrary and there is some overlap, those masses in the anterior mediastinum cause the most severe complications in relation to general anesthesia [115]. An anterior mediastinal mass may be caused by several types of tumors, most commonly neuroblastoma in young children and lymphomas (Hodgkin and non-Hodgkin) in adolescents [116]. Other tumors include germ cell tumors, thymoma, bronchogenic cyst and carcinoma, granuloma, and cystic hygroma [114]. A biopsy diagnosis is necessary to guide chemotherapy, radiation therapy, and/or surgical resection. Biopsy is usually accomplished with CT guidance; however, surgical biopsy through the mediastinum or thorax may be necessary.

While most adults with anterior mediastinal mass will be asymptomatic, 70% of children will manifest symptoms [117]. Typical symptoms include dyspnea, cough, and stridor. Children may prefer to sleep in the lateral, semi-erect, or even upright position. Symptoms that may be associated with increased risk of anesthetic complications include orthopnea, upper body edema, or compression of trachea, bronchus, or great vessels [113,116,118,119].

Imaging of the mass is mandatory before an elective anesthetic. Chest radiograph may reveal a widened mediastinum, but CT is needed to demonstrate the size of the mass and the presence and severity of tracheal or great vessel compression (Figs 26.14–26.16). Angiography or echocardiography may be indicated for further evaluation of vascular compression. Greater than 50% compression of the trachea is associated with obstruction during induction of anesthesia [118]. The size of the tumor, as defined by mediastinal mass ratios, equal to the maximal width of the mass divided by the maximal

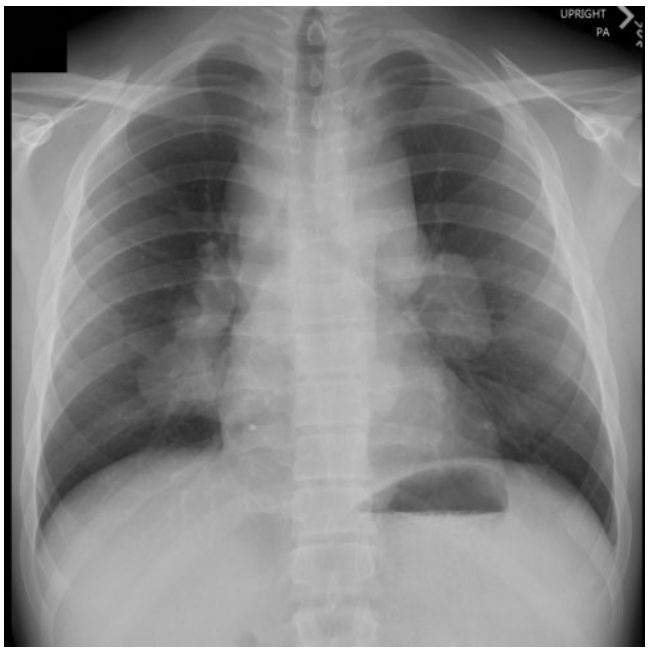

Figure 26.14 Chest radiograph of a 7-month-old patient with anterior mediastinal mass.

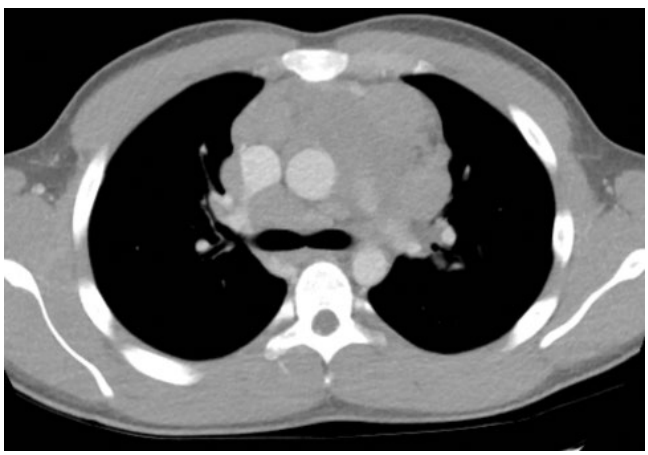

Figure 26.15 Chest CT of a 7-month-old patient with anterior mediastinal mass, showing compression of the trachea.

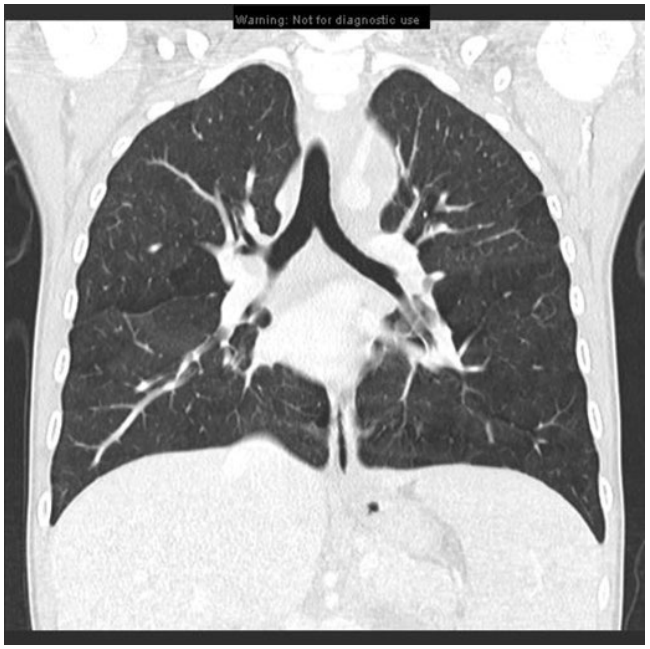

Figure 26.16 Chest CT of a 10-year-old patient with anterior mediastinal mass. There is no visible compression of the trachea.

width of the thorax, has also been shown to correlate with tracheal compression and the development of airway obstruction [110]. One risk stratification system is displayed in Table 26.3 [120].

Pulmonary function tests (PFTs) are commonly ordered with the thought that a decreased peak expiratory flow rate (PEFR) or an increased mid-expiratory plateau when changing from upright to supine position is indicative of variable intrathoracic airway obstruction and a risk for airway collapse during induction of anesthesia [114,121]. Most studies fail to show any correlation between PFTs and degree of airway narrowing [118,121,122] or correlation between a decrease in any specific preoperative PFT and postoperative morbidity [123]. However, flow-volume studies may demonstrate dynamic compression of the airways which may not have been identified on CT.

The first consideration in determining an anesthetic plan is whether the proposed procedure is diagnostic or therapeutic. Diagnostic procedures such as bone marrow biopsy or CT- or ultrasound-guided biopsy of peripheral lymph nodes can be done with local anesthesia alone or with minimal sedation in most children. Ketamine (along with an antisialogog) has the advantage of maintaining hemodynamics in patients with cardiovascular compromise. Respiratory complications are still common, however, even when general anesthesia is avoided [116]. Elective procedures requiring general anesthesia should be delayed until chemotherapy and/or radiation has reduced the size of the mediastinal mass. If tissue diagnosis is necessary prior to chemo/radiation therapy, efforts to proceed under local anesthesia should be made [124]. Therapeutic procedures obviously necessitate general anesthesia.

Anesthesia protocols developed for anterior mediastinal masses in adults [125], using techniques such as awake fiberoptic intubations, are not practical in pediatric patients [121,126] and are dependent on available resources such as cardiopulmonary bypass and radiation therapy. There are, however, anesthetic strategies that can be generally applied (Fig. 26.17).

Before proceeding with general anesthesia, equipment and personnel should be immediately available to perform rigid bronchoscopy. Induction of general anesthesia should be done while maintaining spontaneous ventilation. This can be accomplished by inhalation induction with a volatile anesthetic. The addition of CPAP may help maintain airway patency and prevent atelectasis. Some patients may require induction in the semi-reclined or upright position. Because the loss of airway muscle tone can lead to complete airway obstruction, negative thoracic airway pressure should be maintained and neuromuscular blocking agents should be avoided. Intubation should be accomplished while maintaining spontaneous ventilation.

In the event of airway collapse, maneuvers that may help alleviate obstruction include:

- changing the position of the patient to lateral, recumbent, or prone
- intubating the patient or advancing the endotracheal tube past the obstruction
- rigid bronchoscopy followed by endotracheal tube placement under direct vision or double-lumen tube placement to the most patent bronchus.

Some institutions advocate having a means of cardiopulmonary bypass (CPB) on standby. While there are several reports of patients successfully placed on ECMO or CPB, in each case this was done before the induction of anesthesia [127–131]. We could find no published reports of patients successfully placed on support after the induction of anesthesia with CPB previously available only on standby. Even with a team ready and a primed bypass machine, by the time the

Table 26.3 Risk stratification system for pediatric patients with anterior mediastinal mass

	Low risk	Intermediate risk	High risk
Signs	No radiographic airway compression No cardiac or vascular compression	• Mild tracheal compression <70% • No bronchial compression	• Tracheal • compression >70% • Tracheal CSA <70% with bronchial compression • Great vessel compression • Tamponade physiology on ECHO
Symptoms	None	Mild to moderate postural	Orthopnea Stridor or cyanosis

CSA, cross-sectional area; ECHO, echocardiography.
Source: Reproduced from Pearson and Tan [120] with permission of SAGE.

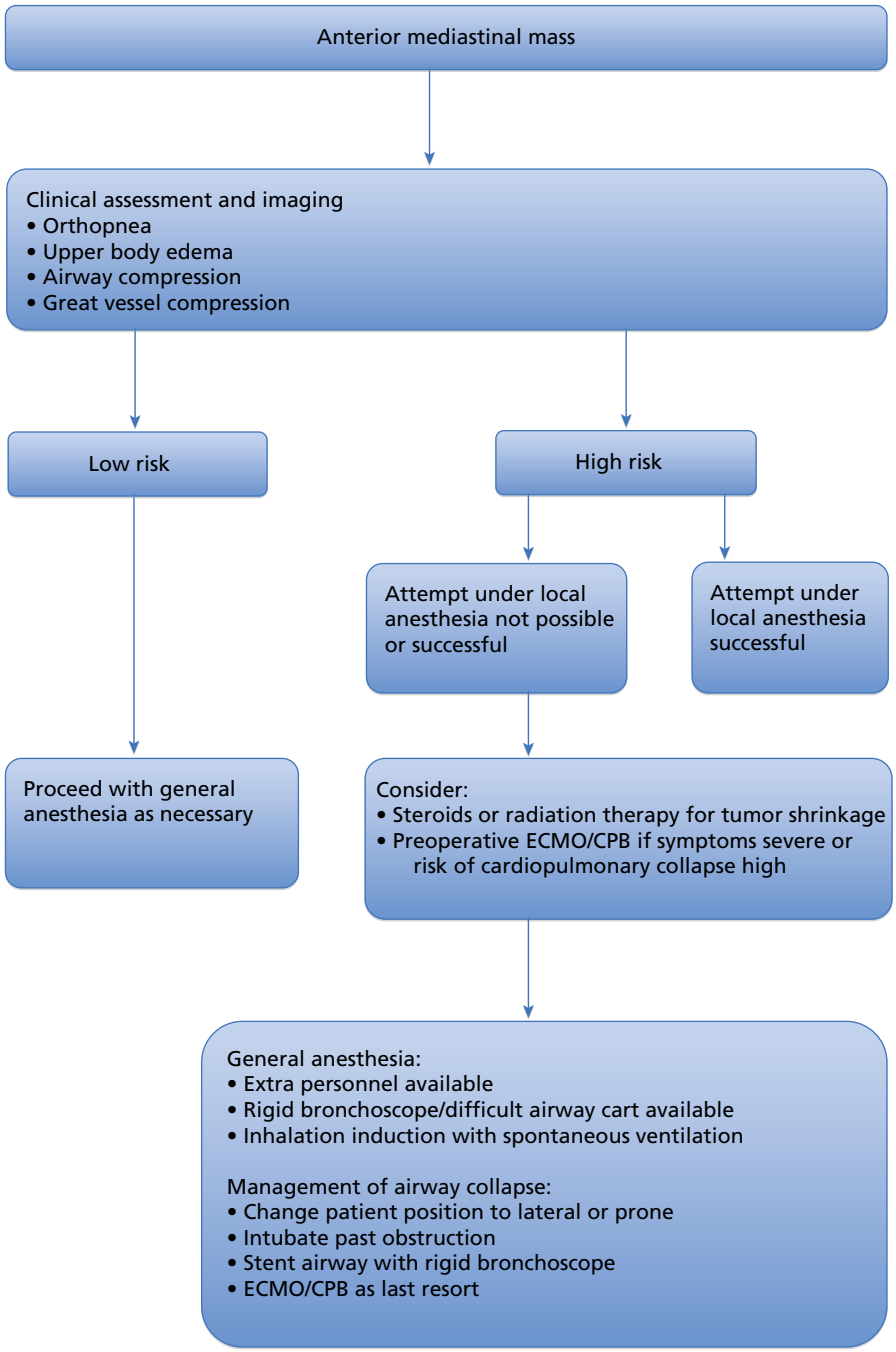

Figure 26.17 An algorithm for management of anterior mediastinal mass.

patient is cannulated and circulation restored, the patient will likely suffer neurological injury [116]. Therefore one should not consider CPB as a reasonable salvage plan. If the risk of cardiopulmonary collapse during induction is high, the patient should be placed on CPB before induction.

For patients presenting for thoracotomy for mediastinal mass resection or open biopsy, thoracic epidural or paravertebral block are excellent techniques to reduce the need for intravenous opioids and maintain spontaneous ventilation [132]. Postoperative symptoms may be worse after surgery, particularly after a biopsy procedure with the adverse effects of anesthesia without the benefit of resection [115]. Surgical complications may also include phrenic or recurrent laryngeal nerve damage.

Pectus excavatum

Pectus excavatum is the most common chest wall deformity. It is a congenital defect, the result of excessive growth of the costochondral cartilages leading to the inward depression of the sternum. It comprises 90% of chest wall deformities with an incidence of approximately 1 in 1000 and a male preponderance (4:1). Pectus carinatum (pigeon chest) comprises most of the remaining chest wall deformities. Pectus excavatum is sometimes associated with connective tissue disorders such as Ehlers–Danlos and Marfan syndrome. As many as 50% of pectus excavatum/carinatum patients have a family history of pectus deformity [133].

The severity of the lesion varies widely, from mild asymptomatic cases to severe deformities associated with

distortion of the heart and great vessels (Figs 26.18, 26.19). Lung compression can lead to respiratory compromise and can be associated with chronic airway obstruction and large negative inspiratory pressures. Compression of the stomach can lead to appetite loss and impairment of weight gain [134,135]. Most symptoms worsen with adolescence, and more than half of adults have some physical complaints [136]. Psychological complaints are also not uncommon [133]. Cardiorespiratory complaints can be resolved with surgery [137].

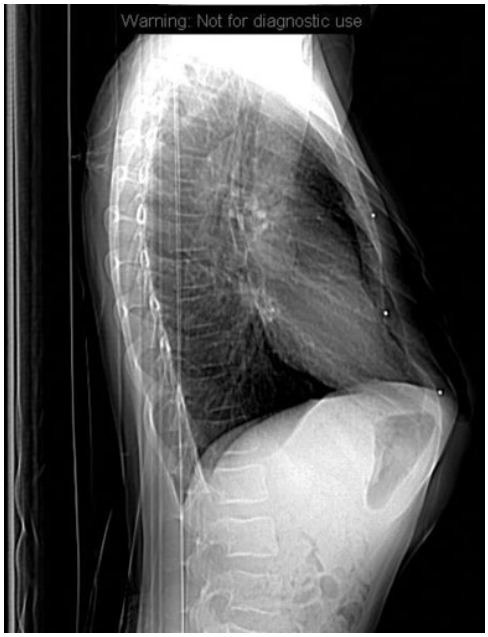

Figure 26.18 Chest radiograph of a 12-year-old patient with pectus excavatum.

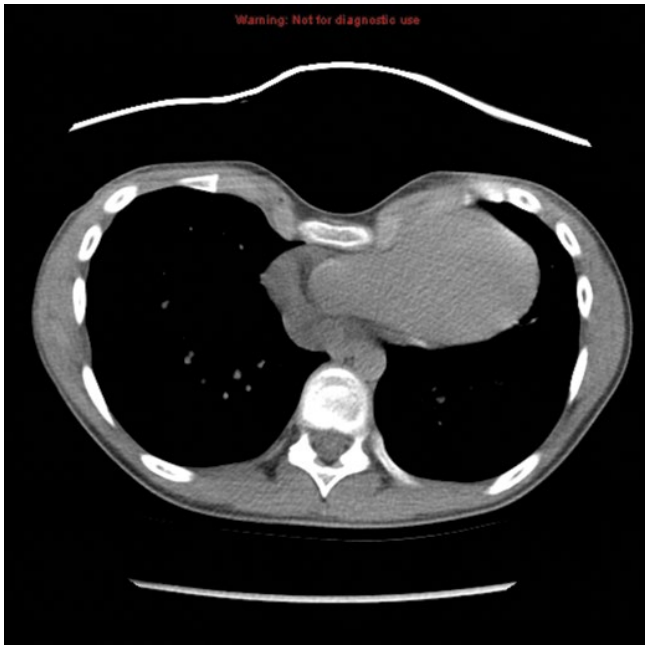

Figure 26.19 Chest CT of a 12-year-old patient with severe pectus excavatum showing cardiac compression.

Diagnosis of pectus excavatum is made by physical examination. Scoliosis is sometimes also seen, particularly in female patients. Many patients have a murmur from compression of the chest wall onto the right ventricle or from mitral valve prolapse [138]. Characteristic ECG findings include a negative P wave in V1, negative T wave in V1 to V2 or V4, and incomplete bundle branch block [136].

Surgical repair is typically delayed until late childhood to allow calcification of the sternum and ribs. Techniques have evolved from rib resection to external traction to cartilage resection, sternal osteotomy, and internal fixation [139]. A new minimally invasive procedure reported by Nuss et al in 1998, in which a preformed convex steel bar is inserted through bilateral thoracic incisions under the sternum and then turned to elevate the sternum, has gained acceptance as the preferred method of repair [140]. It is associated with shorter operative time, smaller incisions, less dissection, and less blood loss than the traditional Ravitch procedure and is successful 92% of the time compared to 70% for the Ravitch procedure [139]. Pneumothorax is common but resolves spontaneously in nearly all cases [139,140]. Less common complications include cardiothoracic injuries, dysrhythmias, pleural effusions, hemorrhage, subcutaneous emphysema, and bar infection [140,141].

Preoperative concerns include possible heart compression, right ventricular outflow tract obstruction, dysrhythmia, scoliosis, and V/Q mismatch. Studies to help delineate the severity of disease include chest radiograph, CT, ECG, and possibly echocardiography. Positioning can be a challenge, and placing patients' arms in arthroscopy slings instead of over the head can help reduce the incidence of brachial plexus injuries [142]. Arterial blood pressure monitoring may be of benefit in patients with cardiac disease. Both the Ravitch and Nuss procedures are painful, and postoperative pain control can be a challenge [143]. Epidural analgesia is effective [144–146] and superior to patient-controlled analgesia [146,147]. A systematic review of six studies (three prospective randomized controlled studies and three retrospective comparison studies) in 430 patients concluded that pain scores were modestly lower with epidural analgesia immediately after surgery (0.5–1 points on a 10-point visual analog scale), through 48 h postoperatively [148]. There were no significant differences with regard to side-effects, complications, operating room time, or length of hospital stay.

Clonidine is an effective alternative to epidural opioids with fewer side-effects [44] and there may even be a role for perioperative hypnosis [149].

Empyema

Empyema, or pleural space infection, is a complication of bacterial pneumonia. Historically, only 0.6% of admissions for pneumonia progressed to empyema [150] but the incidence is rising and more virulent strains of resistant organisms are implicated [151,152]. Empyema should be considered in any child with pneumonia. There is neither much consensus nor evidence on the best treatment of pleural infections, mostly because there are few prospective randomized controlled studies [152,153]. Options range from conservative

therapy with antibiotics to thoracocentesis, chest tube drainage, fibrinolysis, and finally surgical intervention [152].

Empyema evolves over three stages [154]:

1. exudative, in which fluid is thin with low cellular content and easily aspirated
2. fibrinopurulent, in which there is accumulation of leukocytes, fibrin deposition, and loculation
3. organized, with the formation of a thick fibrous peel causing lung entrapment.

During this last stage, drainage alone is ineffective in re-expanding the lung, and decortication may be necessary. The exudative stage can be as short as 24 h, the fibrinopurulent 2–10 days, while the organizing stage generally lasts between 2 and 4 weeks [155].

Pleural fluid analysis has long been used to stage empyema based on leukocytes, lactate dehydrogenase (LDH), glucose, and pH, but these criteria, developed for adult patients, have not been validated in pediatric patients [152]. Chest radiograph is not specific for diagnosis or staging. CT scanning is a useful tool for the diagnosis and evaluation of empyema with respect to consolidation, loculation, and pleural thickening (Figs 26.20, 26.21). Ultrasound has the advantage of being portable, benefiting those unable to undergo CT. It can estimate the size of effusion, show pleural thickening or loculi, and guide chest tube insertion.

Initial treatment for pleural infection is uncontroversial and consists of intravenous antibiotics, analgesics, and antipyretics. Effusions that are enlarging and/or compromising respiratory function should not be treated with antibiotics alone, but need drainage. The dilemma is which treatment option should follow next. The options include: (1) thoracocentesis, (2) thoracostomy tube drainage without or (3) with fibrinolysis, or (4) surgery. Tube drainage is recommended over repeated taps for larger pleural infections, especially for younger children who will not tolerate thoracocentesis

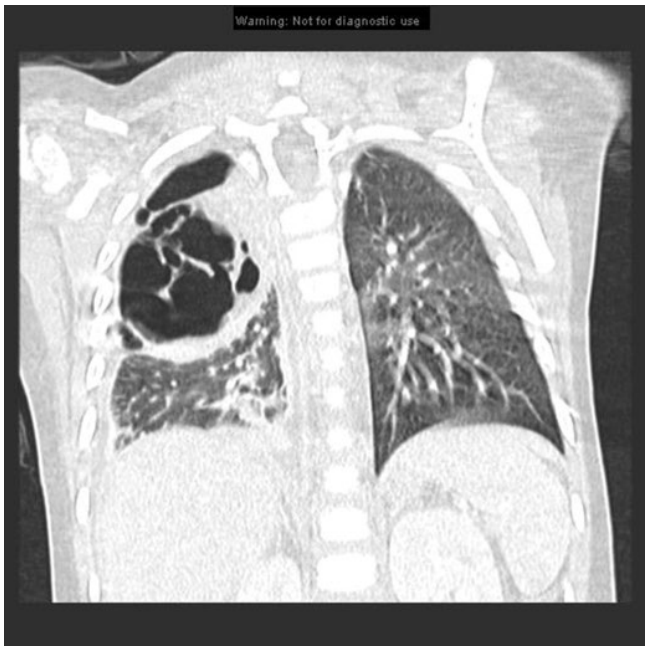

Figure 26.20 Chest CT of a 2-year-old patient with empyema, coronal view.

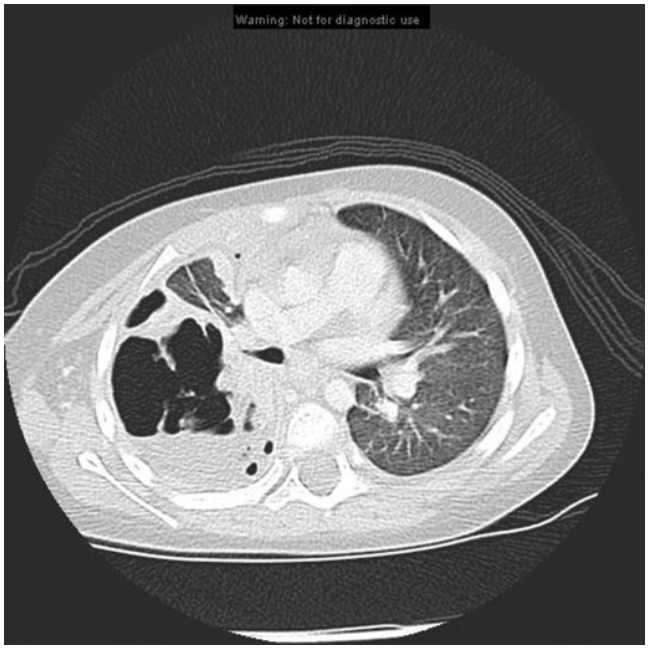

Figure 26.21 Chest CT of a 2-year-old patient with empyema, transverse view.

under local anesthesia alone. Intrapleural fibrinolytics may lyse fibrinous strands in a loculated empyema, leading to improved pleural drainage and successful outcomes without surgery in up to 90% of cases [156]. Failure of chest tube drainage, fibrinolytics, and antibiotics should, however, prompt surgical intervention.

Surgical management of empyema consists of VATS, minithoracotomy, or open thoracotomy. Patients who undergo thoracotomy and debridement versus chest tube placement may have earlier resolution of fever and shorter hospitalization [152], but the procedure is associated with significant morbidity [157]. VATS is less traumatic than open thoracotomy and has been advocated by many, but is more likely to be effective when used early (within 1 week of diagnosis) in the course of empyema [155]. A small prospective randomized trial of 18 patients studying VATS versus thoracostomy drainage showed that hospital length of stay, number of chest tube days, opioid use, and number of radiographic and interventional procedures were all less in patients receiving VATS [158]. Several meta-analyses showed that primary operative therapy is associated with shorter hospital length of stay [159–162] and lower failure rate (by 11-fold) when compared to non-operative treatment [159]. Patients with necrotizing pneumococcal pneumonia or preoperative ICU admission, however, are more likely to have complications and prolonged admissions after thoracoscopy [163]. A recent systematic review of six randomized controlled studies in children of VATS versus open thoracotomy revealed no difference in mortality, but shorter hospital stay by 2.5 days and significantly fewer procedural complications (by 54%) with VATS [164].

Patients who are treated conservatively (tube thoracostomy) for an extended period of time may have an empyema that was initially treatable by VATS progress to the organized stage, when open thoracotomy is likely the only viable treatment. Treatment with VATS should be done early while empyema is still in the fibrinopurulent stage.

For this reason, many now advocate VATS as initial therapy before tube thoracostomy [165]. There is, however, no clear single therapy strategy for all patients. Each must be evaluated based on stage of the disease and therapeutic recourses available.

KEY POINTS: ANTERIOR MEDIASTINAL MASS, PECTUS EXCAVATUM, AND EMPYEMA

- High-risk features of anterior mediastinal mass include orthopnea, upper body edema, airway compression, great vessel involvement, and cardiac tamponade
- Pectus excavatum is repaired by the minimally invasive Nuss bar procedure; pain management via epidural or patient-controlled analgesia is equally effective
- Empyema treatment with VATS results in shorter hospital stay and fewer complications versus open thoracotomy

Anesthetic technique for patients with empyema will depend on the procedure performed. Many patients will tolerate pleurocentesis or tube thoracostomy placement with local anesthesia or minimal sedation. VATS or thoracotomy may necessitate OLV. Good postoperative pain control is necessary to allow the patient adequate lung re-expansion postoperatively. A paravertebral block or a thoracic epidural should be considered in non-septic patients requiring a thoracotomy.

Conclusion

Over the course of this chapter we reviewed the pathophysiology of OLV, discussed the anesthetic practice and equipment necessary to facilitate the perioperative management of the pediatric thoracic surgery patient, including analgesia for thoracic surgery, and finally discussed in a little more detail some of the finer nuances of certain specific thoracic surgical challenges within the pediatric population, namely lobectomy, pneumonectomy, congenital cystic lung disease, anterior mediastinal mass, pectus excavatum, and empyema.

CASE STUDY

A 14-year-old otherwise healthy girl presents for VATS for biopsy of a mediastinal mass.

- What additional information would you want to know at this point? *Additional information should include a detailed history, physical examination, and review of radiological studies with specific emphasis on evaluation of airway and vascular compression.*

The patient presented with a 6-week history of cough, increasing shortness of breath, and wheezing. After failed antibiotic treatment for suspected pneumonia, symptoms progressed to dyspnea and then orthopnea. A chest radiograph showed anterior mediastinal mass and CT showed a mass obstructing approximately one-third of the distal trachea.

- Would you proceed to surgery? *No. There are alternatives to proceeding with general anesthesia for thoracoscopy. A tissue diagnosis can often be made from a lymph node biopsy with local anesthesia. Alternatively she can receive radiation therapy until the mass is no longer compressing the bronchus and she is asymptomatic.*

Lymph node biopsy under local anesthesia was unsuccessful and the oncologist wanted a tissue diagnosis prior to initiating radiation therapy.

- How would you induce anesthesia in this patient? *First, the proper equipment and personnel must be available, including a difficult airway cart, rigid bronchoscope, and personnel trained in its use. We would perform an inhalation induction maintaining spontaneous ventilation then place an endotracheal tube under deep inhalational anesthesia, avoiding the use of muscle relaxation.*
- You are having difficulty ventilating the patient, what would you do next? *The anesthesiologist would first try to position the patient on her side. If this failed to relieve the obstruction, we would advance the endotracheal tube in an attempt to stent past the obstruction, even to the point of endobronchial intubation. Finally, the available otolaryngologist could perform rigid bronchoscopy to stent the airway.*
- The obstruction was relieved by advancing the endotracheal tube slightly. What other intraoperative and postoperative considerations need to be considered? *Maintenance of spontaneous ventilation for the remainder of the case with judicial use of opioids would be prudent. The patient should be extubated awake in the operating room and admitted to the pediatric ICU for close postoperative monitoring and early intervention if needed.*

Acknowledgments

The authors would like to thank Teresa Chapman from the Department of Radiology, Seattle Children's Hospital, for her assistance in acquiring radiographic images.

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 27
Anesthesia for Congenital Heart Disease

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Introduction

Congenital anomalies comprise the largest diagnostic category among the causes of infant mortality in the United States [1]. Structural heart disease leads the list of congenital malformations. Approximately 4 million children are born each year in the United States and nearly 40,000 of these have some form of congenital heart disease (CHD). Approximately half of these children present for therapeutic intervention within the first year of life, and the vast majority of them require care by an anesthesiologist.

Initial reports of anesthetic mortality ranging from 3% to 10% in operations for CHD indicated a significant risk of anesthesia in this patient population [2,3]. However, the principles and techniques of pediatric anesthesia presented in this volume allow one to anesthetize CHD patients with minimal anesthetic mortality and morbidity [4–6]. This low anesthetic risk is predicated not only on adherence to these principles but also on an understanding of the pathophysiological circumstance of each patient and the nature of the planned surgical procedure. Implicit in all surgical procedures are potential complications that anesthesiologists, by virtue of their primary role in monitoring and maintaining vital functions, are able to identify and treat. For cardiac surgery, knowledge of specific problems related to each type of cardiac repair helps to identify complications during the post-bypass and postoperative periods, as well as later complications that affect subsequent anesthesia for non-cardiac procedures. The diagnostic information now available intraoperatively, in the form of intracardiac pressures and oxygen saturations as well as echocardiographic diagnoses, provides the pediatric cardiac anesthesiologist with the opportunity and responsibility to assess the adequacy of surgical intervention and its impact on hemodynamics.

This chapter describes general principles relevant to anesthesia for children with CHD. It does not present care

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

protocols for individual cardiac defects. The pathophysiology is presented as it relates to principles of management, patient assessment, selection and application of an anesthetic regimen, and specific cardiac lesions and procedures. Knowledge of these principles should permit safe administration of anesthesia to children with CHD undergoing both cardiac and non-cardiac operations. Optimal management will occur when the anesthesiologist regularly becomes involved in the care of these patients and has special insight and rapport with the entire cardiovascular staff, such that care is provided by a cohesive team in a smooth continuum from the preoperative preparation and diagnosis through postoperative discharge.

Pathophysiology of congenital heart disease

Principles of management

The pathophysiological consequences of CHD are derived primarily from anatomical circumstances that produce abnormalities of flow: outflow obstruction, regurgitant lesions, shunt lesions, and common mixing lesions. In more complex lesions, shunts and obstructions may occur in combination. The pathophysiology of the most common purely obstructive lesions occurring outside the neonatal period is comparable to adult disease (e.g. aortic and mitral valve stenosis) and is not extensively reviewed here. Regurgitant lesions rarely exist as pure primary congenital defects except in Ebstein malformation of the tricuspid valve, in which a regurgitant volume flows back through the tricuspid valve and is directed across the patent foramen ovale to produce cyanosis and varying degrees of heart failure. Regurgitant lesions produce a volume-overload circulation with progressive ventricular dilation and failure. This is seen most commonly in regurgitation associated with atrioventricular canal defects, semi-lunar valve incompetence as seen in tetralogy of Fallot with absent pulmonary valve, in truncal valve regurgitation in truncus arteriosus, or after interventions for aortic stenosis. Much of the remaining pathophysiology of CHD can be best understood by characterizing lesions with regard to the nature and magnitude of the shunt and the interaction of these shunts with obstructive lesions. Understanding the interactions of the various types of shunts and obstructions simplifies the variety of congenital heart lesions.

Many congenital heart lesions alter pulmonary blood flow and have intracardiac shunts with some degree of pulmonary and systemic venous blood mixing. Varying degrees of hypoxemia may occur. These pathophysiological mechanisms alter the volume and pressure load of the heart as well as cardiovascular development. Although such acquired developmental abnormalities may be adaptive, they can also further compound the effects of the original CHD. The resultant cardiac and pulmonary vascular structural changes may become as important as the pathophysiology of the original heart defects (e.g. severe left ventricular hypertrophy, seen with coarctation of the aorta, and right ventricular hypertrophy with progressive outflow obstruction, seen with tetralogy of Fallot). However, the intracardiac shunting and alterations in pulmonary blood flow comprise the major unique problems encountered with CHD. These problems complicate the task of administering adequate anesthesia while maintaining normal cardiac output and oxygen transport.

Shunt lesions

Cardiac shunting is the process whereby venous return of one circulatory system flows to the arterial outflow of the same circulatory system without passing through a capillary bed. Flow of blood from the systemic venous (right) atrium (RA) to the aorta produces recirculation of systemic venous blood. Flow of blood from the pulmonary venous (left) atrium (LA) to the pulmonary artery (PA) produces recirculation of pulmonary venous blood. Recirculation of pulmonary venous blood produces a physiological left-to-right (L-R) shunt, whereas recirculation of systemic venous blood produces a physiological right-to-left (R-L) shunt. A physiological R-L or L-R shunt is often the result of an anatomical R-L or L-R shunt. In an anatomical shunt, blood moves from one circulatory system to the other via a communication orifice at the level of the cardiac chambers or great vessels. Physiological shunts can exist in the absence of an anatomical shunt. Transposition physiology is the primary example of this process.

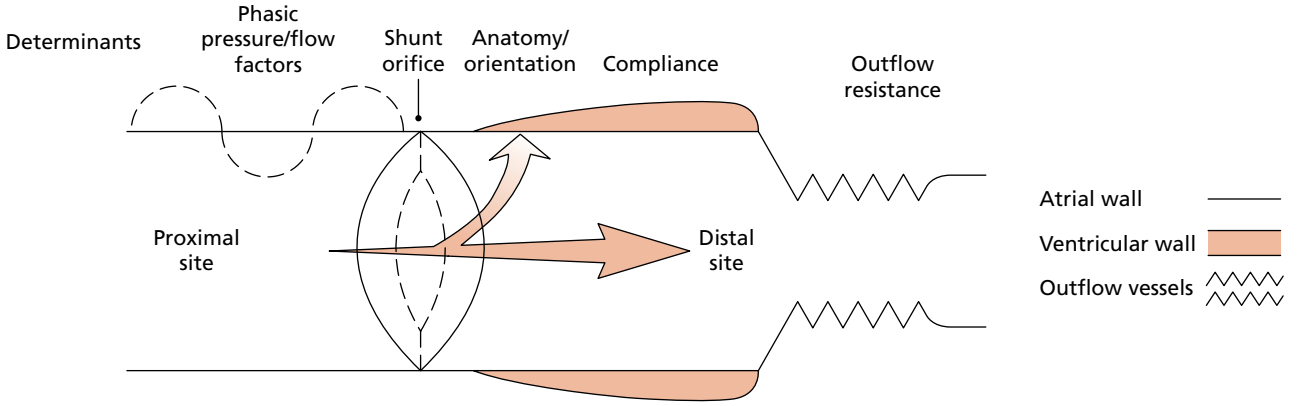
Shunts may occur alone as simple shunts (e.g. a ventricular septal defect (VSD)) or with complicating obstructive lesions in complex shunts such as tetralogy of Fallot. The direction and magnitude of shunts are variable, both within each cardiac cycle and as a consequence of anesthesia and operative manipulation of the heart, great vessels, and lungs, potentially destabilizing the circulation.

The hemodynamics in intracardiac shunts are complex and depend on many factors that determine shunt magnitude and direction (Fig. 27.1). Complete description of the dynamics of a particular shunt requires more data than are usually clinically available. The determinants of shunting may change considerably during anesthesia and operative manipulations without being readily measurable. Nevertheless, the concepts of control of shunting outlined here are useful during the perioperative period when it must be decided which shunts are hemodynamically significant and which are subject to intraoperative change.

Shunt orifice and outflow resistance are the most important determinants of shunting, particularly in ventricular and great vessel shunts. Ventricular compliance may also be important particularly with atrial level shunts. To simplify this discussion, ventricular compliance as a determinant of shunting is not further considered.

Simple shunts

Simple shunts are shunts without a fixed obstruction to outflow distal to the vessels or chambers involved in the shunt. Outflow resistance is determined by the pulmonary vascular resistance (PVR) on the right side and systemic vascular resistance (SVR) on the left side of the heart (Fig. 27.2). The effects of SVR and PVR on the magnitude of the shunt are small when the shunt orifice is small and a large pressure gradient exists across the shunt. These shunts are considered restrictive. The effects of shunt orifice and vascular resistances on simple shunts are outlined in Table 27.1. A simple shunt is non-restrictive when there is no pressure gradient across the shunt. The direction and magnitude of a non-restrictive shunt is dependent on the relative differences in the PVR and SVR. When the communication becomes large enough, the structures connected by the shunt effectively become a common chamber and complete mixing occurs.



Level	Potential effect on shunt				
Atria	Large	Large	Small	Large	Possible with high PVR
Ventricles	Conduction related	"	Moderate	Small	Large
Great vessels	Conduction related	"	Moderate	NA	Large

Figure 27.1 Effects of the many determinants on central cardiac shunting at various levels. PVR, pulmonary vascular resistance. *Source*: Reproduced from Berman [353] with permission from Wolters Kluwer.

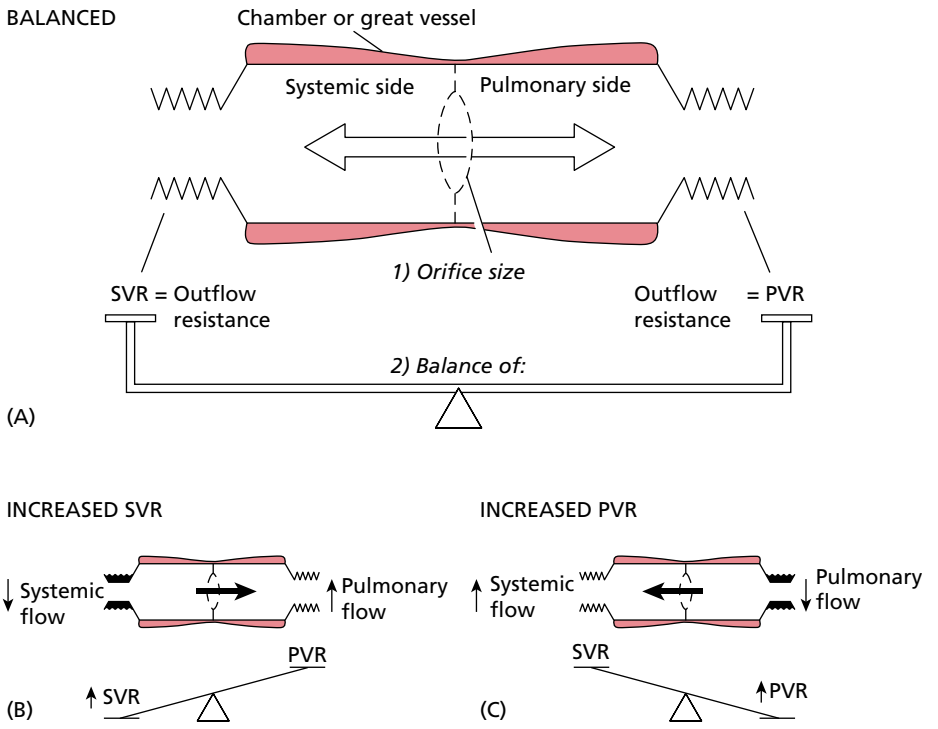


Figure 27.2 Determinants of the magnitude and direction of simple central shunts. (A) Balanced pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR). (1) Orifice size, generally fixed, is important for determining the magnitude of shunting and the pressure gradient across a shunt. (2) Balance of PVR and SVR is dynamic and determines the direction of shunt and variations in magnitude around the limits fixed by the orifice size. (B) Increased pulmonary flow with increased SVR. (C) Increased systemic flow with increased PVR. *Source*: Reproduced from Hickey and Wessel [354] with permission from Elsevier.

A number of factors affect PVR/SVR. Some are relatively fixed whereas others are variable and dynamic. Simple shunting can change intraoperatively as dynamic factors change. Shunting may be manipulated to varying degrees depending on the size of the communication and the ability to alter the dynamic portions of the PVR and SVR. Non-restrictive shunts with a large orifice are more amenable to manipulation of the SVR and PVR. Because normal PVR is often much less than SVR (as little as 5% of SVR in older children and adults), pulmonary blood flows can become large with a non-restrictive simple shunt, even during the neonatal period when the PVR is relatively high.

Complex shunts

A complex shunt has a fixed obstruction distal to the shunt (Fig. 27.3). A fixed outflow obstruction can be present at the

Table 27.1 Simple shunts, no obstructive lesions

Restrictive shunts (small communications)	Non-restrictive shunts (large communications)	Common chambers (complete mixing)
Large pressure gradient	Small pressure gradient	No pressure gradient
Direction and magnitude more *independent* of PVR/SVR	Direction and magnitude more dependent on PVR/SVR	Bidirectional shunting
Less subject to control	More subject to control	Net Qp/Qs totally depends on PVR/SVR
Examples: small VSD, small PDA, Blalock shunts, small ASD	*Examples:* large VSD, large PDA, large aortopulmonary shunts	*Examples:* single ventricle, truncus arteriosus, single atrium

PDA, patent ductus arteriosus; PVR, pulmonary vascular resistance; Qp, pulmonary blood flow; Qs, systemic blood flow; SVR, systemic vascular resistance; VSD, ventricular septal defect.

level of the ventricular outflow tract (subvalvular, valvular, or supravalvular), or in major vessels such as the pulmonary artery or aorta. Resistance caused by the fixed obstruction is additive to resistance across the shunt and resistance of the downstream vascular bed (PVR/SVR). If the fixed outflow obstruction is large, the resultant shunting away from the obstructed side is substantially affected by the fixed obstruction and is less dependent on the downstream vascular bed. This is particularly true for the right side of the circulation, where normal PVR is low compared with the resistance of most right-sided obstructive lesions. For example, in tetralogy of Fallot with severe pulmonary stenosis, a component of the R-L shunting across the VSD is fixed by the pulmonary valve stenosis, but an additional variable component of shunting may be due to variations in PVR or, more commonly, dynamic infundibular obstruction in the right ventricular outflow tract. Dynamic changes in variable portions of the total right-sided outflow obstruction may increase or decrease the total amount of R-L shunting, thereby increasing or decreasing cyanosis. Right-to-left shunting in the baseline state when the dynamic obstructive components are minimal is determined largely by the fixed pulmonary stenosis. These statements presume a constant SVR and cardiac output; large changes in SVR, of course, change shunting by altering the other side of the balance (Fig. 27.3). Characteristics and examples of complex shunts are listed in Table 27.2.

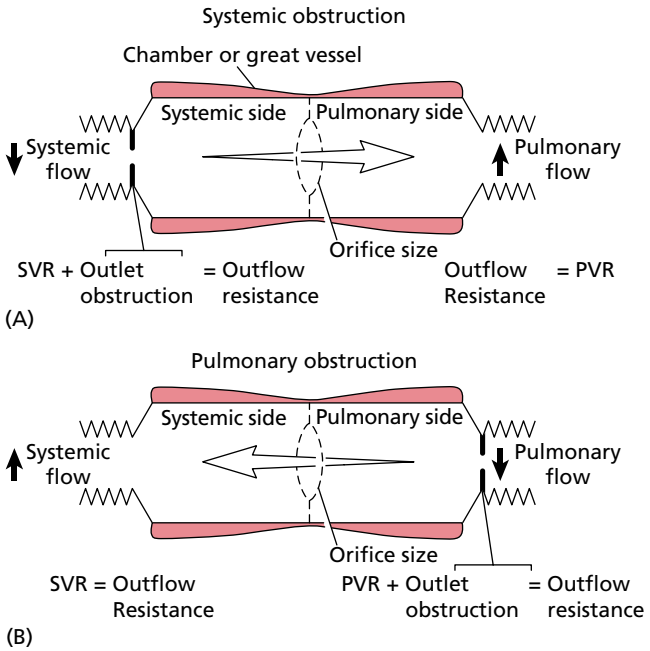


Figure 27.3 Determinants of complex shunting with (A) systemic or (B) pulmonary outflow obstruction. Orifice size limits the magnitude of the shunt. Outflow resistances are balanced by outlet obstruction on either side of the circulation and by the systemic vascular resistance (SVR) or pulmonary vascular resistance (PVR). Addition of outlet obstruction increases flow on the opposite side and decreases flow on the same side. *Source*: Reproduced from Hickey and Wessel [354] with permission from Elsevier.

Complete obstruction and shunts

When obstruction to central outflow of blood becomes complete as in tricuspid atresia, pulmonary atresia, or aortic atresia, shunting across communications proximal to the obstruction becomes total and obligatory. This type of shunting must be associated with another downstream shunt that provides flow to the obstructed side of the circulation. An example of a downstream shunt is a patent ductus arteriosus (PDA) which provides pulmonary blood flow when pulmonary valvular atresia is present or provides systemic blood flow when aortic valvular atresia is present. The downstream shunting is variably dependent on PVR/SVR, depending on the restrictive nature of the shunt orifice.

Table 27.2 Complex shunts (shunt and obstructive lesion)

Partial outflow obstruction	Total outflow obstruction
Shunt magnitude and direction largely fixed by obstructions	Shunt magnitude and direction totally fixed
Shunt depends less on PVR/SVR	All flow goes through shunt
Orifice and obstruction determine pressure gradient	Pressure gradient depends on orifice
Examples: tetralogy of Fallot, VSD and pulmonary stenosis, VSD with coarctation	*Examples:* tricuspid atresia, mitral atresia, pulmonary atresia, aortic atresia

PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

Manipulation of pulmonary and systemic resistance

Alterations in PVR and SVR allow some measure of control over shunting. Manipulation of PVR is particularly important because of the frequency of right-sided defects in CHD with disturbances in pulmonary blood flow. PVR can be decreased to improve pulmonary blood flow and right heart function or increased to improve systemic blood flow when pulmonary blood flow is excessive. Intraoperative events including sympathetic stimulation, encroachments on lung volumes that produce atelectasis (surgical retraction, pleural and peritoneal

collections, abdominal packing), cardiopulmonary bypass (CPB), alveolar hypoxia, and hypoventilation may increase PVR because of the increased reactivity and resistance of the abnormal pulmonary vasculature often found with CHD.

Ventilatory control of pulmonary vascular resistance

The PVR can be controlled independently of the SVR by manipulating various aspects of ventilation (Table 27.3), whereas specific or selective pharmacological control of PVR is difficult unless the pulmonary vascular bed is responsive to inhaled nitric oxide. Even with selective infusions of rapidly metabolized vasoactive drugs into the pulmonary circulation, systemic drug concentrations and systemic hemodynamic effects can be appreciable [7]. In contrast, high levels of inspired oxygen, especially 100% oxygen, decrease elevated PVR in infants without changing (or slightly increasing) SVR, whereas inspired oxygen concentrations of 21% or less increase PVR [8,9]. The effectiveness of oxygen (i.e. hyperoxia) as a pulmonary vasodilator after CPB, however, is unclear [10]. Hypoventilation, with associated acidosis and hypercapnia, also increases PVR (Fig. 27.4) [9]. In contrast, hyperventilation to a pH of more than 7.5 reliably decreases PVR in infants with dynamically vasoconstricted small vessels [11,12]. This maneuver increases pulmonary blood flow and decreases R-L shunting in neonates, increasing the PaO_2

Table 27.3 Manipulations altering pulmonary vascular resistance

Increased PVR	Decreased PVR
Hypoxia	Oxygen
Hypercarbia	Hypocarbia
Acidosis	Alkalosis
Hyperinflation	Normal FRC
Atelectasis	Blocking sympathetic stimulation
High hematocrit	Low hematocrit
Surgical constriction	

FRC, functional residual capacity; PVR, pulmonary vascular resistance.

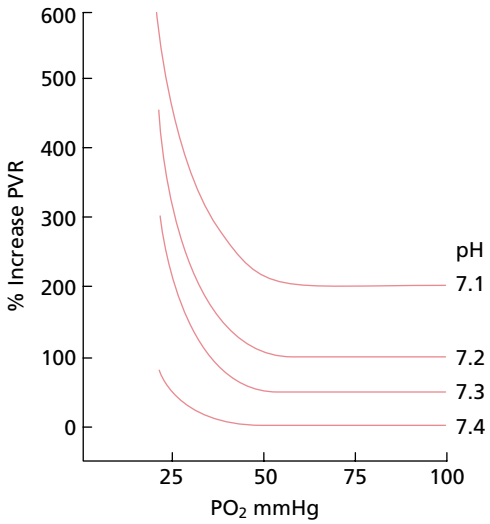


Figure 27.4 Changes in PVR with changes to in PaO_2 and arterial pH. *Source*: Reproduced from Rudolph and Yuan [9] with permissionfrom Journal of Clinical Investigation.

[13,14]. Some caution is required as prolonged hyperventilation to decrease PVR may in theory cause problems from decreased cerebral blood flow. Recent clinical observations support a link between the extent and duration of hypocapnia and development of white matter injury and subsequent neurobehavioral deficiencies in neonates [15].

The pattern of ventilation and use of positive end-expiratory pressure (PEEP) can alter PVR. PVR is lowest at normal functional residual capacity (FRC) and increases at lower lung volumes because of alveolar collapse [16]. The application of PEEP can treat atelectasis and pulmonary edema and lower PVR, however high levels of PEEP may overinflate alveoli and increase PVR. Different patterns of ventilation may further reduce PVR by stimulating production of prostacyclin in the pulmonary vasculature [17,18].

Anesthetics and pulmonary vascular resistance

The direct effects of anesthetic agents on PVR are minimal, however anesthetic agents can attenuate stress responses in the perioperative period and prevent stress-induced increases in PVR. Large doses of synthetic opioids (e.g. fentanyl) attenuate pulmonary vascular responses to noxious stimuli, such as endotracheal suctioning in infants, but they do not change the baseline PVR [19,20]. Reactive hypertensive responses in the pulmonary bed are partially mediated by the sympathoadrenal axis and therefore are attenuated by an adequate depth of anesthesia, usually without changing the baseline PVR. Ketamine and nitrous oxide have been reported to increase PVR in adults, particularly in patients with mitral stenosis, but do not affect the PVR of infants with normal or elevated PVR when ventilation and FiO_2 are held constant [21–23]. A rise in PVR with ketamine given to sedated children spontaneously breathing room air during cardiac catheterization has been noted [24]. However, in a cohort of patients with pulmonary hypertension spontaneously breathing 0.5% sevoflurane, no change in PVR was seen with ketamine administration.

Manipulation of systemic vascular resistance

When deleterious intracardiac shunting cannot be controlled by manipulating PVR, it may be necessary to change SVR. In the presence of a complex shunt with fixed pulmonary outflow obstruction and R-L shunting (e.g. tetralogy of Fallot), an increase in SVR decreases the R-L shunting and increases arterial oxygen saturations [25]. Dynamic increases in infundibular outflow obstruction with tetralogy of Fallot that acutely increase baseline R-L shunting (hypercyanotic spells) can be treated with IV pressor agents, which are shunted right to left directly into the systemic circulation, thus increasing SVR and decreasing R-L shunting.

Increases in systemic arterial pressure (SVR) with pressor agents can increase pulmonary blood flow in the presence of a severely restrictive aortopulmonary shunt (e.g. Blalock–Taussig, Waterston, or Potts shunt) and increase coronary blood flow when coronary perfusion is compromised by low diastolic blood pressure. Use of phenylephrine, norepinephrine, or other α-agonists to maintain high systemic perfusion pressure may be beneficial under these circumstances. Alternatively, partially occluding the aorta with a clamp mechanically increases pressure in the proximal aorta and left ventricle, thus increasing the SVR.

Pulmonary circulation

Alterations in pulmonary blood flow caused by shunting in patients with CHD may produce different problems as the PVR changes with development (Fig. 27.5). These problems include pulmonary vascular occlusive disease and systemic arterial desaturation as well as chronic sequeale from an increased volume load on the heart. Dramatic alterations in pulmonary blood flow are seen during the neonatial period as the transition to adult-type circulation occurs.

Transitional circulation

The transitional circulation of normal neonates can be viewed as a transient form of CHD. Shunting occurs in either direction through the ductus arteriosus and the foramen ovale until these structures functionally, and later anatomically, close. Neonates have high PVR that promotes R-L shunting through the ductus arteriosus and foramen ovale causing hypoxemia (Fig. 27.6). Later, as PVR falls, shunting through the ductus reverses and becomes left to right until the ductus closes anatomically (Figs 27.5 and 27.6).

Neonates may revert to transitional circulation despite previous functional closure of the ductus arteriosus and foramen ovale. Hypoxia, acidosis, hypercapnia, hypothermia, sepsis, and prolonged stress increase PVR and favor return to the transitional circulation pattern. These changes are sometimes seen when neonates undergo major non-cardiac surgery. The degree of reactive hypoxic pulmonary vasoconstriction is much greater in normal newborns than in adults. The resulting high pulmonary artery pressure may exceed aortic pressure and produce intermittent or continuous R-L shunting through a PDA or foramen ovale [26]. Once the period of perioperative stress is over, high PVR returns to age-determined normal levels and the developmental changes resume to functionally eliminate the ductus arteriousus.

Transitional circulation can be continued after birth by maintaining patency of the ductus arteriosus with prostaglandin E1 (see section 'Severe hypoxemia'). In these cases, maintenance of transitional circulation serves a palliative role by providing either adequate pulmonary or systemic flow.

Precapillary pulmonary artery hypertension

In the presence of a non-restricted simple shunt (e.g. a large VSD), blood flow into the lungs increases as PVR falls (Fig. 27.5). The increase in pulmonary artery pressure and volume resulting from such shunts may over time alter pulmonary vascular development and cause precapillary pulmonary artery hypertension (Fig. 27.7) [27,28]. This can occur when a large VSD, atrioventricular canal, transposition of the great arteries, truncus arteriosus, or a large PDA is present. Pulmonary vascular disease can occur even during the first year of life in patients with an atrioventricular canal or in the first weeks of life in those with transposition of the great arteries and VSD [29]. A progressive rise in PVR may lead to chronic R-L shunting and right ventricular failure. In contrast, pulmonary vascular disease takes decades to develop with lesions such as atrial septal defect (ASD), where only flow is increased and pulmonary artery pressures are initially normal [30].

The resistance to flow in pulmonary arteries with pulmonary vascular occlusive disease is increased because of higher smooth muscle content and a reduction in arborization of the pulmonary arteries. The pulmonary vasculature is also more reactive to intraoperative changes in surgical stimuli and stress. Right-to-left shunting may appear or increase dramatically. Minimizing the reactive component of PVR without lowering SVR is often critical in anesthetic management.

Decreased flow in the pulmonary circulation during development can also lead to significant abnormalities in the pulmonary arterial tree. Hypoplasia may result in areas seeing reduced blood flow, and vascular obstructive disease may occur in regions seeing increased blood flow [31]. This is especially true in patients with tetralogy of Fallot and pulmonary atresia, in whom the pulmonary artery anatomy must be addressed early in life.

Arterial oxygen desaturation

Systemic arterial desaturation in CHD is usually from shunting of systemic venous blood directly into the systemic arterial circulation. Pulmonary parenchymal disease can also be

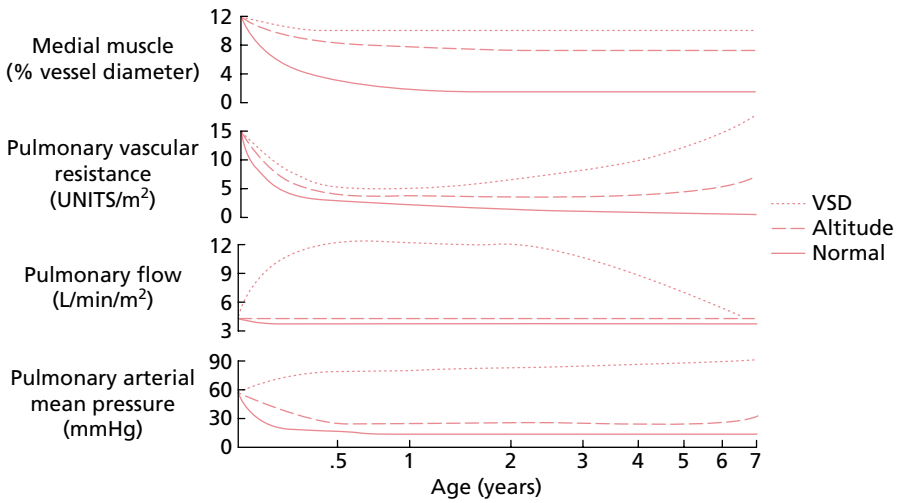


Figure 27.5 Normal and abnormal developmental changes in the pulmonary arterial tree during the first years of life. Pulmonary vascular resistance, arterial smooth muscle (%) and pressure normally decrease during the first year of life. A large, non-restrictive VSD with a large left to right shunt results in an immediate increase in flow and a later increase in vascular resistance. *Source*: Reproduced from Rudolph [355] with permission of John Wiley and Sons.

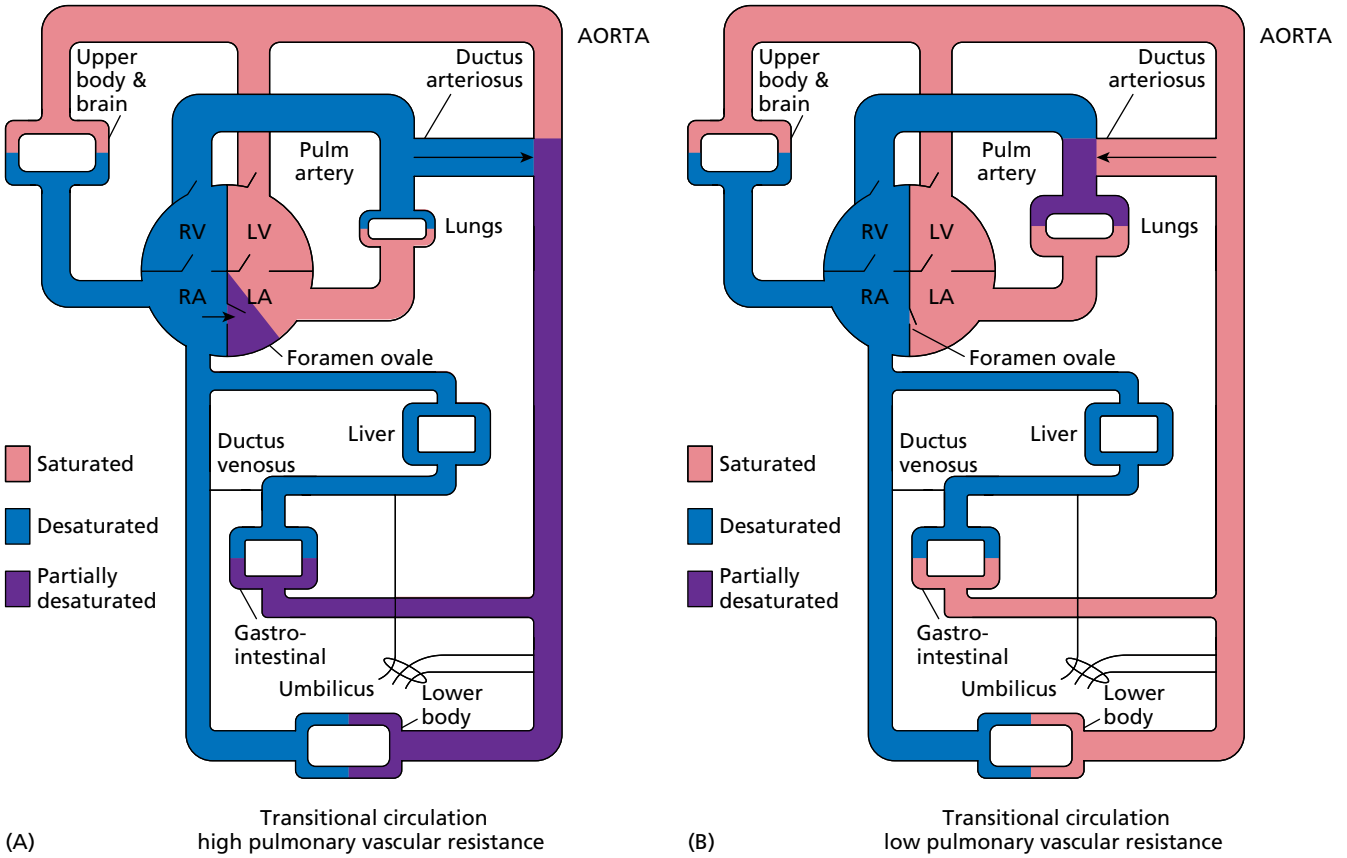


Figure 27.6 Central shunting and blood saturations that occur normally in the transitional circulation during the first few hours and days after birth. (A) During the first few hours, the foramen ovale is widely patent and PVR is high, leading to right-to-left shunting. (B) A second, later stage of transitional circulation occurs when PVR decreases and the ductus arteriosus remains patent, resulting in left-to-right shunting. The foramen ovale is functionally closed. *Source*: Reproduced from Hickey and Crone [356] with permission from Elsevier.

present, making it even more difficult to achieve adequate arterial oxygenation. Shunt-related arterial desaturation can occur when pulmonary blood flow is greater than, equal to, or less than systemic flow. The effects of alterations in pulmonary blood flow on arterial oxygenation in the presence of various shunts are listed in Table 27.4. It is important to realize that an FiO_2 of more than 0.21 has little effect on arterial oxygen tension in the presence of a large R-L shunt since the hypoxemia is caused by a reduction in pulmonary blood flow, but the effect increases as the shunt becomes smaller (Fig. 27.8). This statement presumes no pulmonary parenchymal disease and fully saturated pulmonary venous blood.

Hypoxemia also occurs in situations other than those with a pure R-L shunt with decreased pulmonary blood flow. If systemic and pulmonary venous blood mix in a vascular chamber, arterial desaturation occurs, even though pulmonary blood flow may be normal or increased (Table 27.4). Mixing can occur at any anatomical level: right atrium (e.g. total anomalous pulmonary venous connection), left atrium (e.g. tricuspid atresia), ventricle (e.g. single ventricle), or great vessel (e.g. truncus arteriosus and aortopulmonary window). When mixing is complete and pulmonary blood flow is normal or increased, hypoxemia is mild. When mixing is incomplete, hypoxemia may be severe, as occurs with the parallel circulation seen in patients with transposition of the great arteries.

Many poorly understood adaptations occur in patients with severe hypoxemia to allow acceptable levels of oxygen transport and consumption. Adaptations include erythrocytosis, increases in 2,3-diphosphoglutarate concentrations, systemic vasodilation with increased blood volume, neovascularization, and alveolar hyperventilation with chronic respiratory alkalosis [32]. These and other poorly defined adaptive mechanisms maintain near-normal levels of mitochondrial oxygen utilization at rest without increases in lactate production. Elevated cardiac output and substantial shifts in the oxyhemoglobin dissociation curve are not significant adaptations in patients with severe hypoxemia [33].

These adaptations may be associated with adverse physiological effects. Erythrocytosis increases blood viscosity, vascular resistance, and therefore ventricular afterload, especially in the pulmonary circulation [34]. Increased blood viscosity elevates ventricular afterload so cardiac output decreases, opposing the benefit of erythrocytosis to oxygen-carrying capacity. The net reduction in oxygen delivery is maladaptive and occurs when the hematocrit (Hct) exceeds 60%. Such high Hcts are associated with an appreciable incidence of cerebral and renal thrombosis, which increases with dehydration. This situation makes pre- and postoperative hydration crucial in these patients.

Cyanosis has been implicated in the genesis of coagulation and fibrinolytic defects particularly when secondary erythrocytosis produces a Hct greater than 60%. The majority of studies investigating the effects of cyanosis on hemostasis have been conducted in chronically cyanotic adults and children more than 1 year old. Thrombocytopenia and qualitative

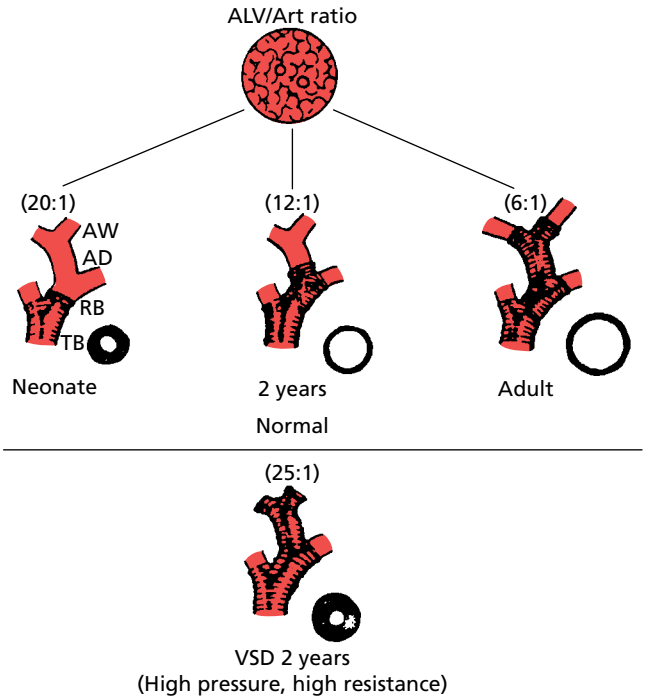


Figure 27.7 Developmental changes in the peripheral pulmonary arterial tree in normal infants and in those with a ventricular septal defect (VSD) and large left-to-right shunt. The alveolar/arteriolar (ALV/Art) ratio decreases with age becasue of extensive arborization of the arterial tree as the arteriolar lumen increases and the muscle layer thins and spreads distally. Pulmonary hypertension and high flow of blood from a left-to-right shunt in a patient with a VSD cause pulmonary vascular obstructive disease as evidenced by a decreased number of pulmonary arterioles (ALV/Art of 25:1), a decrease in vessel lumen, an increase in muscle thickness and a more distal spread of muscle. Letters indicate arterioles from the level of the terminal bronchiolus (TB) to the alveolar wall (AW). AD, alveolar duct; RB, respiratory bonchiolus. *Source*: Reproduced from Rabinovitch et al [28] with permission from Wolters Kluwer.

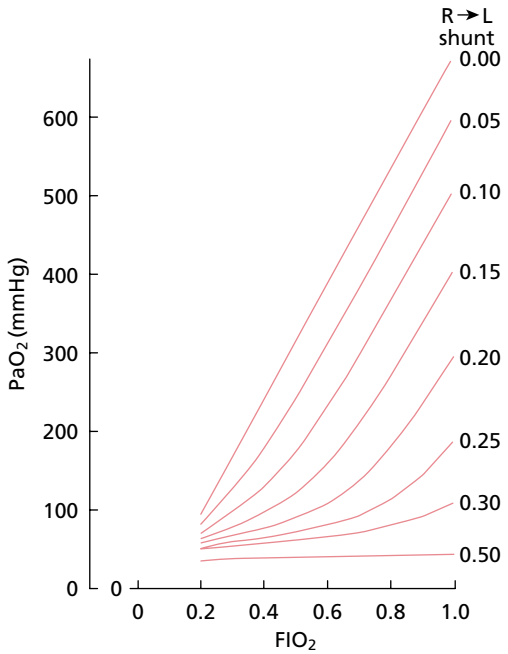


Figure 27.8 Isoshunt graph depicting the relation between inspired FIO_2 and arterial PaO_2, with different amounts of right-to-left shunting. It assumes normal values of pH, $PaCO_2$, pulmonary venous saturation, and mixed venous saturation. *Source*: Reproduced from Lawler and Nunn [96] with permission from Elsevier.

platelet defects are common and are positively correlated with the level of erythrocytosis and arterial oxygen desaturation [35–42]. Defects in bleeding time, clot retraction, and platelet aggregation to a variety of mediators have all been described [37,38,43,44]. The importance of erythrocytosis in the genesis of these quantitative and qualitative defects is underscored by the observation that multiple therapeutic phlebotomies using either plasma or isotonic saline to replace whole blood and reduce the Hct to the 50–60% range result in improvement of the platelet count and platelet aggregation [37,39]. In addition, shortened platelet survival time has been reported. Reduced survival time was weakly positively correlated with the level of erythrocytosis and arterial oxygen desaturation [40]. More recently, a baseline deficit in platelet glycoprotein 1b receptors has been reported in cyanotic children [45]. These receptors play a pivotal role in inducing platelet aggregation and adhesion via von Willebrand factor. The platelets of cyanotic neonates and infants exhibit a hyporeactive response to protease activated receptor 1 agonists compared to non-cyanotic neonates and infants.

Prolonged prothrombin time, partial thromboplastin time, and low levels of fibrinogen and factors II, VII, IX, X, XI, and XII have also been reported in association with cyanosis [35,36,38,42,46]. Therapeutic phlebotomies using isotonic saline to replace whole blood and reduce the Hct to the 50–60% range result in an increase in factor II, VII, and V levels [39]. Coagulation factor abnormalities appear to occur with lower frequency than platelet defects but the full extent of coagulation factor abnormalities is unknown because this issue has been incompletely studied.

Chronic disseminated intravascular coagulation (DIC) has been proposed as an additional mechanism leading to a coagulopathic state in cyanotic heart disease [47]. While evidence of accelerated ongoing thrombin generation and fibrinolysis has been detected in cyanotic versus non-cyanotic patients, chronic DIC has not been substantiated [48,49].

Recent evidence documents the overproduction of platelet microparticles in erythrocytotic CHD patients whose Hct is greater than 60% [50]. Microparticles are cellular fragments that result from exocytotic budding and contain both cytoplasmic and membrane components. These microparticles express factor Va and Xa and are highly procoagulant. Microparticle formation occurs as a result of the high microvascular shear forces that accompany erthrocytosis and can be reduced via hematocrit reduction with therapeutic phlebotomy [50].

Table 27.4 Effects of central shunting and pulmonary blood flow on oxygenation

Pulmonary blood flow Qp	L→R shunt only	L→R + R→L (mixing)	R→L shunt only
Qp > Qs	Normoxemia	Hypoxemia*	–
Qp = Qs	–	Hypoxemia	–
Qp < Qs	–	Hypoxemia (severe)	Hypoxemia (severe)

* Normoxemia when Qp/Qs ≥7–10.
Qp, pulmonary blood flow; Qs, systemic blood flow; –, does not occur.

Increased pulmonary blood flow

A volume load is imposed on the heart when pulmonary flow is greater than systemic flow (Qp/Qs greater than 1). The additional pulmonary flow does not increase arterial oxygen content. This increased volume load decreases not only cardiovascular reserve but also pulmonary reserve, because the work of breathing is increased owing to decreased pulmonary compliance and increased airway resistance [51]. These changes are due to increased lung water, compression of bronchi by distended pulmonary vessels at all levels, and generalized pulmonary vascular congestion. Lung compliance improves immediately when L-R shunts are closed (e.g. ligation of a PDA) [52].

KEY POINTS: PATHOPHYSIOLOGY OF CONGENITAL HEART DISEASE

- Manipulating pulmonary vascular resistance by altering ventilation (FiO_2 and $PaCO_2$), and systemic vascular resistance with vasodilators or vasoconstrictors is a fundamental principle of management of congenital heart disease
- Neonates with CHD often revert to the state of transitional circulation with stresses such as acidosis and hypoxemia, with high pulmonary vascular resistance and continued R-L shunting through the PDA and foramen ovale
- Right-to-left shunting lesions can result in profound arterial desaturation, and maintaining the PDA with prostaglandin E1, as well as adequate hemoglobin, inotropy, and oxygenation with mechanical ventilation, are important principles in preoperative stabilization
- Increased pulmonary blood flow from L-R shunting lesions can worsen in the first few weeks postnatally as PVR drops and Qp/Qs increases dramatically

Preoperative assessment and preparation

Successful anesthetic management of patients with CHD begins with a complete preoperative assessment and adequate patient preparation. Involvement of the anesthesiologist in preoperative preparation and early postoperative management is imperative and improves perioperative care. The clinical and laboratory information routinely available preoperatively (Box 27.1) should be integrated with information from continuous monitoring during surgery and the immediate recovery phase. The anesthesiologist must be aware of the physical and laboratory findings that are of particular importance for CHD.

Box 27.1: Clinical and laboratory preoperative assessment

- History and physical examination
- Laboratory data
- Chest radiography
- Electrocardiogram
- Echocardiography and Doppler assessment
- Cardiac catheterization
- Magnetic resonance and computed tomographic imaging and angiography

History and physical examination

A history and physical examination is the beginning of a complete preoperative assessment. Attention should be directed to the extent of cardiopulmonary impairment and the presence of associated extracardiac congenital anomalies. Upper and lower airway problems in patients with Down syndrome, calcium and immunological deficiencies in patients with aortic arch abnormalities, and renal abnormalities in patients with esophageal atresia and CHD are a few of the associated congenital abnormalities with which the anesthesiologist should be familiar. Intercurrent pulmonary infection is a common and significant finding in lungs with chronically elevated pulmonary blood flow.

Laboratory data

The complete blood count, blood urea nitrogen, creatinine, and serum electrolytes can reflect the patient's condition and affect perioperative management. An elevated hemoglobin, for example can reflect the presence, degree, and duration of hypoxemia (in the absence of iron deficiency). A low hemoglobin, as seen in the nadir of physiological anemia during infancy, may contribute to L-R shunting by decreasing the relative PVR [34]. Electrolyte abnormalities caused by congestive heart failure and forced diuresis must also be evaluated preoperatively. Severe hypochloremic metabolic alkalosis may occur in some patients. Digoxin may need to be discontinued perioperatively in these patients, as ventricular fibrillation is more likely to occur in patients with hypochloremic metabolic alkalsosis, particularly when induction of anesthesia is associated with hypotension and treated with calcium chloride or gluconate. Serum calcium and glucose levels must be monitored in critically ill infants.

Chest radiography

A chest radiograph is helpful for evaluating heart size, the presence and degree of pulmonary vascular congestion, airway compression, and lung consolidation or atelectasis.

Electrocardiogram

The electrocardiogram (ECG) may reveal rhythm disturbances and demonstrate ventricular strain patterns (ST and T wave changes) characteristic of unphysiological pressure or volume burdens on the ventricles.

Echocardiography and Doppler assessment

Two-dimensional and real-time three-dimensional echocardiography has revolutionized imaging in pediatric cardiology. Comprehensive cardiac assessment of the pediatric patient by transthoracic echocardiography is possible since echocardiographic windows are usually acceptable. Doppler measurements expand diagnostic capabilities. Measurements

of pressure gradients across semi-lunar valves and other obstructions are reproducible but may not always correlate with peak systolic ejection gradients measured at catheterization. Three-dimensional echocardiography may add new information about valvular lesions, particularly the site and mechanism of regurgitation [53]. In addition, 3D echocardiography offers new perspectives on atrial and ventricular septal defects, and more complex lesions such as atrioventricular septal defect, complex transposition of the great arteries, truncus arteriosus, and double outlet right ventricle.

Cardiac catheterization

Catheterization is necessary to clarify anatomy and physiology when clinical information is ambiguous or contradictory, or to clarify coronary or aortopulmonary collateral anatomy. Nonetheless, most neonates are able to proceed to surgery without catheterization studies. Normal intracardiac pressure and saturation values in children are shown in Figure 27.9.

Shunt localization is usually accomplished using a combination of angiography and measurement of O_2 saturations in the pulmonary veins, superior and inferior vena cavae, right and left heart chambers, aorta, and pulmonary arteries. Oxygen saturation sampling is used to detect an O_2 saturation step-up in the right heart in the case of a L-R shunt. A step-up is defined as a greater than 5% increase in the O_2 saturation of blood in a particular location that exceeds the normal variability in that location, whereas a step-down is a greater than 5% decrease in saturation for a given location.

Shunt quantification is based on comparison of systemic and pulmonary blood flows. Systemic (Qs) and pulmonary (Qp) blood flows are calculated by the Fick method:

$$Qp = VO_2 / (PvO_2\,\text{content} - PaO_2)$$

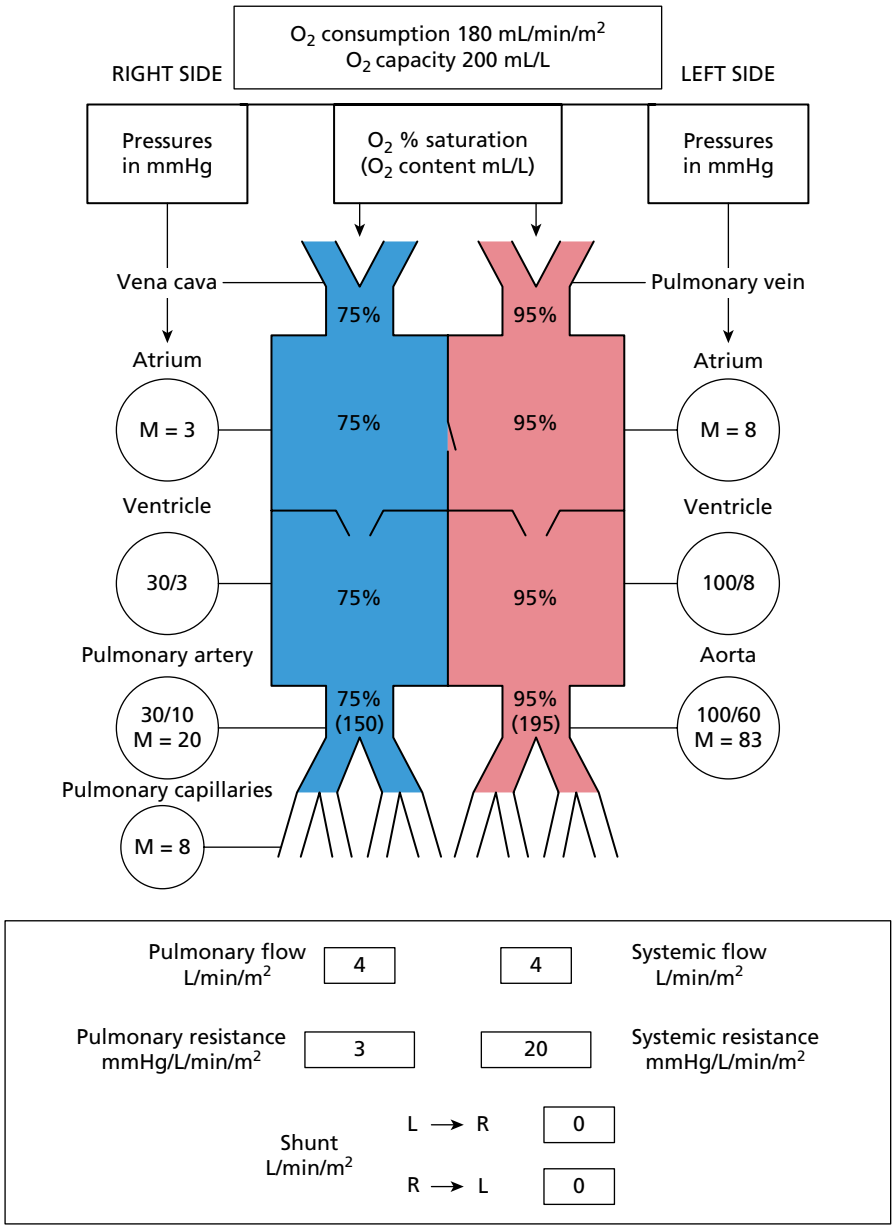


Figure 27.9 Cardiac catheterization findings in a normal child. Numbers in chambers are oxygen saturation (percent) and numbers in parentheses are oxygen content. Pressure in chambers are shown in circles. Note "probe-patent" foramen ovale. M, mean pressure. *Source*: Reproduced from Nadas and Fyler [357] with permission of Elsevier.

PaO_2 content is the pulmonary arterial O_2 content, PvO_2 content is the pulmonary venous O_2 content, and VO_2 is oxygen consumption. Sampling blood from the left atrium (when the pulmonary veins return to the left atrium) will provide a weighted average O_2 content of the four pulmonary veins. If a R-L atrial level shunt is present, this sampling site will not provide an accurate assessment of pulmonary vein O_2 content. Each of the four pulmonary veins can be entered and sampled separately to assess for pulmonary sources of venous admixture (e.g. pneumonia, atelectasis, or other pulmonary disease). When this is done, segmental areas of intrapulmonary shunt and V/Q mismatch can be detected. The PaO_2 or saturation of pulmonary venous blood from a lung segment with V/Q mismatch will improve with an increase in FiO_2 while there will be no improvement if an intrapulmonary shunt is present.

$$Qs = VO_2 / (SaO_2\,\text{content} - MvO_2\,\text{content})$$

SaO_2 content is systemic arterial O_2 content and MvO_2 content is mixed venous O_2 content. True mixed venous blood is a mixture of desaturated blood from the inferior vena cava (IVC), superior vena cava (SVC), and coronary sinus. In a normal heart a mixed sample of venous blood from these three locations can be obtained from the pulmonary artery. In the presence of an intracardiac L-R shunt, PaO_2 saturation will overestimate true MvO_2 saturation because pulmonary arterial blood will be a mixture of mixed venous blood and oxygenated pulmonary venous blood from the left heart. In children, SVC O_2 content is commonly used as a surrogate for MvO_2 content.

After Qp and Qs have been calculated, shunts can be quantified. For an isolated L-R shunt, the magnitude of the shunt is Qp – Qs. For an isolated R-L shunt, the magnitude of the shunt is Qs – Qp. The ratio Qp/Qs is also useful. It can be calculated from content data alone because the VO_2 term cancels out:

$$Qp / Qs = \frac{(SaO_2\,\text{content} - MvO_2\,\text{content})}{(PvO_2\,\text{content} - PaO_2\,\text{content})}$$

Furthermore, if the blood is sampled using a low FiO_2, the dissolved O_2 portion of the content equation ($PO_2 \times 0.003$) can be ignored. The hemoglobin × 1.34 term cancels out and the equation can be simplified further using just the oxygen saturation data from the four sites:

$$Qp / Qs = \frac{(SaO_2\,\text{saturation} - MvO_2\,\text{saturation})}{(PvO_2\,\text{saturation} - PaO_2\,\text{saturation})}$$

A Qp/Qs >2.0 constitutes a large shunt, whereas a Qp/Qs of 1.25–1.5 constitutes a small shunt. A Qp/Qs <1.0 indicates a net R-L shunt.

Effective pulmonary blood flow (Qp_{eff}) and effective systemic blood flow (Qs_{eff}) must be calculated when birectional shunts are present. Qp_{eff} is the quantity of desaturated systemic venous blood that traverses the pulmonary capillaries to be oxygenated. Qs_{eff} is the quantity of oxygenated pulmonary venous blood that traverses the systemic capillaries to deliver oxygen to tissue. Qs_{eff} and Qp_{eff} are always equal.

$$Qs_{eff} = Qp_{eff} = VO_2 (PvO_2\,\text{content} - MvO_2\,\text{content})$$

The L-R shunt is defined as $Qp - Qp_{eff}$ while the R-L shunt is defined as $Qs - Qs_{eff}$. The net shunt is the difference between these two calculated shunts.

In the presence of a L-R shunt and elevated PVR, pressure and saturation measurements are often repeated with the patient breathing 100% oxygen to assess both the reactivity of the pulmonary vascular bed and any contribution of ventilation/perfusion abnormalities to hypoxemia. If breathing 100% oxygen or nitric oxide increases pulmonary blood flow and dramatically increases Qp/Qs with a fall in PVR, potentially reversible processes such as hypoxic pulmonary vasoconstriction might be contributing to the elevated PVR. Patients with high PVR not responsive to 100% oxygen or nitric oxide and a small L-R shunt despite a large shunt orifice may have extensive pulmonary vascular damage from irreversible obstructive pulmonary vascular disease.

Anatomical abnormalities are identified angiographically during cardiac catheterization. Special angled views provide specific information about the location and extent of congenital defects. Ventricular function is assessed angiographically and physiologically (e.g. by pressure measurements). The calculated size of cardiac chambers may have an important bearing on its ability to support the circulation of a child with hypoplastic ventricles.

Magnetic resonance and computed tomography imaging and angiography

Magnetic resonance imaging (MRI) and angiography (MRI/A) has emerged as an important diagnostic modality in the evaluation of the cardiovascular system following the development of ECG-gated MRI technology. Image acquisition is triggered by the patient's ECG to counter motion artifacts and to acquire cine sequences that allow imaging of cardiac structures and visualization of blood flow throughout the cardiac cycle. MRI/A can provide excellent anatomical and three-dimensional images, particularly of the pulmonary veins and thoracic aorta. It is also possible to qualitatively assess valves and quantify flow as well as measure ventricular function, volume, mass, and ejection fraction [54,55]. Contraindications include patients with non-MRI compatible pacemakers, recently implanted endovascular or intracardiac implants, and aneurysm clips on vessels that will be exposed directly to the magnetic field. Ferromagnetic implants near the region of interest produce imaging artifacts, but sternal wires and vascular clips from previous procedures usually produce relatively minor imaging artifacts.

Sedation is necessary for most children undergoing cardiac MRI/A procedures as the small bore of the magnet and noise during imaging may induce claustrophobia and anxiety. Breath holding is necessary for acquisition of many three-dimensional MRI/A images and gradient echo sequences to measure blood flow. General anesthesia with neuromuscular blockade is required for neonates, infants, young children, and older children who are not able to follow instructions from the technologist. Dobutamine stress MRI/As may require additional monitoring and MRI compatible infusion pumps or extension tubing for pumps outside of the imaging area. The environment for MRI is often a difficult one in which to administer sedation or general anesthesia and hemodynamic monitoring may be limited [56].

Computed tomography (CT) imaging and angiography is also useful for visualizing intra- and extracardiac structures. The imaging time is brief but sedation is usually required in infants and children, and general anesthesia is necessary when breath holding is important for imaging. Imaging may require slowing the heart rate with a βblocker. Careful communication with the cardiologist and imaging technician is imperative to make sure hemodynamics are not compromised by induced bradycardia. CT imaging exposes the patient to ionizing radiation so the risks and benefits of the procedure must be assessed when other imaging modalities are possible.

Assessment of patient status and predominant pathophysiology

Congenital heart defects are complex and can be difficult to conceptualize. Understanding physiological concepts and their management is more helpful than trying to individualize an approach to each anatomical defect. Organization of preoperative patient data, preparation of the patient, and decisions about monitoring, anesthetic agents, and postoperative care are best accomplished by focusing on a few major pathophysiological problems. Some useful questions to consider include:

- Is the patient in congestive heart failure (suggesting low cardiac output or excessive pulmonary blood flow versus systemic blood flow)?
- Is the patient cyanotic (suggesting decreased pulmonary blood flow or low cardiac output)?
- Is the circulation in series or parallel?
- What intracardiac mixing, shunting, or outflow obstruction exists?
- How is ventricular function? Is there a volume load or pressure load on the ventricles?

Optimal preparation of the patient usually involves consideration of one of the following major problems: severe hypoxemia, excessive pulmonary blood flow, congestive heart failure (CHF), obstruction of blood flow from the left heart, or poor ventricular function. Although some patients with CHD present with only one problem, many have multiple interrelated problems.

Severe hypoxemia

Many of the cyanotic forms of CHD present with severe hypoxemia, defined as PaO_2 less than 50 mmHg during the first few days of life despite adequate ventilation. Cyanotic patients may have an elevated hemoglobin and require adequate preoperative and postoperative hydration to prevent thrombotic complications. Neurological examination and blood chemistry analysis of renal, hepatic, and hematological function is necessary to assess the effects of hypoxemia as well as potentially altered systemic blood flow caused by an end-organ function. Sedation-related hypoventilation can exacerbate hypoventilation and worsen hypoxemia. Infusion of prostaglandin E1 (PGE1) in patients with decreased pulmonary blood flow maintains or re-establishes pulmonary flow through the ductus arteriosus. Consequently, neonates rarely require surgery while they are severely hypoxemic.

Prostaglandin E1 dilates the ductus arteriosus of the neonate with life-threatening ductal-dependent cardiac lesions and improves the patient's condition before surgery. It can reopen a functionally closed ductus arteriosus for several days after birth, or it can maintain patency of the ductus arteriosus for several months postnatally [57,58]. Pulmonary blood flow is improved by shunting blood from the aorta through the ductus arteriosus to the pulmonary artery. PGE1 usually improves the arterial oxygenation of hypoxemic neonates who have poor pulmonary perfusion due to obstructed pulmonary flow (critical pulmonary stenosis or pulmonary atresia), and may also improve the mixing of venous and arterial blood at the atrial level in patients with transposition of the great arteries [57]. The improved oxygenation reverses the lactic acidosis that may have developed during episodes of severe hypoxemia. PGE1 administration for 24 h usually markedly improves the condition of a severely hypoxemic neonate with restricted pulmonary blood flow [59].

The common side effects of PGE1 infusion (apnea, hypotension, fever, central nervous system excitation) are easily managed in the neonate when normal therapeutic doses of the drug (0.01–0.1 μg/kg/min) are used [60]. However, PGE1 is a potent vasodilator, so intravascular volume frequently requires augmentation. Patients with intermittent apnea resulting from administration of PGE1 may require mechanical ventilation preoperatively.

Excessive pulmonary blood flow

Excessive pulmonary blood flow is sometimes the primary problem of patients with CHD. Children with L-R shunts may have chronic low-grade pulmonary infection and congestion that cannot be eliminated despite optimal preoperative preparation. If so, surgery should not be postponed further. Respiratory syncytial virus infections are particularly prevalent in this population, but improvements in intensive care and palivizumab prophylaxis have markedly improved outcome with this and other viral pneumonias [61].

The hemodynamic effects of excessive pulmonary blood flow and L-R shunts may include CHF as cardiac ouput is ineffectively circulated back to the lungs. Pulmonary venous return may be many times normal causing the left heart to dilate so the heart responds less efficiently to increased demand. Most of the increment in cardiac output is recirculated to the lungs, worsening symptoms of CHF.

Congestive heart failure

Children with failing hearts have elevated endogenous catecholamine production that increases heart rate and cardiac output and redistributes output from the extremities to highly perfused organs. In severe cases, the patient may be tachypneic, tachycardic, and dusky in room air with body weight below the third percentile for age. The child may have intercostal and substernal retractions and skin that is cool to the touch. Capillary refill may be prolonged. Expiratory wheezes are usually audible (Box 27.2). These clinical signs and symptoms suggest that profound pathophysiological alterations have occurred and the patient has significant respiratory compromise and minimal cardiac reserve. Medical management with digoxin, diuretics, and afterload reduction may improve the patient's condition, but the diuretics may induce profound hypochloremic alkalosis and potassium depletion. The anesthetic plan needs to be tailored accordingly, potentially

Box 27.2: Symptoms and signs of cardiac failure in a neonate and infant

Failure to thrive
- Poor feeding
- Diaphoresis

Increased respiratory work
- Tachypnea
- Wheezing
- Grunting
- Flaring of ala nasi
- Chest wall retraction

Altered cardiac output
- Tachycardia
- Gallop rhythm
- Cardiomegaly
- Poor extremity perfusion
- Hepatomegaly

avoiding potent inhaled anesthetics in favor of an opioid-based technique that is expected to provide more hemodyamic stability than high concentrations of potent anesthesia vapor. Inotropic support and pressor drugs should be immediately available. Mildly symptomatic patients should tolerate premedication and sevoflurane/nitrous oxide inhalation induction of anesthesia for an elective operation.

Obstruction of left heart outflow

Patients with obstruction to outflow from the systemic ventricle are often critically ill. Neonates present with inadequate systemic perfusion and profound metabolic acidosis. The initial pH may be below 7.0 despite a $PaCO_2$ of less than 20 mmHg. Systemic blood flow is largely or completely dependent on blood flow into the aorta from the ductus arteriosus. These lesions include interruption of the aortic arch, coarctation of the aorta, aortic stenosis, and mitral stenosis or atresia as part of the hypoplastic left heart syndrome.

Ductal closure in the neonate causes dramatic worsening of the patient's condition. The patient becomes critically ill or even moribund and requires PGE1 infusion for survival. PGE1 allows blood flow into the aorta from the pulmonary artery because it maintains the patency of the ductus arteriosus [59,62,63]. In neonates with acidosis, metabolic derangements, and renal failure due to inadequate systemic perfusion, PGE1 infusion improves perfusion and metabolism, and surgery can be deferred until the patient's condition improves. Ventilatory and inotropic support and correction of metabolic acidosis, along with calcium, glucose, and electrolyte abnormalities are indicated preoperatively. The stabilization period also allows assessment of the magnitude of end-organ dysfunction caused by inadequate systemic perfusion. Adequacy of resuscitation as well as severity of illness at presentation has an important influence on postoperative outcome [64].

Ventricular dysfunction

Ventricular dysfunction in CHD may be multifactorial. Cyanotic CHD patients who have a large shunt and complete mixing of systemic and venous blood may have excessive pulmonary blood flow that imposes a large volume load on the heart leading to left heart dilation and dysfunction. Ventricular function can be further worsened by poor systemic and coronary perfusion secondary to excessive pulmonary blood flow.

Preoperative assessment should include an estimation of the patient's functional limitation as an indicator of myocardial performance and reserve, quantification of the degree of hypoxia and the amount of pulmonary blood flow, and evaluation of PVR. Narrowing of the shunt or a staged approach to single-ventricle palliation may be indicated before additional palliation or definitive repair can be undertaken.

Anesthetic management may need to be altered to increase or decrease pulmonary blood flow. Systemic blood flow needs to be optimized during induction of anesthesia in patients with increased Qp/Qs without further augmenting pulmonary flow. Hypoxemia may be exacerbated during emergence from anesthesia and intraoperatively by positional changes, retraction of the lungs, and abdominal distention, further compromising the function of a potentially dilated and dysfunctional ventricle.

Older patients with CHD and poor ventricular function due to chronic ventricular volume overload (aortic or mitral valve regurgitation or long-standing pulmonary-to-systemic arterial shunts) may have systolic and diastolic ventricular dysfunction. Systolic function of the ventricle may be impaired by intrinsic myopathic abnormalities related to drug toxicity (e.g. anthracycline-based chemotherapy), inborn enzyme deficiencies, or acquired inflammatory or infectious disease. Patients with such dilated cardiomyopathies require optimization of ventricular performance with an emphasis on inotropic support and afterload reduction.

KEY POINTS: PREOPERATIVE ASSESSMENT AND PREPARATION

- Besides a through history, physical examination, and laboratory data, echocardiography is the mainstay of preoperative assessment in the CHD patient
- Cardiac catheterization, magnetic resonance imaging, and computed tomography imaging and angiography also can add crucial data to aid in preanesthetic planning
- Classification of patients into predominant pathophysiology can aid in planning an appropriate anesthetic: severe hypoxemia, excessive pulmonary blood flow, obstruction to systemic ventricular outflow, or ventricular dysfunction

Principles of anesthetic management

The variations of severity and pathophysiology of CHD mandates individualized anesthetic management based on the known effects of anesthetics and other drugs. Once the critical aspects of the patient's pathophysiology are understood, the anesthetic management plan is formulated to manage anticipated pre-, intra-, and postoperative events.

General care of patients with congenital heart disease

The patient's condition should be optimized prior to elective cardiac or non-cardiac surgery. Cardiac medications such as antiarrhythmic drugs should be continued preoperatively except for angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, which are usually discontinued 24 h prior to induction of anesthesia. In addition, aspirin or other antiplatelet agents or anticoagulants are often discontinued up to 7–10 days preoperatively. Consultation with the patient's cardiologistand surgeon is important to formulate a perioperative plan.

Systemic air emboli are a constant concern in children with CHD. Usual shunting patterns may change during anesthesia and surgery. Transient R-L shunts may occur during some portions of the cardiac cycle or during straining or coughing in patients with open communications between the left and right sides of the heart when normal transatrial pressure gradients are transiently reversed [65]. Right-to-left shunting may occur across functionally closed communications. A probe-patent foramen ovale is common in children, regardless of whether or not they have CHD, and transient R-L shunting through the foramen ovale has been documented during emergence from anesthesia [66]. Air traps or filters are advisable in all IV lines and constant vigilance is necessary to prevent systemic embolization of air.

Prevention of infective endocarditis is an important consideration in patients with CHD undergoing non-cardiac surgery [67]. The American Heart Association (AHA) recommends antibiotic prophylaxis only for patients deemed at highest risk (Box 27.3) who are undergoing procedures at risk for transient bacteremia. Prophylaxis is recommended prior to all dental procedures that involve the manipulation of gingival tissue or the periapical region of teeth or with anticipated perforation of the oral mucosa. Prophylaxis is also recommended for all respiratory tract procedures that involve perforation of the mucosa and for all procedures on infected skin or musculoskeletal tissues. Antibiotic therapy should be continued and expanded to cover enterococci in patients being treated for infections in the gastrointestinal or urinary tracts. Antibiotic prophylaxis is no longer recommended for routine gastrointestinal or urinary tract endoscopy even with biopsies. It is best to consult the literature for the most current recommendations.

Box 27.3: Cardiac conditions associated with the highest risk of adverse outcome from endocarditis for which prophylaxis with dental procedures is recommended

- Prosthetic cardiac valve
- Previous infective endocarditis
  - Congenital heart disease (CHD)*
  - Unrepaired cyanotic CHD, including palliative shunts and conduits
  - Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure†
  - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
- Cardiac transplantation recipients who develop cardiac valvulopathy

* Except for the conditions listed, antibiotic prophylaxis is no longer recommended for any other form of CHD.
† Prophylaxis is recommended because endothelialization of prosthetic material occurs within 6 months after the procedure.

Preanesthetic management

The immediate preoperative period is an anxious time for patients and parents. Many patients may have undergone prior surgery or diagnostic procedures and separation from parents may be difficult. Many patients are now admitted on the day of surgery so adequate preparation for surgery in the preoperative clinic with a thorough explanation of the planned procedure and conduct of anesthesia, including a plan for induction, is essential. Clear fluids can be administered up to 2 h preoperatively, and an extended period of fasting should be avoided when possible, particularly in cyanotic patients.

Given the many types of pathophysiology in CHD patients, no single premedication regimen is recommended. Ideally, one wants a sedated, quiet patient who maintains adequate ventilation and circulation. Oral midazolam 0.5–1.0 mg/kg is an effective anxiolytic and should enable separation from parents without producing hypnosis. The addition of oral ketamine 5–7 mg/kg is sometimes necessary. An intramuscular premedication with ketamine 3–5 mg/kg and midazolam 0.1 mg/kg is also effective. Adequate premedication reduces separation anxiety and facilities inhalational induction of anesthesia with lower concentrations of potent anesthetic vapors. This is particularly beneficial in patients with limited hemodynamic reserves. Patients must be continuously monitored after premedication. CHD patients often have fragile circulatory and ventilatory status. Cyanotic patients, in particular, have decreased hypoxic drive [68].

Induction of anesthesia

Because of the potential for rapid and dramatic hemodynamic changes in young patients with CHD, especially infants, complete preparation of anesthetic and monitoring equipment and required drugs is essential. Adequate assistance should be immediately available during the induction of anesthesia in case problems develop.

The choice of induction technique is influenced by the response to premedication, the parent–child–anesthesiologist relationship, and the anesthetic management plan. In older, non-hypoxemic patients who have minimal compromise of their cardiac reserve, the choice of induction techniques is large. Inhalation, intravenous, or intramuscular induction of anesthesia can be accomplished with a variety of drugs with reasonable degrees of safety if individual pathophysiological limitations are understood. For younger, sicker, and less cooperative patients, the choices diminish.

In children with adequate peripheral veins, the quick insertion of a small-bore IV catheter for induction of anesthesia can be virtually painless. Preoperative use of a topical anesthetic preparation may facilitate intravenous placement. Cooperative children with an adequate cardiac reserve and difficult intravenous access or a morbid fear of needles can have anesthesia induced cautiously with inhaled anesthetics, even if they are cyanotic. An IV catheter can then be inserted to facilitate

administration of muscle relaxants; these drugs facilitate tracheal intubation and avoid the risk of deep levels of inhalational anesthesia for tracheal intubation in patients whose circulatory systems may have little reserve.

An intravenous induction should be used for all patients with severely limited hemodynamic reserve, particularly those with severe ventricular failure or pulmonary hypertension. In situations where hemodynamic instability during induction is likely, starting an inotropic agent such as dopamine prior to induction should be considered. While the stress of placing an IV catheter may be considerable for some patients, particularly those with difficult IV access following previous procedures, this is preferable to potential myocardial depression during an inhalation induction with sevoflurane.

Fentanyl 15–25 μg/kg attenuates the stress-induced increase in PVR associated with endotracheal intubation, provides hemodynamic stability, and facilitates prompt airway control when given with rocuronium 1 mg/kg. Ketamine 1–3 mg/kg IV is also a safe and reliable anesthetic and provides hemodynamic stability with minimal increases in PVR. It is particularly useful in patients with severe CHF and ventricular outflow obstructions. Atropine 20 μg/kg or glycopyrrolate 10 μg/kg can be given concurrently to mitigate the ketamine-induced oral secretions. If intravenous access is difficult in infants, a combination of 3 mg/kg ketamine, glycopyrrolate 10 μg/kg, and succinylcholine 2 mg/kg IM allows prompt induction and airway control.

Propofol can be used in patients with normal ventricular function and no systemic outflow tract obstruction. Titrated doses are suitable for short procedures such as cardioversion or transesophageal echocardiography (TEE). Midazolam 0.1–0.2 mg/kg is also a useful adjunct during an opioid induction but may cause hypotension in patients who are dependent on a high sympathetic drive.

An inhalation induction with sevoflurane (not to exceed an inhaled concentration of 4%) in order to obtain intravenous access is suitable for most infants and children, provided they have stable ventricular function and adequate hemodynamic reserve. This emphasizes the importance of preoperative evaluation when planning the induction technique. Inhalational induction can be used safely in patients with cyanotic heart disease, although uptake may be slower due to the R-L shunt [69]. Saturations will generally increase, provided cardiac output is maintained and airway obstruction avoided.

For many younger children, the presence of a parent during inhalation induction may be preferable for both the patient and parent. This is a common technique for normal children undergoing induction of anesthesia for non-cardiac surgery, but careful preoperative preparation and explanation are necessary before this is undertaken in the cardiac operating room.

Maintenance of anesthesia

Anesthesia maintenance techniques depend on the patient's preoperative cardiorespiratory status and pathophysiology of the underlying cardiac defect, the surgical procedure, the conduct of CPB, potential postoperative surgical problems, and the anticipated postoperative management. Once induction of anesthesia and control of the airway are accomplished and monitoring is adequate, anesthesia can be maintained with inhaled anesthetics or additional intravenous drugs as dictated by the response of each patient, intraoperative events, and postoperative plans.

Stress responses to pain and other noxious stimuli are profound in even the youngest neonates, regardless of postconceptual age [70–72]. These hormonal and metabolic stress responses can be deleterious [73], particularly in patients with marginal hemodynamic reserve. Intraoperative deterioration in the patient's condition is not always clear, but changes in shunting, surgical manipulation of the heart, lungs, or great vessels, and depression of the myocardium by anesthetics are common causes. Decreases in arterial oxygenation or in systemic blood flow and pressure frequently are due to alterations in intracardiac shunting. When circulating blood volume is adequate and anesthesia-related myocardial depression is unlikely, these problems are corrected by appropriately manipulating PVR and SVR. If PVR cannot be altered or is not part of the problem, vasopressor and inotropic drugs are used where indicated to increase SVR and cardiac function.

KEY POINTS: PRINCIPLES OF ANESTHETIC MANAGEMENT

- In general, all cardiac medications should be continued on the day of surgery, except angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, and possibly aspirin, other antiplatelet agents, and anticoagulants
- Meticulous attention to prevent systemic air emboli is important in all patients with intra- or extracardiac shunting
- Infective endocarditis prophylaxis should be administered according to the latest guidelines; both a cardiac indication and a surgical indication are needed
- Judicious use of oral premedication with midazolam and/or ketamine, and parental presence as appropriate, can minimize anxiety and hemodynamic perturbation in the preanesthetic period
- Induction techniques vary, but sevoflurane inhaled induction is appropriate for many CHD patients with preserved ventricular function. Intramuscular induction with ketamine can be used in cyanotic patients; and in very ill patients or those with easily accessible peripheral veins, intravenous induction with agents such as ketamine, fentanyl, or etomidate may be appropriate
- Propofol induction can be used for patients with preserved ventricular function and no systemic ventricular outflow tract obstruction

Choice of anesthetic agents

Use of inhaled anesthetics in children with intracardiac shunting is complicated by differences in uptake and distribution of these agents. A complex computer model has suggested that induction of anesthesia is slowed by the presence of central R-L shunts, slowed less by mixed shunts, and changed little by pure L-R shunts; the changes are proportional to the size of the shunt [69]. These theoretical effects assume a constant

cardiac output and are most marked for insoluble gases (e.g. nitrous oxide). Induction of anesthesia with more soluble gases (e.g. halothane) is less affected. Similar studies comparing the speed of induction with sevoflurane to other potent inhalation agents have not been performed; however, because it is less soluble than halothane, induction with sevoflurane should be expected to be slower in patients with a right-to-left shunt. In children with left-to-right shunts, the speed of inhalation induction is little altered clinically [74]. Data from children with right-to-left shunts corroborate this slower rise in blood to inhaled concentration of halothane, that is corrected when the shunt is closed during cardiac catheterization (Fig. 27.10) [75,76]. Inhalation induction often seems slower in children with pure R-L shunts but this effect is not marked, probably because multiple other variables are affecting uptake. The potentially slow induction of anesthesia in children with pure R-L shunts should be remembered when one must rapidly increase the concentration of potent inhaled anesthetics in these patients. The direct effect of inhaled agents on Qp/Qs appears to be limited. Sevoflurane, halothane, isoflurane, and fentanyl/midazolam do not change Qp/Qs in children with atrial and ventricular septal defects when cautiously administered with 100% oxygen [77].

Potent inhaled anesthetics

The volatile agents most commonly used during pediatric anesthesia are desflurane, isoflurane, and sevoflurane. Halothane is rarely, if ever, used at present. All three can be used safely to maintain anesthesia in children with cardiac disease, although this depends to some extent on the child's cardiac anomaly and related pathophysiology. Cyanotic children with reasonable functional cardiac reserve can have anesthesia induced with sevoflurane or halothane and oxygen (even 70% nitrous oxide does not significantly decrease arterial oxygen saturation) [78–80]. Nevertheless, it is important that the anesthesiologist has an understanding of the potential effects of these anesthetics in young children with CHD.

Increased sensitivity of the immature cardiovascular system and decreased cardiovascular reserves are more serious problems with potent inhaled anesthetics. Use of these agents may considerably reduce the margin of safety in infants and younger children with severe CHD. Volatile anesthetics depress myocardial function primarily by limiting calcium availability within the myocyte, i.e. by reducing trans-sarcolemmal and sarcoplasmic reticulum calcium flux. The net result is depletion of intracellular calcium stores and, given the immaturity of the neonatal and infant myocardium, the potential for systolic dysfunction in these patients may be increased when volatile agents are used. In addition, diastolic ventricular function may also be impaired because of limited reuptake of calcium into the immature sarcoplasmic reticulum, and dependence upon trans-sarcolemmal sodium–calcium exchange [81].

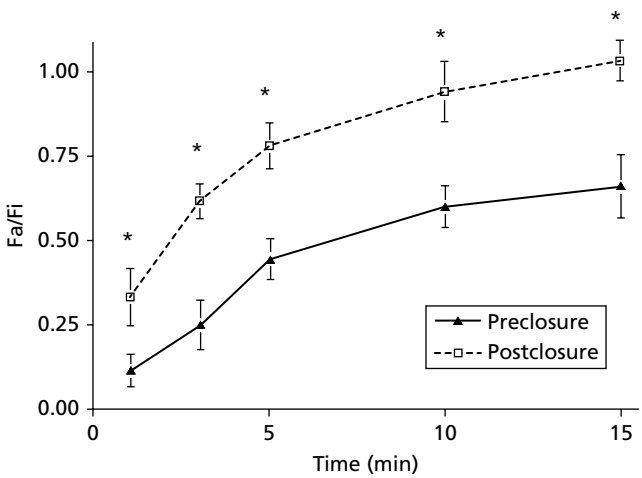


Figure 27.10 Mean ratio values of arterial to inspired halothane in patients pre- and postclosure of right-to-left shunt in cardiac catheterization laboratory. *P = 0.05 versus preclosure.

Therefore, it is not surprising that numerous studies have shown that the immature cardiovascular system of normal infants does not tolerate high concentrations of halothane and isoflurane well; up to 50% of infants with normal cardiovascular systems develop substantial hypotension and bradycardia during induction of anesthesia with these agents unless the cardiovascular system is supported [82,83]. The ventricular function of normal infants declines when anesthesia is induced with isoflurane; stroke volume and ejection fraction decrease by as much as 38% [83]. Somewhat less myocardial depression occurs with halothane in older children [84]. Halothane (1 and 1.5 minimum alveolar concentration (MAC)) depresses cardiac index and contractility in patients with CHD more than comparable levels of sevoflurane, isoflurane, and fentanyl/midazolam anesthesia [85]. In addition, halothane anesthesia may result in more severe hypotension and emergent drug use than sevoflurane anesthesia in infants and children with CHD [86]. Isoflurane causes less direct myocardial depression, is less soluble and therefore has a faster uptake and emergence, has no effect on intracardiac conduction, and much less sensitization of the myocardium to catecholamines compared with halothane. As with isoflurane, sevoflurane causes less myocardial depression and has a low risk for arrhythmias in children compared with halothane [87–89]. Sevoflurane anesthesia is associated with prolongation of the QTc interval in infants [90]. Sevoflurane (1 MAC) and fentanyl/midazolam anesthesia have no significant effect on myocardial function in patients with a single ventricle [91]. Desflurane's effects on myocardial contractility and cardiac rhythm have not specifically been studied in CHD. A single, small, randomized trial of desflurane-based anesthesia versus opioid-based anesthesia for systemic-to-pulmonary shunt surgery in infants revealed no discernable differences in hemodynamic parameters, inotrope use, or complications [92].

Nitrous oxide

The use of nitrous oxide in children with CHD and shunts is controversial because of its potential for enlarging systemic air emboli and for increasing PVR. Nitrous oxide may expand intravascular air emboli and exaggerate the effects of other anesthetics on the circulation, even without systemic air embolization [93]. However, neither has been demonstrated to be a clinical problem in patients with CHD.

Nitrous oxide has been reported to decrease cardiac output, systemic arterial pressure, and heart rate in adults, and toincrease PVR, especially when the pre-existing PVR is elevated [94,95]. The latter would be detrimental to children with R-L

shunts, pulmonary hypertension, and decreased pulmonary flow. However, increases in pulmonary artery pressure or PVR in infants given 50% nitrous oxide do not occur, regardless of pre-existing PVR [19]. Mild but significant decreases in cardiac output, systemic arterial pressure, and heart rate were seen in these infants. Furthermore, inhalation induction of anesthesia with 70% nitrous oxide and halothane did not decrease the arterial oxygen saturation of cyanotic children, suggesting that pulmonary blood flow is not decreased and that PVR is not substantially increased by nitrous oxide [77,78]. Although the administration of nitrous oxide prevents the use of 100% oxygen, the arterial oxygen saturation of cyanotic children may not decrease because changes in FIO_2 have little effect on the arterial oxygenation of these patients (see Fig. 27.8) [96]. Arterial desaturation that is caused by pulmonary disease is, however, probably a contraindication to the use of nitrous oxide.

Intravenous anesthetics

Some intravenous anesthetics provide a large margin of safety for induction of anesthesia in the immature and compromised cardiovascular system of neonates and infants with severe cardiac disease. However, very high transient arterial, cardiac, and brain concentrations of IV agents can occur when normal IV doses of drugs are given as a rapid infusion in children with known R-L shunts because mixing, uptake, and metabolism in the pulmonary circulation are bypassed. In dogs with R-L shunts, a 1 mg/kg bolus of IV lidocaine resulted in arterial drug concentrations above those reported to cause irreversible myocardial toxicity [97]. Routinely administered bolus doses of lidocaine used for dysrhythmias or intubation, or other drugs such as barbiturates, β-blockers. or calcium channel blockers, may be potentially toxic to children with substantial R-L shunts.

Ketamine

Intramuscular ketamine 3–5 mg/kg is well tolerated in sick infants and children with cyanosis or congestive heart failure when IV access or lack of patient cooperation is a problem [98]. The use of an antisialagogue (e.g. atropine or glycopyrrolate) should be considered because of the potential effects of ketamine-induced oral secretions on airways and ventilation, especially in children with decreased oxygen reserves. Ketamine can be mixed with atropine and succinylcholine in the same syringe, the final volume being relatively small, and injection of this mixture allows rapid control of the airway. Small IV doses of ketamine (1–3 mg/kg) are effective for supplemental sedation in uncooperative or apprehensive children who are unwilling to leave their parents. Excessive secretions, airway problems, and apnea do not occur with these doses as they occasionally do with larger IM doses and frequently do with IV doses of ketamine.

Although increased PVR is reported with ketamine in adults, 2 mg/kg IV in premedicated infants and young children usually does not increase pulmonary artery pressure or PVR, even when the baseline PVR is elevated [20,21,23,99]. If hypoventilation or apnea occurs after an IV dose of ketamine, undesirable increases in PVR can occur because of the associated changes in PaO_2 and $PaCO_2$ [20]. Little change in cardiac output, heart rate, or arterial pressure is seen after IV ketamine in infants and small children with CHD [20,21]. Despite reports of ketamine having a negative inotropic effect on isolated heart muscle in animal studies (at very high doses), the ejection fraction of children with CHD is well preserved after ketamine. Furthermore, arterial saturation, for the most part, is improved when ketamine is used to induce anesthesia in cyanotic patients. Clinical experience with ketamine as the induction agent has been excellent for sick infants and children with most forms of heart disease, including those with limited pulmonary blood flow and cyanosis. Ketamine alone or in combination with propofol or dexmedetomidine is also useful for sedation and for anesthesia for cardiac catheterization in children with CHD [100].

Opioid anesthesia

The doses of synthetic opioids required to blunt systemic and pulmonary stress responses in younger and sicker children are generally well tolerated [24,70]. The changes in pulmonary and systemic hemodynamics are usually not significant in infants with bolus doses of fentanyl up to 15–25 μg/kg. Used with 100% oxygen, high-dose opioids are safe and result in increased arterial oxygenation in cyanotic children [101]. High doses of opioids (fentanyl 25–75 μg/kg or sufentanil 5–15 μg/kg) used for induction of anesthesia provide excellent cardiovascular stability in children with CHD. A bolus dose of 10–15 μg/kg effectively ameliorates the hemodynamic response to intubation in neonates, however rapid infusion of high doses of synthetic opioids produces chest wall rigidity and glottic closure in neonates, children, and adults [102,103], so a muscle relaxant needs to be co-administered. Pancuronium is theoretically the muscle relaxant of choice to facilitate endotracheal intubation since its vagolytic effects balance the bradycardia often seen with high doses of synthetic opioids [101,104–107]. Pancuronium is no longer available in most institutions. Rocuronium, vecuronium, and cistracurium all can be used effectively in this setting.

Fentanyl doses as low as 10 μg/kg/h may be sufficient for effective baseline anesthesia in neonates, but larger doses are necessary for prolonged anesthesia [108–110]. Small amounts of potent inhaled anesthetics may be necessary for complete suppression of hemodynamic responses to intense stimulation in vigorous babies and children. Morphine 1 mg/kg or more given slowly provides reasonable cardiovascular stability but histamine-induced hypotension can occur.

The high-dose opioid technique is most suitable for sick infants and older children in whom postoperative mechanical ventilation is planned. Traditionally, fentanyl doses of 50 μg/kg were administered prior to CPB depending on hemodynamic stability. Additional doses of opioids (fentanyl 25 μg/kg with onset of rewarming and fentanyl 25 μg/kg post CPB, for example) or a continuous infusion were necessary as opioid concentrations are known to decrease markedly during CPB [111]. This technique provides hemodynamic stability although it does not guarantee suppression of the endocrine response to surgical stimulation.

Neonates and infants undergoing deep hypothermic CPB surgery are able to generate a significant stress response [72]. A 17-fold increase in epinephrine and 10-fold increase in norepinephrine levels in infants were seen after 1 h of circulatory arrest at 18°C [112]. The reported magnitude of the stress response after cardiac surgery is variable and is influenced by

patient age, type of anesthesia, level of hypothermia, and the duration of CPB and circulatory arrest [113]. In a recent study of stress hormone release during infant cardiac surgery and deep hypothermic CPB using this fentanyl dosing regimen, the endocrine response was not obtunded, yet there were no adverse outcomes. In addition, no specific relationship between opioid dose, plasma fentanyl level, and hormone or metabolic stress response was established [114]. Most centers have abandoned the routine use of high-dose opioid anesthesia in favor of low or moderate doses (fentanyl 5–25 μg/kg or sufentanil 0.5–2.5 μg/kg) in conjunction with volatile anesthetics agents, benzodiazepines, or dexmedetomidine. These lower doses of opioids also facilitate early postoperative tracheal extubation, which has been increasingly adopted in many centers [115]. The high-dose opiate technique is usually reserved for critically ill and hemodynamically vulnerable patients.

Remifentanil is a synthetic ultrashort-acting opioid, rapidly metabolized by non-specific tissue esterases [116]. It is unique among the currently available opioids because of its extremely short context-sensitive half-time (3–5 min), which is largely independent of the duration of infusion. Remifentanil may cause significant respiratory depression and is usually administered to patients who are mechanically ventilated. It may be useful for patients with limited cardiorespiratory reserve undergoing procedures such as cardiac catheterization or pacemaker placement because intense analgesia is provided without significant hemodynamic complications. It may also be used to maintain anesthesia during mild hypothermic CPB for patients who are extubated immediately after surgery in the operating room, such as after atrial septal defect repair [117]. Patients usually emerge quickly once the infusion has been stopped, and opioid side-effects are reduced because of the short duration of action.

Other intravenous agents

The benzodiazepine derivatives (e.g. midazolam) can be useful when titrated in small doses (0.05–0.1 mg/kg), especially in older patients with CHD. Lack of pain on injection and lack of vascular damage make water-soluble midazolam a more useful benzodiazepine than diazepam, particularly because it has a shorter duration of action. Benzodiazepines are commonly used to ensure adequate hypnosis during opioid-based anesthesia, but may also improve hemodynamic stability. In a study of children with acyanotic heart disease undergoing cardiac surgery, the addition of diazepam to fentanyl-based anesthesia (75 μg/kg) resulted in a more stable hemodynamic profile without an increase in epinephrine levels when compared with an isoflurane-based anesthetic technique [118]. In a study of younger children undergoing correction of tetralogy of Fallot, the combined use of sufentanil and flunitrazepam provided a more stable hemodynamic profile and catecholamine response compared with a sufentanil-based technique alone [119].

Propofol can be used judiciously in patients with CHD. The predominant hemodynamic effect of propofol 1–3 mg/kg is a reduction in SVR with no effect on PVR. In patients with R-L shunting this results in a decrease in pulmonary blood flow and arterial oxygenation saturation [120,121]. Propofol should be avoided or used with great caution in patients with systemic outflow tract obstruction because the decrease in SVR can exacerbate the obstruction and lead to coronary ischemia and cardiovascular compromise. The venodilation associated with propofol administration also requires that it be used with caution in patients who have undergone a previous cavopulmonary connection. The resting venous tone is increased in this patient group, and the fall in preload could result in significant hypotension during induction.

Etomidate is an anesthetic induction agent with the advantage of minimal cardiovascular and respiratory depression. An intravenous dose of 0.3 mg/kg induces a rapid loss of consciousness with minimal respiratory depression for a duration of 3–5 min. At this dose it does not substantially alter hemodynamics or either R-L or L-R shunting in patients with CHD [122,123]. It may cause pain on injection and is associated with spontaneous movements, hiccoughing, and myoclonus. Etomidate may be used as an alternative to the synthetic opioids for induction of patients with limited myocardial reserve. A single dose of etomidate can suppress adrenal steroidogenesis and as a result it is not approved for continuous infusion [124].

Dexmedetomidine is an imidazole derivative presynaptic α2-binding agent that binds to the locus ceruleus and spinal cord to provide sedation and some analgesia. It is highly selective for α2 binding (1600:1 α2 to α1), and is US Food and Drug Administration (FDA) approved in adults 18 years or older for intensive care unit (ICU) sedation, procedural sedation, and as an adjunct to intraoperative anesthesia and sedation [125,126]. It is now being used extensively in the postoperative cardiac surgery ICU setting in children, and increasingly in the operating room, and in the catheterization laboratory as a sedative agent and an adjunct to general anesthesia [127]. Dexmedetomidine can cause bradycardia, hypotension, heart block, sinus arrest, and junctional bradycardia; the mechanism is decreased sympathetic outflow from the central nervous system [125,126,128,129]. Slow loading doses over 10 min, and avoiding excessive infusion dosing, reduces the risk of these adverse effects. Dexmedetomidine preserves normal breathing patterns and may facilitate early extubation protocols [130]. In addition, dexemedetomidine reduces the incidence of postoperative tachydysrhythmias, both supraventricular and ventricular [131]. It also reduces the dose of opioids and volatile anesthetic agents when used for congenital cardiac surgery with bypass [132]. Dexmedetomidine is contraindicated in patients with pre-existing heart block or junctional or other bradyarrythmias.

Pharmacokinetics of dexmedetomidine both during and after infant cardiac surgery have been studied; clearance is significantly lower in neonates and loading and infusion doses should be reduced by about 50% in this age group [133]. Loading doses of 0.5–1.0 μg/kg and infusions of 0.5–0.75 μg/kg/h will result in therapeutic plasma concentrations of 300–700 pg/mL. This dose, added to other sedative and analgesic agents such as midazolam and fentanyl, may be adequate for procedural sedation for CHD. Intraoperatively, the same doses can be utilized in conjunction with a reduced dose of opioids, e.g. fentanyl 10–20 μg/kg, and volatile agents to provide surgical anesthesia [130]. Caution must be exercised to monitor heart rate and rhythm carefully, and reduce the dose or discontinue dexmedetomidine if bradyarrythmia occurs. Dexmedetomidine should be avoided in electrophysiological studies because it is likely to suppress many tachydysrhythmias [134]. Dexmedetomidine will also

reduce pulmonary artery pressure and maintain pulmonary vascular resistance in patients with pulmonary hypertension [135]. Finally, large rapid bolus doses above 0.75–1.0 μg/kg can cause hypertension due to some peripheral α1 receptor binding [136].

KEY POINTS: CHOICE OF ANESTHETIC AGENTS

- Right-to-left shunting slows the rate of rise of the arterial level of volatile anesthetic agents as blood bypasses the lungs; the effect is greatest with less soluble agents such as sevoflurane, and less with more soluble agents such as halothane
- Right-to-left shunts can result in high arterial and brain levels of IV induction agents
- Left-to-right shunting has minimal effect on the uptake of volatile anesthetic agents
- Nitrous oxide does not affect PVR in children, but may have a mild effect in decreasing cardiac output and systemic arterial pressure
- Volatile agents, ketamine, propofol, opioids, benzodiazepines, etomidate, and dexmedetomidine provide a wide variety of choices for anesthetic maintenance. Knowledge of the patient's pathophysiology and the hemodynamic effects of these drugs is essential to formulate an appropriate anesthetic plan

Anesthesia for cardiac surgery

Communication between the anesthesia and surgical teams is of utmost importance during surgery for CHD. The manipulations of each team influence the other, and close coordination of activities is necessary for optimal patient care. Specific problems occurring with total repair or palliation of specific congenital cardiac lesions are covered later in the chapter. General problems that occur with various types of closed and open cardiac surgical procedures are considered here.

Anesthetic management of closed cardiac procedures

Patent ductus arteriosus, coarctation of the aorta, and repair of vascular rings are the only congenital cardiac anomalies corrected with closed procedures. Closed palliative procedures, including systemic-to-pulmonary shunts, pulmonary artery banding, and procedures to improve interatrial mixing (Blalock–Hanlon atrial septectomy), are performed infrequently as the trend to definitively correct the CHD early continues. Anesthesia for closed palliative procedures is in some ways more demanding because CPB is not available if the patient's hemodynamic status deteriorates. Therefore, monitoring requirements are stringent, and central venous and arterial access are usually mandatory. Pulse oximetry is invaluable in these cases to evaluate the infant's condition and to assess the effectiveness of the closed surgical procedure.

Acid–base and electrolyte balance are meticulously maintained at normal levels throughout closed procedures. When these procedures are done via a thoracotomy, the operative field is rarely visible to the anesthesiologist, and marked deterioration of cardiopulmonary function may result from surgical manipulations. Any deterioration in the infant's condition should be immediately communicated to the surgeon, who has a view of the surgical field and knows what is being done there. Some compromise of ventilation and pulmonary blood flow inevitably occurs during these procedures, occasionally with severe decreases in arterial oxygen saturations. Surgical manipulations can be altered or temporarily stopped while maneuvers are undertaken to recover the patient's status to baseline.

Mechanical ventilation

Altered lung mechanics and ventilation/perfusion abnormalities are common problems in the immediate postoperative period [137]. Besides preoperative problems secondary to increased Qp/Qs, additional considerations include the surgical incision and lung retraction, increased lung water following CPB, possible pulmonary reperfusion injury, surfactant depletion, and restrictive defects from atelectasis and pleural effusions.

In general, neonates and infants with their limited physiological reserve should not be weaned from mechanical ventilation until hemodynamically stable, and factors contributing to an increase in intrapulmonary shunt and altered respiratory mechanics have improved.

Volume-limited ventilation

A traditional approach to mechanical ventilation in children with CHD has been the use of a volume-limited, time-cycled mode, with large tidal volumes of 15–20 mL/kg and no PEEP. This approach was developed in the early years of congenital heart surgery when older generations of ventilators existed and the monitoring of ventilation was frequently less than ideal. While the peak inspiratory and mean airway pressure are usually increased using large tidal volumes in this mode, changes in compliance and resistance can be readily detected. If there is a sudden change in pulmonary mechanics from atelectasis, pneumothorax, or endotracheal tube obstruction, the peak inspiratory pressure alarm limit is reached as the ventilator tries to deliver the preset tidal volume.

However, for neonates and infants, the compressible volume of the ventilator circuit (1–1.5 mL/cmH_2O peak inspiratory pressure) means that the delivered tidal volume is less than the preset volume. For older patients receiving larger tidal breaths, the volume lost by compression of gas in the circuit is minimal and rarely affects their tidal ventilation. But for neonates and infants, this compressible volume may be a considerable component of their tidal ventilation. Further, any leak around the endotracheal tube means that a proportion of the delivered tidal volume may be lost. Inspiratory and expiratory times also need to be closely observed to prevent excessive auto-PEEP. Variable time constants (i.e. compliance × resistance) within regions of the lung are common in children with defects associated with high pulmonary blood flow, as well as following CPB. Using a volume-limited, time-cycled mode, those areas of lung with an increased time constant may be preferentially ventilated and overdistended, contributing to ventilation/perfusion mismatch and potential lung

injury. Contemporary approaches to volume-limited ventilation emphasize reduction in risk for volutrauma and barotrauma and recommend lower tidal volumes of 5–7 mL/kg, which have been demonstrated to reduce lung injury in ventilated adult patients in the intensive care setting; outcome data are less clear in pediatric patients [138]. Modern anesthesia ventilators with smaller internal compression volumes, and more accurate calibration of tidal volumes accounting for internal and external compression volumes, enable more accurate volume ventilation even in smaller infants [139].

Pressure-limited ventilation

A pressure-limited, time-cycled mode of ventilation is often appropriate in children weighing less than 10 kg, particularly those with significant alteration in lung compliance and airway resistance. A decelerating flow pattern is used when a breath is delivered to the patient until a preset peak inspiratory pressure is achieved. The delivered tidal volume will vary according to the compliance and resistance of the lung, and therefore from breath to breath. Both the peak inspiratory pressure and the inspiratory time can be manipulated to increase or decrease the delivered tidal volume. A square wave pressure waveform is generated by changing the inspiratory time, which will also alter the mean airway pressure. In general, it is preferable to set a minute ventilation using the lowest possible mean airway pressure. In-line monitoring enabling breath to breath assessment of tidal volume and mean airway pressure is essential, with appropriate alarm limits set such that acute changes in compliance and resistance can be detected.

Cardiorespiratory interactions

Cardiorespiratory interactions vary significantly between patients, and it is not possible to provide specific ventilation strategies or protocols that will cover all patients. Rather, the mode of ventilation must be matched to the hemodynamic status of each patient to achieve the appropriate cardiac output and gas exchange. Frequent modifications to the mode and pattern of ventilation may be necessary during recovery after surgery, with attention to changes in lung volume and airway pressure.

Lung volume

Changes in lung volume have a major effect on PVR, which is lowest at FRC, while both hypo- and hyperinflation may result in a significant increase in PVR (Fig. 27.11). At low tidal volumes, alveolar collapse occurs because of reduced interstitial traction on alveolar septae. In addition, radial traction on extra-alveolar vessels such as the branch pulmonary arteries is reduced, thus reducing the cross-sectional diameter. Conversely, hyperinflation of the lung may cause stretching of the alveolar septae and compression of extra-alveolar vessels.

An increase in PVR increases the afterload or wall stress on the right ventricle (RV), potentially compromising RV function and contributing to decreased left ventricle (LV) compliance secondary to interventricular septal shift. In addition to low cardiac output, signs of RV dysfunction including tricuspid regurgitation, hepatomegaly, ascites, and pleural effusions may be observed.

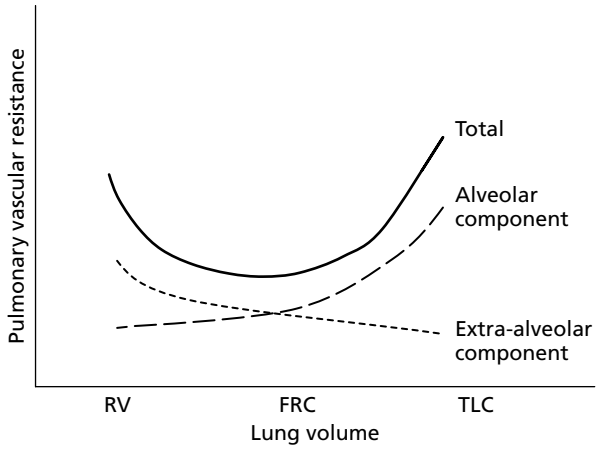


Figure 27.11 Lung volume impacts pulmonary vascular resistance (PVR). In the diagram, there is a marked decrease in PVR when increasing lung volume from residual volume (RV) to functional residual capacity (FRC). This is mainly a function of opening alveoli and shutting open extra-alveolar vessels (a drop in extra-alveolar resistance; dotted line). Further increases in lung volume from FRC to total lung capacity (TLC) cause increases in PVR. This is mainly due to compression of intra-alveolar vessels by air trapping (alveolar component; dashed line). Total PVR is minimized at FRC (solid line).

Intrathoracic pressure

An increase in mean intrathoracic pressure during positive pressure ventilation decreases preload to both pulmonary and systemic ventricles, but has the opposite effect on afterload to each ventricle (Table 27.5)[140].

Right ventricle

The reduction in RV preload that occurs with positive pressure ventilation may reduce cardiac output (Fig. 27.12) Normally the RV diastolic compliance is extremely high and the pulmonary circulation is able to accommodate changes in flow without a large change in pressure. An increase in mean intrathoracic pressure increases the afterload on the RV from direct compression of extra-alveolar and alveolar pulmonary vessels.

Table 27.5 The effect of a positive pressure mechanical breath on afterload and preload to the pulmonary and systemic ventricles.

	Afterload	Preload
Pulmonary ventricle	Elevated effect: ↑ RVEDp ↑ RVp ↓ Antegrade PBF ↑ PR and/or TR	Reduced effect: ↓ RVEDv ↓ RAp
Systemic ventricle	Reduced effect: ↓ LVEDp ↓ LAp ↓ Pulmonary edema	Reduced effect: ↓ LVEDv ↓ LAp Hypotension

LAp, left atrial pressure; LVEDp, left ventricle end-diastolic pressure; LVEDv, left ventricle end-diastolic volume; PBF, pulmonary blood flow; PR, pulmonary regurgitation; RAp, right atrial pressure; RVEDp, right ventricle end-diastolic pressure; RVEDv, right ventricle end-diastolic volume; RVp, right ventricle pressure; TR, tricuspid regurgitation.

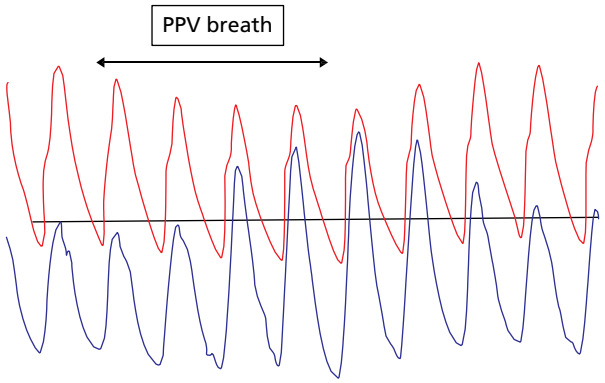


Figure 27.12 Positive pressure ventilation (PPV) effects on the right ventricle. Simultaneous tracings of aortic (red) and right ventricle (blue) pressure waveforms during PPV in a child with pulmonary artery stenosis. Note the increase in right ventricular pressure to approximately systemic (aortic) level during mechanical inspiration when the afterload on the right ventricle is increased.

Patients with normal RV compliance and without residual volume load or pressure load on the ventricle following surgery usually show little change in RV function from the alteration in preload and afterload that occurs with positive pressure ventilation. However, these effects can be magnified in patients with restrictive RV physiology, in particular neonates who required a right ventriculotomy for repair of tetralogy of Fallot, pulmonary atresia, or truncus arteriosus. While systolic RV function may be preserved, diastolic dysfunction is common with increased RV end-diastolic pressure and impaired RV filling.

The potential deleterious effects of mechanical ventilation on RV function are important to emphasize. The aim should be to ventilate with a mode that enables the lowest possible mean airway pressure, while maintaining lung volume. While the use of a low peak inspiratory pressure, short inspiratory time, increased intermittent mandatory rate, and low levels of PEEP has been recommended as one ventilation strategy in patients with restrictive RV physiology, the smaller tidal volumes (e.g. 6–8 mL/kg) during this pattern of ventilation may reduce lung volume and FRC, thereby increasing PVR and afterload on the RV. An alternative strategy in a pressure-limited mode of ventilation is to use larger tidal volumes of 12–15 mL/kg, with a longer inspiratory time of 0.8–1.0 s, increased peak inspiratory pressure of around 30 cmH_2O and low PEEP (i.e. wide ΔP), and slow intermittent mandatory rate of 12–15 breaths/min. For the same mean airway pressure, RV filling is maintained and RV output augmented by maintaining lung volume and reduced RV afterload.

Left ventricle

Left ventricular preload is also affected by changes in lung volume. Pulmonary blood flow, and therefore preload to the systemic ventricle, may be reduced by an increase or decrease in lung volume secondary to alteration in radial traction on alveoli and extra-alveolar vessels.

The systemic arteries are under higher pressure and not exposed to radial traction effects during inflation or deflation of the lungs. Therefore, changes in lung volume will affect LV preload, but the effect on afterload is dependent upon changes in intrathoracic pressure alone rather than changes in lung volume.

In contrast to the RV, a major effect of positive pressure ventilation on the LV is a reduction in afterload (Fig. 27.13). Using LaPlace's Law, wall stress is directly proportional to the transmural LV pressure and the radius of curvature of the LV. The transmural pressure across the LV is the difference between the intracavity LV pressure and surrounding intrathoracic pressure. Assuming a constant arterial pressure and ventricular dimension, an increase in intrathoracic pressure, as occurs during positive pressure ventilation, will reduce the transmural gradient and therefore wall stress on the LV [140]. Therefore, positive pressure ventilation and PEEP can have significant beneficial effects in patients with LV failure.

Patients with LV dysfunction and increased end-diastolic volume and pressure can have impaired pulmonary mechanics secondary to increased lung water, decreased lung compliance, and increased airway resistance. The work of breathing is increased and neonates can fatigue early because of limited respiratory reserve. A significant proportion of total body oxygen consumption is directed at the increased work of breathing in neonates and infants with LV dysfunction, contributing to poor feeding and failure to thrive. Therefore, positive pressure ventilation has an additional benefit in patients with significant volume overload and systemic ventricular dysfunction by reducing the work of breathing and oxygen demand.

Lung injury

It is important to appreciate that mechanical ventilation may result in significant lung injury, particularly when high tidal volumes are used [141]. Large, rapid changes in tidal volumes may lead to shear stress on the alveolar septae and subsequent alveolar capillary disruption. The same mechanisms that result in air leak may also result in disruption of the microcirculation, causing an increase in total lung water with subsequent increase in airway resistance and reduction in lung compliance.

Lung disease is usually not homogenous, with regions of the lung having different time constants, i.e. the concept of "fast" alveoli and "slow" alveoli. When using a volume-limited strategy, the more compliant alveoli will distend in preference to regions of lung that are collapsed or have slow time constants, thereby resulting in regional alveolar overdistension and trauma. This may be less evident with a pressure-limited strategy, as the more compliant or faster alveoli will distend to the preset pressure limit and then, depending on the inspiratory time, regions of lung with reduced time constants will gradually distend and be recruited.

While a relatively large tidal volume of 12–15 mL/kg is beneficial for many patients following congenital heart surgery for maintaining lung volume at lower PVR, lung injury may occur if a high-volume strategy is continued for a prolonged period (i.e. volutrauma). Using a pressure-limited mode of ventilation will enable a relatively constant tidal volume without a wide swing in peak inspiratory pressure or regional alveolar overdistension. It is essential to continually re-evaluate the mode of ventilation and modify it according to hemodynamic responses. Fortunately, most patients undergoing congenital cardiac surgery do not have parenchymal lung disease and changes in pulmonary mechanics, such as secondary to changes in lung water, are generally resolved following complete surgical repair and diuresis after CPB.

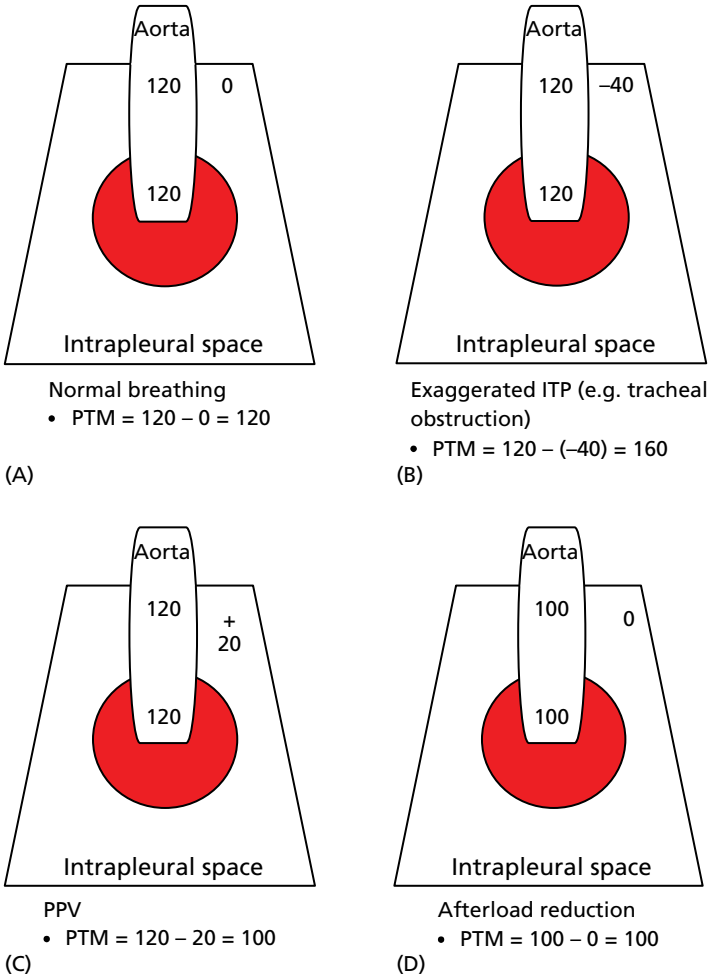


Figure 27.13 Transmural aortic pressure affects left ventricular afterload. LaPlace's Law, the transmural aortic pressure (PTM) is affected by intrapleural pressure. (A) During normal breathing there is very little effect of the intrapleural pressure on PTM and thus left ventricular afterload. (B) The generation of pathological degrees of negative intrapleural pressure (as with severe airway obstruction or decompensated heart failure) significantly increases left ventricular afterload. (C, D) Provision of positive pressure ventilation (PPV) (C) or pharmacological afterload reduction (D) can both independently reduce left ventricular afterload. Pressure units are in mmHg. ITP, intrathoracic pressure.

Positive end-expiratory pressure

The use of PEEP in patients with CHD has been controversial. It was initially perceived not to have a significant effect in terms of improving gas exchange, and there was concern that the increased airway pressure could have a detrimental effect on hemodynamics and contribute to lung injury and air leak.

Nevertheless, PEEP increases FRC, enabling lung recruitment, and redistributes lung water from alveolar septal regions to the more compliant perihilar regions. Both of these effects will improve gas exchange and reduce PVR. However, excessive levels of PEEP may be detrimental by increasing afterload on the RV. Usually 3–5 cmH_2O of PEEP will help maintain FRC and redistribute lung water without causing hemodynamic compromise.

Management of cardiopulmonary bypass

The cardiac anesthesiologist must be familiar with CPB techniques and their effects on multiple organ systems. A schematic representation of a common arrangement for a pediatric cardiopulmonary bypass circuit is depicted in Figure 27.14. An important component of the improvement in early outcome following congenital heart surgery has been the advances in CPB techniques, myocardial protection, and perioperative pharmacological and mechanical support. The exposure of blood elements to the non-epithelialized CPB circuit induces a systemic inflammatory response (Fig. 27.15). The effects of the interactions of blood components with the extracorporeal circuit are magnified in children due to the large bypass circuit surface area and priming volume relative to patient blood volume. Humoral responses include activation of complement, kallikrein, eicosanoid, and fibrinolytic cascades. Cellular responses include platelet activation and an inflammatory response with an adhesion molecule cascade stimulating neutrophil activation and release of proteolytic and vasoactive substances [142].

The clinical consequences of the systemic inflammatory response include increased interstitial fluid and generalized capillary leak with the potential for multiorgan dysfunction. Total lung water is increased with an associated decrease in lung compliance and increase in the alveolar-to-arterial O_2 ($A–aO_2$) gradient. Myocardial edema results in impaired ventricular systolic and diastolic function. Impaired myocardial function is sometimes exacerbated by an additional 20–30% decrease in cardiac output frequently seen in neonates in the

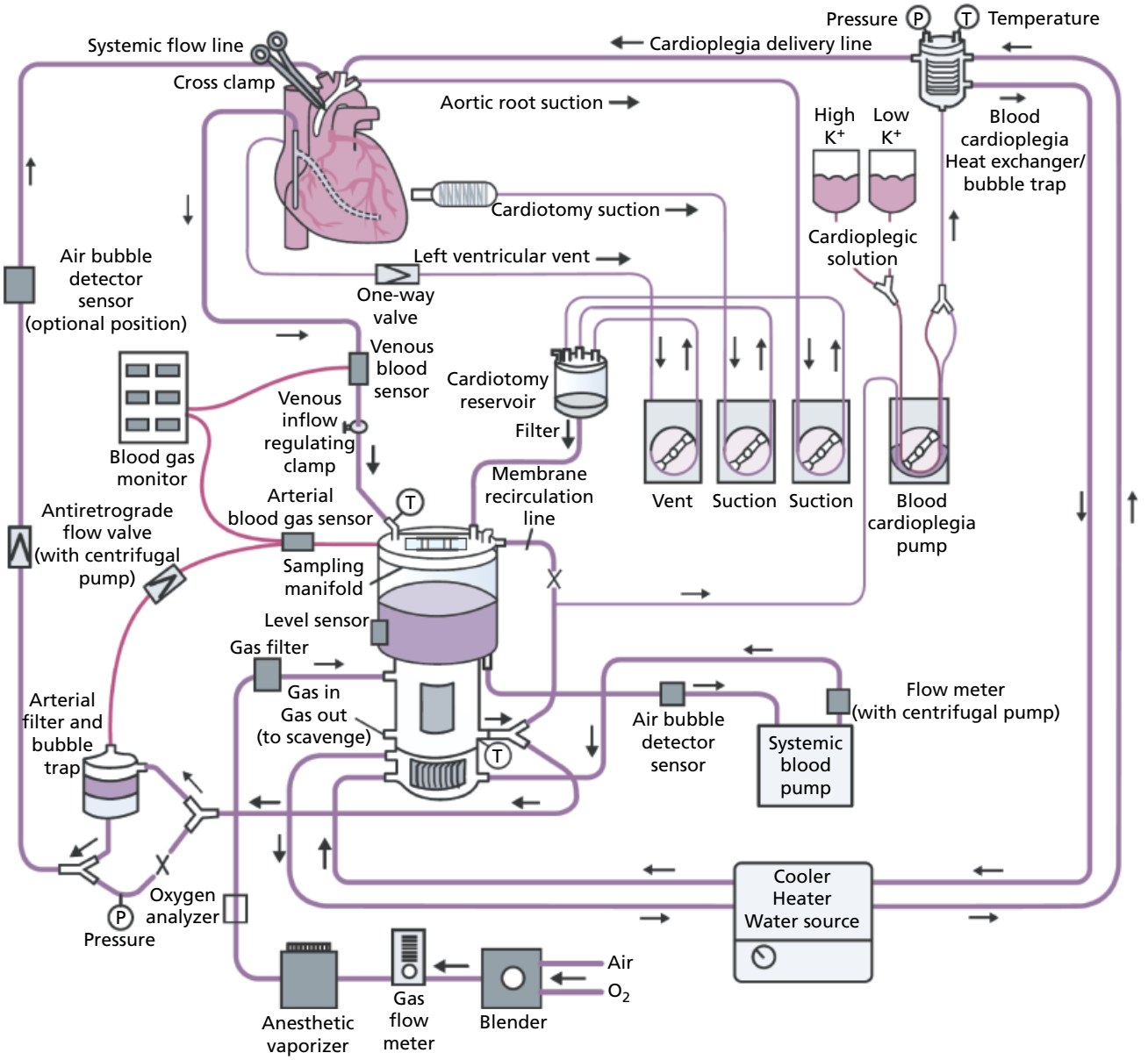


Figure 27.14 Schematic diagram of a cardiopulmonary bypass circuit. This scheme depicts a membrane oxygenator with integral hard-shell venous reservoir and external cardiotomy reservoir. Many circuits have the cardiotomy reservoir, venous reservoir, and oxygenator integrated into one single unit. The systemic blood pump may be either a roller or centrifugal pump. Most pediatric venous cannulations are bicaval with two separate venous cannulas instead of the single venous cannula depicted here. Carbon dioxide can also be added to the inspired gas to facilitate pH stat blood gas management. There are many variations of the CPB circuit and the anesthesiologist needs to be familiar with the configuration in their local institution. Arrows indicate the direction of flow; X, placement of tubing clamps; P, pressure sensor; T, temperature sensors. *Source*: Reproduced from Hessel and Hill [358] with permission of Wolters Kluwer.

first 6–12 h following surgery. Renal function is compromised by the inflammatory response and by lower cardiac output. Sternal closure may need to be delayed due to mediastinal edema if cardiorespiratory compromise is noted when closure is attempted. Ascites, hepatic congestion, and bowel edema may lead to abdominal distention that affects mechanical ventilation and can cause a prolonged ileus that delays feeding. An inflammatory-based coagulopathy post CPB may contribute to delayed hemostasis.

Numerous strategies have evolved to limit the effect of endothelial injury resulting from the systemic inflammatory response. The most important strategy is limiting the time spent on bypass and the duration of deep hypothermic circulatory arrest. Hypothermia and corticosteroids are important pre-bypass measures to limit activation of the inflammatory response, as is the use of antioxidants such as mannitol. Interstitial fluid accumulation can be reduced by increasing the oncotic pressure of the circuit prime with albumin or blood products and by using ultrafiltration to reduce body water and tissue edema.

Ultrafiltration during CPB

A number of different ultrafiltration techniques can be used in association with pediatric CPB. Conventional ultrafiltration (CUF) refers to ultrafiltration during CPB. CUF can only be performed if the volume in the venous reservoir is sufficient

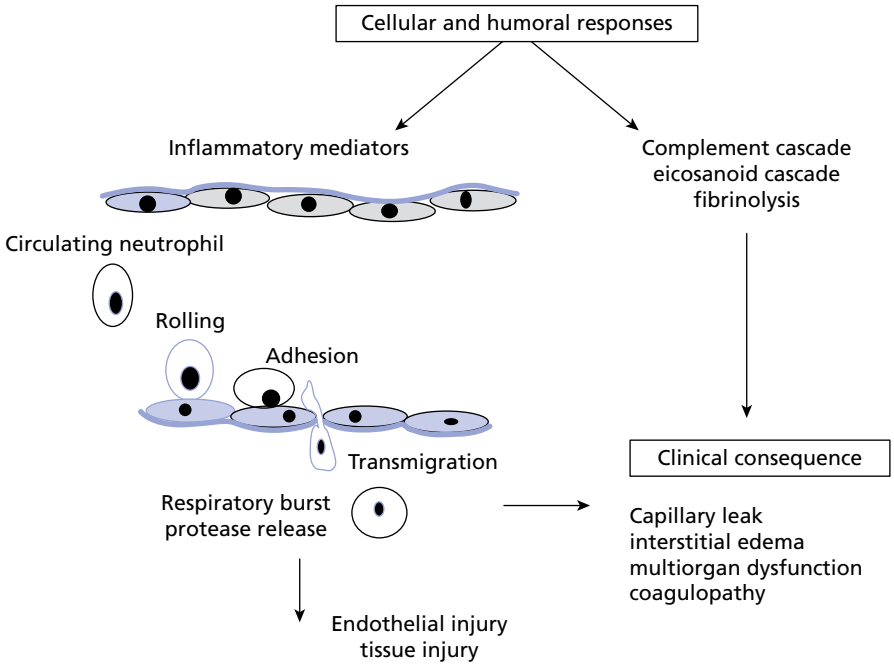


Figure 27.15 Cellular and humoral response to cardiopulmonary bypass.

to allow removal of ultrafiltrate fluid volume. Modified ultrafiltration (MUF) is a similar technique that allows ultrafiltration to continue after weaning from CPB. Blood from the CPB circuit is pumped to an ultrafiltrator through an arteriovenous or venovenous limb before returning to the patient. The CPB circuit remains primed while the CPB and patient's blood is ultrafiltrated. Blood volume is kept constant by adding blood from the CPB circuit to the ultrafiltration circuit as ultrafiltrate volume is removed. The major advantage of MUF over CUF is that it allows hemoconcentration to continue once CPB has been terminated. As a result, MUF normally allows a greater degree of hemoconcentration than can be obtained with CUF alone, particularly in small children. Some institutions utilize both CUF and MUF as the techniques are not mutually exclusive [143]. Heparin anticoagulation must be maintained during MUF with protamine reversal of heparin initiated after termination of MUF. The endpoint for termination of MUF following CPB varies from institution to institution with some institutions terminating MUF after a set time interval (e.g. 15–20 min), a set hematocrit (e.g. 40%), or a set volume removed (e.g. 750 mL/m^2).

Dilutional (DUF) and zero-balance ultrafiltration (ZBUF) are similar to CUF but produce a high-volume ultrafiltrate that is continuously replaced with crystalloid solution during CPB. DUF is performed throughout CPB with ultrafiltration rates of 40–80 mL/kg/h [144,145]. ZBUF is usually done during rewarming and utilizes ultrafiltration rates of 200 mL/min/m^2. These methods do not result in hemoconcentration but may be beneficial in removing inflammatory mediators. MUF is usually used in conjunction with these techniques to obtain hemoconcentration.

MUF has been demonstrated to reduce total body water, attenuate dilutional anemia and coagulopathy, reduce homologous blood requirements, narrow the A–aO_2 gradient, improve LV compliance and systolic function as well as arterial blood pressure, and decrease inotropic requirements in the immediate postfiltration period [146–153]. In a non-randomized, retrospective analysis of cavopulmonary connection procedures (primarily hemi-Fontan and lateral tunnel Fontan procedures), patients in whom MUF was used had a lower incidence of pleural and pericardial effusions and a shorter hospital stay than patients in whom MUF was not used [148]. MUF may reduce postoperative ventilatory support times but this has not been a consistent finding despite short-term improvements in pulmonary compliance [148,150,154].

A number of studies have shown MUF to be effective in removing both anti-inflammatory (interleukin (IL)-10 and IL-1 receptor antagonist) and proinflammatory (tumor necrosis factor α, IL-1β, IL-6, IL-8, complement fragments C3a and C5a, and endotoxins) mediators generated during CPB, while other studies have not confirmed this efficacy [150,155–161]. In addition, MUF may offer no advantage over CUF in terms of inflammatory mediator removal [157]. The extent to which the beneficial effects of MUF are related to reduction of tissue edema, removal of inflammatory mediators, and hemoconcentration has not been clarified [143].

ZBUF in conjunction with MUF has been shown to be more effective than MUF alone in reducing inflammatory mediator concentrations measured immediately following ultrafiltration Patients in the ZBUF group also had reduced blood loss, a shorter duration of postoperative ventilatory support, and a narrower 24 h A–aO_2 gradient [144]. DUF in conjunction with MUF has been shown to be more effective than CUF alone in reducing plasma endothelin 1 and thromboxane B_2 levels following CPB and in attenuating postoperative pulmonary hypertension [145,149,161]. In addition, the duration of postoperative ventilatory support and transfusion requirements was reduced in a group of high-risk patients (neonates, patients with pulmonary hypertension, and patients with prolonged CPB times) [149,162]. A recent study demonstrated a modest reduction in IL-6, a narrowed A–aO_2 gradient, and improved pulmonary compliance but no reduction in the

length of postoperative ventilatory support with CUF in conjunction with MUF as compared with no ultrafiltration [163]. No advantage in terms of improved postoperative course was demonstrated when CUF combined with MUF was compared with CUF alone, despite the fact that a larger filtrate volume was obtained in the combined group [164,165]. In addition, MUF alone and CUF alone were indistinguishable in their effect on hematocrit, mean arterial pressure, heart rate, and LV shortening fraction when equal filtrate volumes were removed in another trial [166]. Finally, combining DUF and MUF offered no clinical advantage over DUF or MUF alone despite larger filtrate volumes in the combined group [167].

Ultrafiltration techniques are useful for hemoconcentration, removal of inflammatory mediators, and reducing total body water following CPB but they do not prevent or treat the inflammatory response to CPB. Inflammation is a multifactorial response to CPB and needs to be treated at multiple levels of the process. Drugs that prevent or modify adhesion molecule–endothelial cell interactions will likely be pivotal in controlling the inflammatory response and are being pursued in laboratory and clinical studies.

CPB in patients with CHD involve different techniques than those used in adult patient undergoing correction of acquired heart disease. Venous cannulation in neonates and infants may be more complicated than in adults. Multiple cannulas may be required depending on the anatomy and bypass technique, and positioning of the cannulas may be challenging because of the small size of the vessels. Malpositioned venous cannulas may result in elevated venous pressures that will decrease perfusion pressures, particulary in the cerebral and splanchnic circulations. Signs of malpositioned venous cannulas include reduced venous return to the bypass circuit, abdominal distention from splanchnic congestion, and head suffusion secondary to cerebral congestion. Elevated SVC pressures will reduce cerebral blood flow, increase the risk of cerebral edema, and reduce the rate of cerebral cooling.

Adequacy of systemic perfusion cannot be estimated by pump flow in the presence of systemic-to-pulmonary shunts that are common in patients with CHD (e.g. Blalock–Taussig shunts, patent ductus arteriosus, and native aortopulmonary collateral vessels) These shunts must be controlled prior to onset of CPB, otherwise systemic blood flow will be shunted to the pulmonary circulation. Excessive pulmonary blood flow may lead to pulmonary congestion and myocardial distension from the increased blood return to the heart. Systemic hypoperfusion and uneven cooling or rewarming may result unless perfusion flow is increased to compensate for flows through these shunts.

Moderate and deep hypothermic CPB are frequently used in patients with CHD. Moderate hypothermia requires pumps flows that meet the metabolic needs of the patient on CPB. The metabolic needs of neonates and infants indexed to surface area are higher than in adults. Flow rates of 100–150 mL/kg/min or indexed flows to 2.2–2.5 L/min/m^2 should provide adequate flow at normothermia or moderate hypothermia. Systemic perfusion in young patients is regulated primarily by flow rate, so that perfusion pressures of 30 mmHg or less are usually adequate in these patients especially when hemodilution decreases blood viscosity and SVR. A venous oxygen saturation of >75%, even differential temperature cooling, and low lactate levels suggest adequate perfusion [168]. Perfusion flow and pressure are misleading indices of adequate tissue perfusion in patients with poor venous drainage, severe hemodilution, malposition of the aortic cannula, or in the presence of a large left-to-right shunt. Deep hypothermia (<18°C) is often required to meet metabolic demand if reduced flow or "low-flow" CPB (flow rates of 30–50 mL/kg/min) is indicated for a particular surgical repair.

Optimal flow rates during moderate or deep hypothermic CPB cannot be determined by flow rate calculations alone, so adequacy of perfusion must be assessed by other measures. There is no one measure of index that assures adequate systemic perfusion on CPB, but a venous oxygen saturation of >75%, low lactate levels, and evenness of temperature measured at multiple sites suggest adequate perfusion [168]. Continuous monitoring of blood gases and oxygen saturation is important to identify trends in tissue oxygen extraction, but these numbers only provide global indices of perfusion, and monitoring regional perfusion is ideal. Cerebral perfusion can be monitored using transcranial sonography, near infrared spectroscopy, and electroencephalograms, but to date there are no monitors available for routine clinical use to monitor perfusion of other vascular beds.

Low-flow CPB and deep hypothermic circulatory arrest

Some cardiac repairs cannot be completed with aortic or venous cannulas in place. Deep hypothermic circulatory arrest (DHCA) allows cessation of CPB, removal of venous and arterial cannula, and exsanguination of the heart into the venous reservoir of the CPB circuit to improve surgical exposure. The technique is utilized primarily for the aortic arch reconstruction component of the stage 1 procedure for hypoplastic left heart syndrome, the repair of interrupted aortic arch, neonatal repair of total anomalous pulmonary venous return, and complicated intracardiac repairs in small (<2.5 kg) neonates and infants [169]. There has been substantial refinement of the technique of DHCA since its successful inception in the 1970s, but DHCA is still used selectively and for relatively short intervals (<45 min). The development of brain and body ischemia is directly related to core temperature prior to the onset of DHCA and circulatory arrest time. Arrest times of less than 40 min are associated with a lower incidence of seizures and fewer neurobehavioral deficiencies than longer intervals [170–173].

The large body surface area to mass ratio in neonates and infants makes cooling particularly efficient. A 2–3°C reduction in core temperature is common following induction of anesthesia and prior to CPB. The use of cooling blankets, low ambient room temperature, and reduced overhead operating light intensity helps maintain a low temperature during bypass and minimizes radiant heating of the myocardium. Cooling of the brain is improved by placing bags of ice around the head.

Regional low-flow perfusion (RLFP) techniques have been developed to perfuse limited area of the body to help prevent the potentially deleterious effects of DHCA on cerebral and somatic perfusion and oxygenation. In particular, antegrade cerebral perfusion (ACP) is sometimes used in aortic arch reconstruction in children with hypoplastic left heart syndrome undergoing the stage 1 procedure and in children with

aortic hypoplasia or interruption undergoing repair. A number of techniques to provide ACP via the right innominate artery have been described and are used in conjunction with deep hypothermia [174–177]. These techniques provide both cerebral and somatic perfusion to subdiaphragmatic viscera. Somatic perfusion is thought to occur via the extensive network of arterial collaterals in the neonate which link the supra- and subdiaphragmatic viscera. This network includes the internal thoracic and intercostal arteries.

The flow rates necessary to provide optimal cerebral and somatic perfusion during ACP have yet to be determined, although rates of 30–70 mL/kg/min are common. Efforts to optimize ACP flow rates utilizing near infrared spectrographic analysis of cerebral oximatery and transcranial Doppler have been undertaken [178].

Neurological injury is an inherent risk for any patient undergoing cardiac surgery and CPB, especially in neonates and infants where DHCA or low-flow techniques are commonly used. Reducing modifiable sources of neuronal injury during CPB is essential [179] as brain immaturity, coexistant congenital neurological abnormalities, and perinatal injury also contribute to long-term neurobehavioral deficiencies in CHD patients undergoing repair as a neonate or infant. Strategies to optimize cerebral protection during deep hypothermic CPB or arrest include prolonged duration of cooling (usually over 20 min) [180–182] and pH stat arterial blood gas management that normalizes pH during cooling by adding CO_2 to the sweep gas. Higher partial pressure of CO_2 causes dilation of the cerebral vasculature and allows for more even cooling of the brain [183]. A higher hematocrit (approximately 30%) prior to DHCA [184] and short DHCA intervals of <40 min have also been associated with improved neurological outcome [185].

Weaning from cardiopulmonary bypass

Arterial blood gases, electrolytes, and levels of anticoagulation are checked periodically during CPB and during the rewaming phase when the metabolic demand of the patient is expected to return to prehypothermic levels. Adequacy of rewarming is judged by measuring body temperature at multiple sites, including rectal or bladder and nasopharyngeal or esophageal temperatures. Prior to separation from bypass, electrolytes are normalized and any air is vented from the heart so air does not enter the systemic circulation as the heart begins ejecting blood. When rewarming is complete and cardiac function is judged adequate, weaning from CPB is accomplished by slowly allowing the heart to fill and eject while ventilation is re-established

Epicardial or transesophageal echocardiography can be used to assess ventricular function, competency of the atrioventricular and semi-lunar valves, outflow obstruction, and the presence of residual intracardiac shunts across the ventricular or atrial septa. Cardiac rhythm is assessed by continuous electrocardiograph monitoring. Direct observation of the heart can sometimes identify rhythm or contractility problems. Any necessary inotropic and vasopressor support is optimized prior to and after separation from CPB. Intracardiac and arterial pressures and waveforms are monitored to assess cardiac function, but there is seldom a specific number that needs to be achieved to ensure successful separation from CPB. The small size of the heart and the presence of residual defects sometimes make interpretation of pressures from monitoring lines difficult so trends are usually followed. Optimal ventricular filling pressures are estimated using filling pressures from preoperative catheterization data, the appearance of the heart, and infusion of small increments of volume while watching filling and systemic arterial pressures. The direct measurement of oxygen saturations from chambers of the heart enables calculations of residual intracardiac shunts immediately following surgery, and direct pressure measurements across systemic and pulmonary outflow tracts enable detection of residual obstructions. If systemic arterial pressure or gas exchange is inadequate, CPB is reinstituted while the problem is analyzed and appropriate corrective measures are taken.

Mild hypothermia often develops in neonates and infants after separation from CPB, so active warming of the patient and reduction in radiant and evaporative losses are important. Increased metabolic stress, pulmonary vasoreactivity, coagulopathy, and potential for dysrhythmias are associated with hypothermia. Hyperthermia must also be avoided because neurological injury may occur if the increased metabolic rate is not met when myocardial function is depressed and cerebral autoregulation is impaired post CPB [185].

Dilution of coagulation factors, damage to and dilution of platelets, and endothelial cell injury all contribute to post-CPB coagulopathy. Exposure of blood to surfaces of the CPB circuit leads to stimulation of the intrinsic pathway as well as the activation and aggregation of platelets, also contributing to post-CPB coagulopathy. Prompt management and meticulous control of surgical bleeding is often complicated by concealed suture lines but adequate hemostasis is essential to prevent the complications associated with transfusion of blood products. Preoperative risk factors for prolonged bleeding after bypass include chronic cyanosis in older patients, low cardiac output with associated tissue hypoperfusion, hepatic immaturity, and the use of platelet inhibitors such as PGE1 in neonates and infants [186,187]. See Chapter 12 for more detailed discussion of the management of hemostasis and blood transfusion.

Sternal closure and tamponade after cardiac operations

Chest closure is a time of potential hemodynamic instability in neonates and infants. The mediastinum is small and the presence of myocardial edema, blood, and tubes in the mediastinum can compress the heart and lead to tamponade physiology. This sometimes necessitates leaving the sternum open with closure after edema and any ongoing hemorrhage has resolved. The clinical signs of tamponade are frequently not present in small children even with impending cardiovascular collapse. Tamponade should always be suspected when hemodynamic instability occurs when ventilation and rhythm are adequate after chest closure. The chest is sometimes reopened in this situation with return of hemodynamic stability while the causes of tamponade are being investigated.

KEY POINTS: ANESTHESIA FOR CARDIAC SURGERY

- Non-bypass (closed) procedures include systemic-to-pulmonary artery shunting, coarctation of the aorta, and pulmonary artery banding. These are often performed via thoracotomy in small infants, and cardiorespiratory instability can be significant
- Positive pressure mechanical ventilation may have deleterious effects on hemodynamics, including right ventricular output, pulmonary hypertension, and decreased venous return in single-ventricle patients. It can also be beneficial to reduce systemic ventricle afterload in cases of ventricular dysfunction or obstruction
- Modern cardiopulmonary bypass techniques have reduced the incidence of immediate postoperative complications including severe coagulopathy, acute neurological insults, and severe inflammatory syndromes. Ultrafiltration, limiting deep hypothermic circulatory arrest, and avoiding extreme hemodilution are three approaches that have improved outcomes

Anesthesia for non-cardiac surgery

The approach to anesthesia for children with CHD just outlined is the same whether the proposed operation is cardiac or non-cardiac. Familiarity with the patient's pathophysiology guides preoperative evaluation and preparation, choice of monitors, and facilitates the smooth induction, maintenance, emergence from anesthesia, and helps plan postoperative care. Consultation with the patient's cardiologist to delineate the cardiac lesion and current functional status is an important part of the preoperative evaluation. Some cardiologists may have an incomplete appreciation of the physiological stresses of non-cardiac surgical procedures so preoperative discussion with the anesthesiologist and surgeon prior to the procedure is important. Physiological stresses might include blood loss, prolonged operative time, and surgical manipulations of the airway and peritoneal, thoracic, or cranial cavities. Intraoperatively, surgical manipulations that affect the cardiovascular balance of patient must be anticipated, recognized, and communicated to the surgeon.

Status of the disease

Children with CHD may present for non-cardiac operations before or after surgical repair or palliation. Surgical corrections are classified as anatomical where the circulation is in series and the LV is connected to the aorta, or physiological where the circulation is also in series but the actual anatomy is not corrected. Single-ventricle pallations or repairs where the RV is functioning as a systemic ventricle are examples of physiological corrections (Table 27.6). Palliated CHD in particular may have abnormal circulation with CHF, as well as hypoxemia, polycythemia, and pulmonary vascular disease. Corrected CHD may have significant residual problems including arrhythmias, ventricular dysfunction, shunts, valvular stenosis or regurgitation, and pulmonary hypertension.

Table 27.6 A classification for congenital cardiac surgical repairs

Type of repair	Outcome
Anatomical LV = systemic ventricle RV = pulmonary ventricle Circulation in series Cyanosis corrected	1. Simple reconstruction: structurally normal after repair (e.g. ASD, VSD, PDA). Late complications unlikely 2. Complex reconstruction: baffle, conduit, outflow reconstruction, or atrioventricular valve repair; late complications likely
Physiological Circulation in series Cyanosis corrected	1. Two ventricles: RV = systemic ventricle (e.g. Senning or Mustard procedure) LV = systemic ventricle 2. Single ventricle: Fontan procedure

ASD, atrial septal defect; LV, left ventricle; PDA, patent ductus arteriosus; RV, right ventricle; VSD, ventricular septal defect.

Chapter 28 presents a detailed discussion of anesthesia for non-cardiac procedures in patients with CHD.

Anesthesia for interventional procedures

The cardiac catheterization laboratory

Adequate sedation or general anesthesia during cardiac catheterization is often necessary to facilitate acquisition of meaningful hemodynamic data in infants and children. A recent study demonstrated an increased frequency of cardiac arrest in children undergoing cardiac catheterization, and is higher than that published for cardiac arrest during pediatric non-cardiac and cardiac surgery. Specific procedures have a higher risk, and infants appear to be at the highest risk [188]. This increased risk supports the notion that these patients ought to be managed by an experienced team of anesthesiologists working closely with the interventional cardiologists, nursing staff, and catheterization technicians to ensure a robust system for care is in place for direct communication and anticipation, and to promptly manage critical events when they occur [189].

Many hemodynamic or diagnostic catheterization procedures can be performed under sedation but general anesthesia may be perferable if the procedure is long, has the potential for significant hemodynamic compromise, or involves dilation of vessels that may be painful. Standard American Society of Anesthesiologists (ASA) monitors are required for all patients undergoing sedation and anesthesia. Hemodynamic data should be attained using conditions that are as close to baseline as possible (e.g. ventilating with room air), and the cardiologist will usually have to qualify hemodynamic data obtained under anesthesia or sedation to consider the effects of mechnaial ventilation and anesthetic agents.

Cardiac catheterization laboratories are usually remote from the operating room and are rarely configured to accommodate anesthesia personnel well. Work space is limited and the anesthesia personnel must position themselves for best access to the patient and anesthesia equipment. The anterior–posterior cameras can restrict acesss to the patient's airway,

and the lateral cameras can make transfer to and from the patient's stretcher challenging. The room is usually darkened to facilitate viewing of images and is often kept cold for best function of the radiological equipment. Care must be taken when positioning a patient on the catheterization table because of the risk of pressure ulcers and nerve traction injury, particulary when the arms are positioned above the head to facilitate imaging. Hypothermia from conductive and convective heat loss, as well as heat loss from the numerous flushes of catheters and sheaths, can be significant, so warming devices and temperature monitoring are important. Anesthesia personnel should also be mindful of the risks of radiation exposure and must wear protective clothing and stand an appropriate distance from the fluoroscopy equipment, particularly during cine acquisition.

Interventional cardiology

Transcatheter procedures for CHD in the interventional laboratory are both replacing and complimenting surgical treatments. Procedures that are routinely performed in the catheterization laboratory now include balloon valvuloplasty of congenitally stenotic aortic, mitral, and pulmonary valves; angioplasty for pulmonary arterial stenoses and postoperative aortic recoarctation, or angioplasty combined with transcatheter placement of endovascular stents for sustained relief of obstruction in arterial or subarterial (intracardiac) locations; radiofrequency ablation of abnormal conduction pathways; and embolization or device occlusion procedures of systemic-to-pulmonary arterial communications, venous channels, fistulas, muscular VSDs, ASDs, or PDA. Transcatheter pulmonary valve replacement is now common, particularly in patients with previous tetralogy of Fallot repair. Transcatheter aortic valve replacement has also been performed in pediatric patients and will likely be more common in the future [190]. Many procedures (e.g. PDA closure) are performed on an outpatient basis with the full participation of the anesthesiologist [191].

A collaborative approach to intervention and repair may offer improved results and new futures for patients with many types of serious CHD. The cardiac anesthesiologist is an integral part of catheter-based treatment and of the coordination of hybrid catheter-based and surgical procedures. A good example is the collaboration of catheter- and surgical -based treatments of teteralogy of Fallot with hypoplastic proximal and distal pulmonary arteries. Antergrade flow to the pulmonary artery early in life is established with a surgically placed homograft from the right ventricle to the pulmonary artery. The patient can then undergo serial balloon dilations of the pulmonary arteries with subsequent growth of these arteries which allows eventual complete surgical correction with VSD closure. Single-ventricle patients with a Fontan palliation may have a fenestration or communication at the atrial level that allows right-to-left shunting so that cardiac output is maintained during sudden increases in pulmonary vascular resistance. This fenestration can subsequently be test occluded in the catheterization laboratory and permanently occluded with a device if indicated [192].

Risks and complications

Placement of catheters in and through the heart increases the risk for dysrhythmias, perforation of the myocardium, damage to valve leaflets and chordae, cerebral vascular accidents, and air embolism. The use of radiopaque contrast material may cause an acute allergic reaction (although this is rare in children with non-ionic contrast media), pulmonary hypertension, and myocardial depression. Blood loss may be sudden and unexpected when large-bore catheters are used or vessels are ruptured. More insidious blood loss may occur over several hours in heparinized small children or neonates owing to bleeding around the catheter site or multiple aspirations and flushes of catheters. Transfusion requirements and appropriate vascular access should be continually assessed.

Arrhythmias, albeit transient, may be recurrent and fatal if not promptly treated. These include catheter-induced supraventricular tachyarrhythmias, ventricular tachycardia, ventricular fibrillation, and occasionally complete heart block requiring temporary transvenous pacing support. On most occasions, removal of the wire or catheter is sufficient for the arrhythmia to resolve, but it is always important that full resuscitation and cardioversion equipment be immediately available. An algorithm for treating catheter-induced arrhythmias is shown in Figure 27.16.

All cases share common risks associated with obtaining percutaneous vascular access that include injury to adjacent structures, vessel perforation, and hemorrhage. The underlying cardiac status or ASA classification of the patient increases the risk for adverse events during catheterization, but in many cases the event is directly related to the specific procedure. Some complications of specific interventional procedures are listed in Table 27.7. Many complications are potentially life threatening, and successful treatment of complications depends on prompt action by anesthesiologists cooperating closely with the interventional cardiologists.

Inadvertent release or detachment of embolic and closure devices results in systemic pulmonary arterial embolization. Embolization usually occurs immediately after attempted placement. Embolized devices can sometimes be retrieved by the use of a variety of retrieval catheters, but surgical removal may be necessary. If the device is lodged in the heart or a great vessel, emergent extracorporeal membrane oxygenation cannulation followed by CPB may be required for removal. Femoral artery and vein reconstruction is sometimes necessary following transcatheter removal of devices. Embolization can also be intentional and therapeutic, as when aortopulmonary collaterals are occluded by coils or hemostatic gelatin to decreased excessive pulmonary blood flow.

Balloon dilation of pulmonary arteries

Pulmonary artery balloon dilation and stent placement to relieve stenosis is a common procedure performed in the catheterization laboratory. Pulmonary artery stenosis may be a congenital or acquired lesion, and may be discrete, involving the main or branch pulmonary arteries, or diffuse, involving multiple distal segmental vessels. Some factors that determine whether dilation should be performed under sedation or general anesthesia include the extent of balloon dilation, anticipated complications, and the duration of the procedure.

Transient unilateral or unilobar pulmonary edema sometimes occurs following pulmonary artery dilation when there is a large increase in pulmonary blood flow and distal pulmonary artery pressure in previously underperfused pulmonary vascular beds. New infiltrate seen on fluoroscopy, blood-tinged

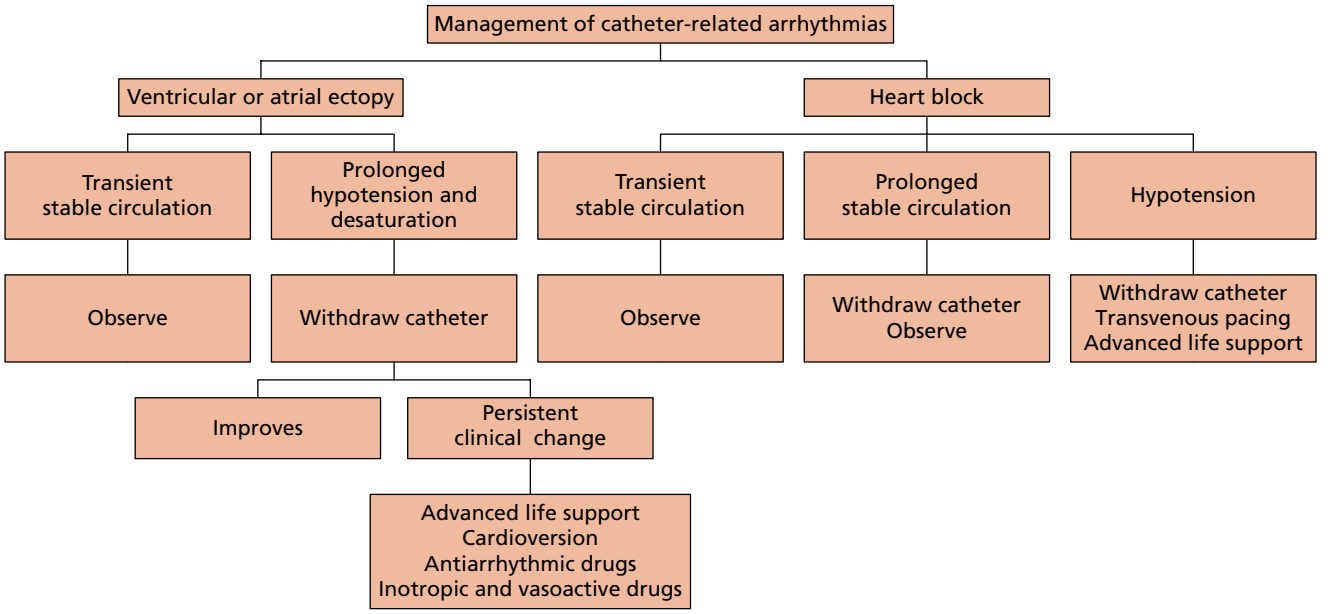


Figure 27.16 Algorithm for treating catheter-induced arrhythmias during cardiac catheterization.

Table 27.7 Complications in specific interventional procedures undertaken in the cardiac catheterization laboratory

Procedure	Representative lesion	Complications
Diagnostic catheterization	Congenital heart disease	Blood loss requiring transfusion Air embolism Cerebral vascular accident Myocardial perforation and tamponade Femoral vessel occusion Arrhythmias; ventricular and supraventricular tachycardia, ventricular fibrillation, complete heart block
Coil embolization	Aortopulmonary collaterals Blalock–Taussig shunts Anomalous coronary arteries Hepatic hemangiomas	Fevers Excessive hypoxemia Systemic embolization Hepatic necrosis
Transcatheter device closure	Patent ductus arteriosus Atrial septal defect Ventricular septal defect Baffle leak	Air or device embolization Blood loss Interference with atrioventricular valve function, ventricular arrhythmias, complete heart block
Balloon and stent dilations	Pulmonary artery stenosis Blalock–Taussig shunt Pulmonary valve stenosis Aortic valve stenosis Mitral valve stenosis Coarctation of the aorta Right ventricular conduit	Pulmonary artery tear and bleeding Unilateral pulmonary edema False aneurysm Cardiac arrest (Williams syndrome) Pulmonary artery tear and bleeding Thrombosis Pulmonary edema Pulmonary insufficiency Aortic regurgitation Ventricular fibrillation (neonate) Mitral insufficiency Pulmonary hypertension Aortic dissection Hypertension False aneurysms Stent embolization
Atrial septotomy	Transposition of the great arteries, mitral stenosis (atresia), and restrictive atrial septum	Perforation of the heart and tamponade
Radiofrequency mapping and ablation	Anomalous conduction pathways	Complete heart block Supraventricular tachycardia Thromboembolus from long sheath and prolonged procedure
Myocardial biopsy	Cardiomyopathy or transplantation	Myocardial perforation Complete heart block

frothy pulmonary secretions, and an increased oxygen requirement may be noted. Pulmonary edema is usually seen shortly after pulmonary artery dilation but can be delayed for up to 24 h. Endotracheal intubation and controlled ventilation are usually necessary until the edema resolves.

Frank hemoptysis may be indicative of a pulmonary artery tear or disruption. The interventionalist might note unusual spread of intravascular contrast medium in the lung parenchyma or the appearance of contrast medium in the pleural space or major lung fissures. Treatment is supportive. Substantial hemoptysis, pulmonary edema, or dyspnea should prompt emergent endotracheal intubation and mechanical ventilation. Avoiding hypertension may decrease hemorrhage, as may the addition of PEEP. Endotracheal suction may be necessary to remove clot that is obstructing the airway, but airway manipulations should be limited to help prevent additional bleeding. Intrapulmonary hemorrhage is often self-limited but can be severe, leading to hemothorax and a need for operation.

The function of the RV is critical during pulmonary artery dilation. Cardiac output may decrease significantly with balloon inflation causing hypotension, bradycardia, arterial oxygen desaturation, and a fall in end-tidal CO_2. These changes are usually temporary with rapid recovery of baseline hemodynamics. Patients who have a hypertrophied, poorly compliant RV with systemic or suprasystemic intraventricular pressures may develop myocardial ischmemia, RV failure, arrhythmias, and loss of cardiac ouput with the sudden increase in afterload associated with balloon dilation. General anesthesia and controlled ventilation are recommended prior to the intervention in this at-risk group of patients.

Patients who have a dilated RV secondary to long-standing volume overload, such as seen with chronic pulmonary regurgitation, are also at risk for arrhythmias and low output during catheter manipulations and interventions. These changes are usually transient and resolve with removal of any intracardiac catheters, but resuscitative equipment including a defibrillator and transvenous pacemaker must be immediately available. Conversion to general anesthesia with endotracheal intubation and mechanical ventilation may be necessary emergently.

Potential movement at the time of balloon dilation or stent placement must be avoided. The dilation of pulmonary arteries is painful in the awake or lightly sedated patient, and may induce dyspnea and coughing. Sedation must be deepened prior to dilations and stent placement, as patient movement may lead to an arterial tear or inadvertent blocking of lobar or segmental pulmonary arteries by a misplaced stent. Balloon dilation of multiple peripheral pulmonary artery stenoses, such as seen in patients with Williams syndrome, is often a prolonged procedure and associated with significant hemodynamic changes so general anesthesia with endotracheal intubation and mechanical ventilation is usually required.

Occlusive device insertion

Umbrella or clamshell device closure of PDA, ASD, and VSD is commonly performed in the catheterization laboratory. The placement of a PDA or ASD device is usually associated with minimal hemodynamic disturbance and can be performed in most patients using sedation techniques. General anesthesia may be necessary for airway protection if transesophageal echocardiography is used to guide device placement or if the procedure is prolonged and procedural complications such as device embolization occur.

In contrast to procedures to close PDAs or ASDs, transcatheter VSD device closure procedures are usually long and associated with profound hemodynamic instability and blood loss [193]. Intensive care management is frequently required following placement. The indications for VSD device placement include closure of a residual or recurrent septal defect, preoperative closure of defects that may be difficult to reach surgically, and closure of acquired defects such as post myocardial infarction or trauma. The preoperative clinical condition or ASA status is not a predictor of hemodynamic disturbance during device placement. Rather, it is the technique necessary for deploying the occlusion device that results in significant hemodynamic compromise and all patients are therefore susceptible. Factors contributing to hemodynamic instability in transcatheter VSD closure include blood loss, arrhythmias from catheter manipulation in the ventricles and across the septum, and atrioventricular or aortic valve regurgitation caused by the stenting open of valve leaflets by stiff-walled catheters. Device-related factors such as malposition of the umbrella device with arms impinging on valve leaflets and dislodgment from the ventricular septum are also potential sources of morbidity. The prolonged duration and positioning required for the procedure increase the risk for peripheral nerve injury and pressure ulcers.

Larger sheaths are required for positioning of transcatheter delivery pods and folded umbrella devices. Considerable blood loss can occur with catheter changes through these large sheaths. This blood loss can be concealed by surgical drapes and is difficult to quantify. A large delivery sheath represents a potential space for air accumulation and subsequent delivery into the heart when unoccupied by the device carrier system and collapsed device. In addition, extreme inspiratory efforts may entrain intracardiac air when the entry port of the sheath is open during removal and reinsertion of various catheters and devices. Meticulous purging of air from the catheter system and sealing of open ports helps to minimize the risk of air embolism.

Air embolization may be life threatening in patients with intracardiac shunts. Air delivered into the right atrium may be shunted right to left across the ASD as shunt direction can transiently change intraoperatively. Left atrial air embolization during these procedures can be seen with fluoroscopy and produces ST segment elevation and often hemodynamic changes as it passes into the aorta. The resultant ST segment changes, hypotension, arterial desaturation, and bradycardia generally respond to hemodynamic support with epinephrine and other inotropic and pressor support. The interventionalist aspirates air and seals the entry port in the sheath to prevent further air entrainment. The use of controlled positive pressure ventilation through an endotracheal tube in an anesthetized, paralyzed patient may also decrease the potential for transcatheter air entrainment during transcatheter closure of intracardiac defects.

Transcatheter radiofrequency ablation

Pediatric patients undergoing radiofrequency ablation vary in age and diagnosis [194]. Ablation may be necessary in the newborn with persistent re-entrant tachycardia or ectopic

atrial tachycardia and cardiac failure, as well as in older children with an ectopic focus and otherwise structurally normal heart. An increasing population of patients undergoing ablation are those who have undergone previous surgical repair of congenital heart defects. Patients with persistent volume or pressure load on the right atrium, and those who have required an extensive incision and suture lines within the right atrium, such as following a Mustard, Senning, or Fontan procedure, may be at increased risk for supraventricular tachyarrhythmia such as atrial flutter and fibrillation. Ventricular tachyarrhythmias may also develop late following repair of certain congenital heart defects, such as RV outflow tract reconstruction for tetralogy of Fallot.

Radiofrequency catheter ablation or cryoablation procedures are usually long procedures that require general anesthesia with mechanical ventilation in most patients. Prior to ablation, the arrhythmogenic focus is located by stimulating areas of the heart until the tachyarrhythmia is induced. This may result in hypotension, but this is usually short lived and can be terminated by intracardiac pacing, if necessary. Transthoracic cardioversion may be necessary and a defibrillator should be immediately available. Movement during ablation may result in a radiofrequency lesion being created at an incorrect site, resulting in heart block if the atrioventricular conduction system is inadvertently ablated. End inspiratory and end expiratory breath holds are sometimes required to ensure adequate contact of the ablation catheter with the arrhythmogenic focus.

A range of techniques can be used to maintain general anesthesia during radiofrequency catheter ablation since anesthetic drugs have minimal effects on intrinsic conduction [88,195–198]. Some tachyarrhythmias, such as ectopic atrial and ventricular tachycardias, are catecholamine sensitive. The focus may be difficult to localize after induction of anesthesia. For this reason, it is preferable to perform the procedure under light sedation or light general anesthesia if necessary. Of note, dexmedetomidine has been demonstrated to lengthen many cardiac conduction intervals, to depress sinus and atrioventricular node function, and to suppress supraventricular and ventricular tachydysrhythmias [131,134]. This agent should probably be avoided in most electrophysiological procedures, and a discussion with the electrophysiologist should ensue before its use.

Cardiac tamponade

Acute myocardial perforation with hemopericardium and tamponade is an occasional complication during interventional cardiac catheterization procedures. Prompt support of the circulation with volume infusions and pressor support, along with immediate catheter drainage of the pericardial space, are essential in the event of this complication. Hemopericardium after ventricular puncture is usually self-limited since the muscular ventricular wall seals the perforation. Punctures of the thin-walled atrium may require suture repair under direct vision in the operating room.

Postoperative tamponade from bleeding immediately after heart surgery usually requires placement of additional chest tube drains or sternotomy with evacuation of mediastinal clots and blood. These patients are usually sedated and mechanically ventilated in the ICU so that new anesthetic considerations and choices are limited. Some children develop pericardial effusions at other phases of their illness owing to hydrostatic influences (e.g. patients with modified Fontan operations) favoring accumulation of pericardial fluid or pericardial fluid from postpericardiotomy syndrome. Fluid in the pericardial space may accumulate under considerable pressure and filling of the heart is impaired. The transmural pressure in the atria diminishes as the pericardial pressures rise and diastolic collapse of the atria can be observed echocardiographically. The patients become symptomatic with a narrow pulse pressure, pulsus paradoxus, tachycardia, respiratory distress, abdominal pain progressing to decreased urine output, hyperkalemia, metabolic acidosis, and hypotension with tremendous endogenous catecholamine response.

Draining pericardial fluid is imperative when hemodynamics are compromised by tamponade physiology. A percutaneous approach to drainage is preferred when the fluid is accessible through a subxyphoid approach. Anesthetic principles guiding sedation for pericardial drainage should focus on maintaining or improving intravascular volume, vascular tone, and the contractile state of the ventricle. Anesthetic agents used for sedation that excessively decrease preload or afterload and transiently impair myocardial function will reduce cardiac output, especially when combined with muscle paralysis and positive pressure ventilation, which further impairs ventricular filling. If a child demonstrates severe tamponade symptoms and a large circumferential, percutaneously accessible pericardial effusion is identified echocardiographically, drainage under sedation using an opioid, benzodiazepine, or ketamine with local anesthesia is safer than an open surgical procedure with a rapid sequence induction and positive pressure ventilation.

KEY POINTS: ANESTHESIA FOR INTERVENTIONAL PROCEDURES

- Diagnostic cardiac catheterization has become less common in recent years; the increasing number of interventional procedures, including occlusion of abnormal communications, stenting of narrowed structures, and percutaneous placement of pulmonary valves, has increased risk for hemodynamic instability and bleeding
- Risk for arrythmias, bleeding, cardiac perforation and tamponade, vascular compromise, extracorporeal membrane oxygenation cannulation, and need for urgent surgery increases with small patients <5 kg undergoing invasive procedures
- Electrophysiological studies with radiofrequency or cryoablation can take a long time and often require general endotracheal anesthesia. Dexmedetomidine should be avoided in most of these procedures because of its multiple effects on the conduction system

Pathophysiology and anesthetic management of specific lesions and procedures

The CHD population is heterogeneous with a wide variety of ages, diagnoses, pathophysiology, and current physical status. The experience at the Boston Children's Hospital over 5 years

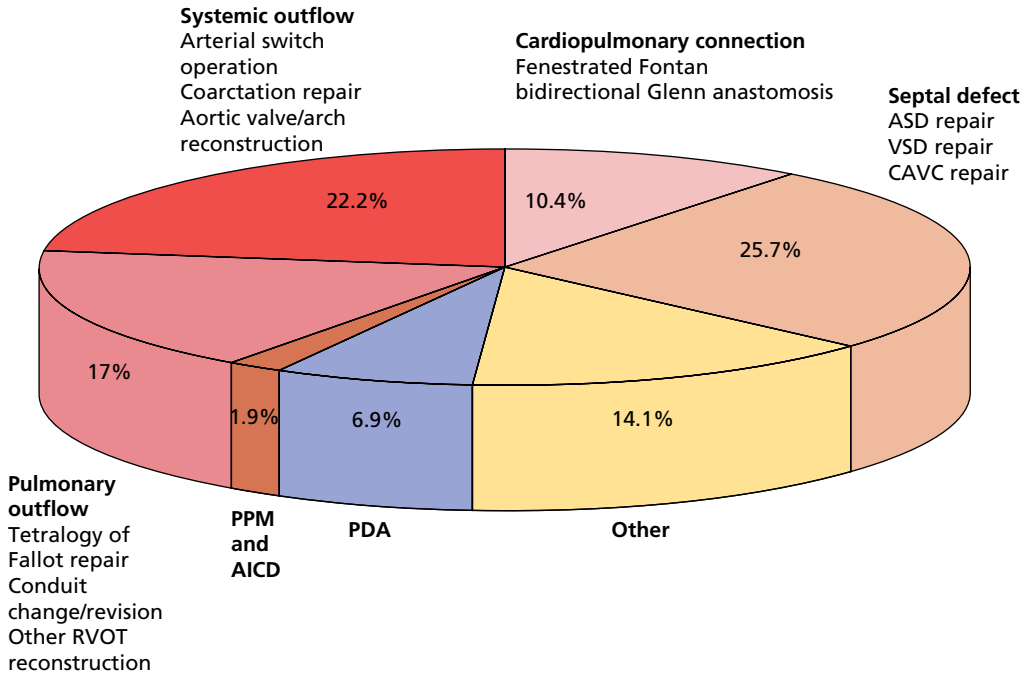


Figure 27.17 Spectrum of congenital cardiac surgical procedures performed at the Children's Hospital, Boston, in a typical year. AICD, automated implantable cardioverter-defibrillator; ASD, atrial septal defect: CAVC, complete atrioventricular canal; PDA patent ductus arteriosus; PPM, permanent pacemaker; RVOT, right ventricular outflow tract; VSD, ventricular septal defect.

is shown in Figure 27.17. There have been changes in management philosophy over the past 20 years towards performing reparative operations on neonates and infants rather than initial palliation and later repair. With the emphasis on early surgical repair, the aim is to promote normal growth and development, and limit the pathophysiological consequences of congenital cardiac defects such as volume overload, pressure overload, and chronic hypoxemia. It is important to note, however, that older children and adults with CHD are an increasing group of patients presenting for cardiac and non-cardiac surgery. This includes patients undergoing a reparative operation, often some years following an initial palliative procedure, and patients who have had previous reparative surgery but subsequently require reintervention because of residual or progressive defects, such as conduit stenosis.

Virtually all congenital cardiac defects are now amenable to either an anatomical or functional repair, but repair is sometimes not complete and there may be short- and long-term consequences of repair. Palliative procedures are often necessary prior to definitive repair. The modified Fontan procedure is the definitive operation for many classes of complex single-ventricle CHD. However, the Fontan procedure requires low PVR and large pulmonary arteries, which are not characteristic of the neonate. Therefore, a shunt may be required to alleviate hypoxemia and allow growth of the pulmonary arteries until the child is older. Alternatively, if the pulmonary blood flow is excessive, a pulmonary band can be placed to restrict pulmonary blood flow to reduce the possibility of CHF and to prevent development of pulmonary vascular obstructive disease until the definitive repair can be done. Palliative procedures have immediate complications and may compromise subsequent complete surgical repair of the lesion.

This section summarizes the basic pathophysiology of each lesion or procedure as a prelude to discussion of anesthetic management of the lesion. The discussion of anesthetic management before the repair applies equally well to non-cardiac procedures in unrepaired patients and to patients undergoing repair of the CHD but before CPB support is initiated. For some lesions, a separate discussion considers the anesthetic complications that occur after repair. This heading, where appropriate, outlines specific complications and problems that may be encountered months or years after repair of the anomaly. Otherwise, this information is found at the end of the section on anesthetic management earlier in the chapter.

Surgical shunts

Pathophysiology

A systemic-to-pulmonary shunt is required when there is severe obstruction to pulmonary blood flow and the patient is not suited for an immediate physiological or anatomical repair. This situation is seen most commonly in patients who have tricuspid atresia with restricted pulmonary blood flow, pulmonary atresia, or single-ventricle patients with severe obstruction to pulmonary blood flow. The surgically created shunt provides sufficient pulmonary blood flow to maintain acceptable arterial oxygen saturation but pulmonary venous blood must mix with systemic venous blood. Optimally, the surgical shunt (a simple shunt) provides restrictive flow to the pulmonary circuit, allowing adequate, but not excessive, pulmonary blood flow.

Types of surgical shunts

Aortopulmonary artery shunts

Systemic-to-pulmonary artery shunts are palliative procedures that increase pulmonary blood flow, thereby relieving severe cyanosis, improving functional status, and allowing for diffuse growth of small pulmonary arteries. The classic

Blalock–Taussig (B-T) shunt redirects subclavian artery blood into the branch pulmonary artery on the side opposite the aortic arch [199]. This graft allows some growth during infancy but is unlikely to induce pulmonary vascular disease. Rather than compromise the subclavian artery and upper limb blood flow, a modified B-T shunt is now preferred using a Gore-Tex™ synthetic tube graft interposed between the subclavian or innominate artery and the pulmonary artery. Performed either via a thoracotomy or median sternotomy, flow across the shunt is dependent upon the size of the Gore-Tex tube (usually 3.5 or 4.0 mm diameter), the length of the tube, and site of take-off from the systemic artery. A shunt arising from the innominate artery is likely to have a higher flow because of a higher perfusion pressure than a more distally placed shunt arising from the subclavian artery. The B-T shunt is associated with low mortality and a low incidence of late postoperative complications. However, distortion of the pulmonary arteries may occur within a few months and affect definitive repair.

The Potts shunt (descending aorta to left pulmonary artery) and the Waterston shunt (ascending aorta to the right pulmonary artery) are rarely used. The size of the shunt orifice is difficult to control precisely and may enlarge substantially with growth, becoming non-restrictive and resulting in excessive pulmonary flow and pulmonary vascular obstructive disease. These shunts distort the branch pulmonary arteries, possibly leading to stenois, and are difficult to dissect and control prior to CPB during subsequent surgery. A central shunt between the ascending aorta and main pulmonary artery is occasionally used when branch pulmonary arteries are hypoplastic and increased flow through the pulmonary artery is expected to increase growth of the pulmonary arteries.

A relatively recent development is the placement of a stent in the PDA of a neonate to create a stable source of pulmonary blood flow, in lieu of a surgically created shunt [200]. This procedure is performed in the cardiac catheterization laboratory, and PDA configuration as determined by angiography is important in determining candidacy for a PDA stent. A PDA that is long and tortuous, or of large diameter but short length, is not suitable for a stent. This procedure is perfomed in neonates and may be accompanied by considerable hemodynamic instability and bleeding. Outcome in carefully selected patients appears to be comparable to surgically created shunts.

Cavopulmonary artery shunt

The first cavopulmonary artery anastomosis (Glenn shunt) was a unidirectional shunt constructed as a palliative procedure for tricuspid atresia, directing systemic venous blood to the lungs for gas exchange. The SVC is disconnected from the right atrium and connected directly to the detached right pulmonary artery, i.e. SVC blood perfuses the right lung and flow depends on the pressure gradient between the SVC and left atrial pressures [201]. Therefore, the Glenn shunt is limited to patients with low PVR, which precludes its use in neonates. This shunt is rarely performed today as the pulmonary arteries are not in continuity, with only the right lung receiving systemic venous blood. Palliation is short lived because of complications such as thrombosis or occlusion leading to SVC syndrome, and progressive cyanosis secondary to the development of pulmonary arteriovenous collaterals.

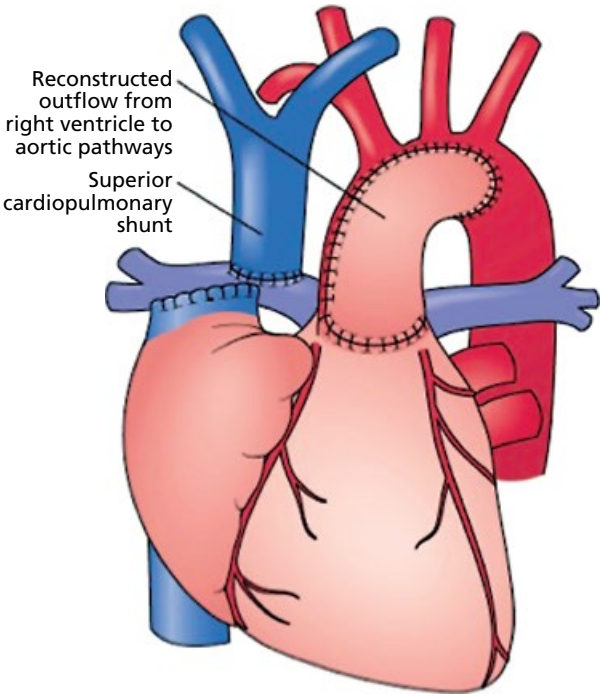


Figure 27.18 Superior cavopulmonary connection. The superior vena cava is anastomosed to the right pulmonary artery. This example demonstrates previous aortic arch reconstruction in the neonatal period. *Source*: Reproduced from Andropoulos and Gottlieb [359] with permission of Elsevier.

An important modification of the Glenn shunt that is now used during staged repair of single-ventricle defects involves the anastomosis of the cephalad portion of the SVC to the right pulmonary artery, as in the original Glenn procedure, except pulmonary artery continuity is maintained and flow is therefore bidirectional through both the right and left pulmonary arteries (hence the term bidirectional cavopulmonary anastomosis or bidirectional Glenn procedure) (Fig. 27.18) [202–204]. It can be performed successfully in children as young as 3–4 months of age, after the PVR has decreased, and has the benefit that effective pulmonary blood flow is increased but with reduced pulmonary artery pressure [205,206]. It avoids imposing the volume load on the ventricle associated with aortopulmonary shunts and minimizes atrial distension and high right atrial pressures inherent in a full Fontan-type operation in a high-risk patient with elevated PVR (see later) [207].

Anesthetic management

Complications of surgical shunts can occur immediately after surgery or years later when another surgical intervention is contemplated. Severe hypoxemia may occur in the operating room during or after creation of the shunt, implying inadequate pulmonary blood flow. Intrapulmonary shunting must always be considered in lungs that are compressed by the surgeons, but mechanical obstruction of flow into the pulmonary artery caused by retraction during surgery or by shunt occlusion (kinking or thrombosis) is the usual cause. An increase in PVR may also reduce flow across the shunt, and inducing an alkalosis by hyperventilation and using a high inspired oxygen concentration may minimize PVR and optimize gas exchange until shunt flow can be improved. As a note of

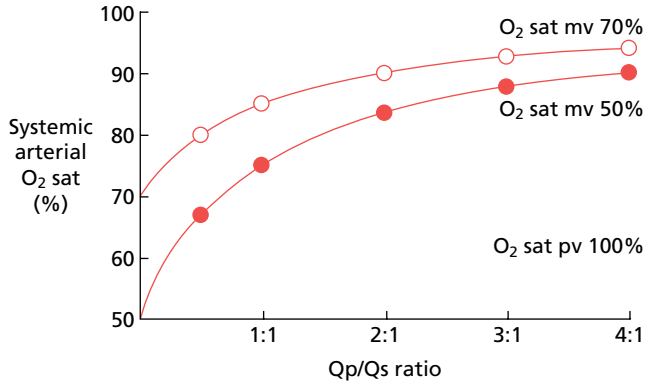


Figure 27.19 Changes in systemic arterial O_2 saturation (sat) with mixing lesions as the Qp/Qs (pulmonary/systemic blood flow ratio) changes with different levels of mixed venous (mv) O_2 saturation. It presumes a pulmonary (pv) O_2 saturation of 100%. *Source*: Reproduced from Rudolph [355] with permission of John Wiley and Sons.

caution, however, an increase in mean intrathoracic pressure and overinflation of the lungs during vigorous mechanical ventilation may further restrict flow across the shunt.

Systemic-to-pulmonary artery shunts are inherently inefficient because they recirculate pulmonary venous blood to the lungs without reaching the systemic circulation. To substantially improve arterial oxygen content, pulmonary blood flow must be several times greater than the systemic flow (Fig. 27.19). However, if the surgically created shunt is not sufficiently restrictive, pulmonary flows become excessive and cause pulmonary edema, wide pulse pressures, and, occasionally, inadequate systemic perfusion. Arterial oxygen saturation is relatively high despite complete mixing of systemic and pulmonary venous blood in the left heart. Maneuvers to increase pulmonary vascular resistance (see earlier) can compensate to a limited degree for excessive pulmonary flow, but shunt revision may be necessary.

Anesthetic considerations after creation of a surgical shunt

Flow through an aortopulmonary shunt is usually restricted by the shunt orifice and regulated by the difference between the pulmonary and systemic vascular resistance. If the shunt is too large, excessive pulmonary blood flow will be evident by high arterial oxygen saturations, reduced systemic perfusion with increasing metabolic acidosis, low diastolic blood pressure, and pulmonary edema. The work of breathing is increased and patients may have difficulty weaning from mechanical ventilation. If the shunt is large enough to allow excessive pressure and flow in the pulmonary vascular bed, precapillary pulmonary artery hypertension may develop over time.

If the shunt is too small, arterial oxygen saturations will remain low, and pulmonary flow will be dependent on systemic arterial pressure. Normal to above normal systemic arterial pressure usually needs to be maintained, as hypotension will lead to hypoxemia, particularly as the shunt becomes more restrictive. Other causes of a low oxygen saturation after shunt placement include a low mixed venous oxygen level secondary to a low cardiac output, and reduced oxygen-carrying capacity of the blood due to relative anemia.

Appropriately sized shunts result in a balanced circulation (Qp/Qs approximately 1:1) with peripheral saturations between 75% and 85% on low FiO_2 and a widened pulse with normal systolic pressure. Tachycardia is common initially once the shunt is open, and volume resuscitation is usually necessary. Inotrope support with dopamine may also be necessary as the increased pulmonary blood flow imposes a volume load on the systemic ventricle. The hematocrit should be maintained between 40% and 45%. Afterload reduction with a systemic vasodilator, such as sodium nitroprusside or a phosphodiesterase inhibitor, may be indicated if the patient has poor extremity perfusion, and to improve systemic perfusion if there is a relatively large shunt and excessive pulmonary blood flow. In general, most patients are mechanically ventilated postoperatively until flow is well balanced and adequate systemic perfusion maintained.

Pulmonary artery banding

Pathophysiology

Pulmonary blood flow can be reduced by placing a surgical band around the pulmonary artery. This is done when pulmonary blood flow is excessive and total correction of the lesion is not possible. Excessive pulmonary blood flow imparts high volume and pressure loads on the pulmonary vasculature. The pulmonary artery band is required to prevent progressive pulmonary vascular obstructive disease or to lessen symptoms of CHF.

Anesthetic management

Induction of anesthesia in a patient with excessive pulmonary flow is challenging because pulmonary vascular resistance may fall with onset of effective mechanical ventilation, leading to increased pulmonary blood flow. This phenomenon is called pulmonary steal and may result in systemic hypotension. Partial occlusion of a branch pulmonary artery with a clamp or ligature reduces pulmonary blood flow and increases peripheral perfusion until the band is applied.

Banding of the pulmonary artery is imprecise, and the hemodynamics after banding are unpredictable. Adequacy of the band is assessed in the operating room by observing a 20–30% increase in systemic blood pressure and a decrease in systemic arterial oxygen saturation. Direct measurement of the pulmonary artery pressure beyond the band may be compared with the systemic arterial pressure. It should be about 50% or less of the systemic pressure. Continuous monitoring of oxygen saturation is helpful for quick assessment of the adequacy of pulmonary blood flow. Saturation by pulse oximeter should be about 80% on low FiO_2 in common mixing lesions [208]. As hemodynamic criteria are used to assess band tightness, anesthesia is best maintained with high-dose opioids, and high concentrations of inhalation agents are avoided. If the band is too tight, bradycardia, hypotension, and cyanosis will develop, requiring urgent band removal.

The large resistance imposed by banding the pulmonary artery stimulates hypertrophy of the ventricle supplying the banded vessel. Consequently, depression of function of that ventricle quickly reduces pulmonary blood flow, particularly if a VSD or ASD is present, allowing shunting of blood into the systemic circulation. Long-term anatomical hazards of pulmonary artery bands relate to distortion of the anatomy and hypertrophy of the ventricle.

Single-ventricle and parallel circulation physiology

Pathophysiology

Patients with a repaired two-ventricle heart have an in series circulation whereby one ventricle ejects blood into the pulmonary artery and another ventricle ejects pulmonary venous blood to the systemic circulation. Systemic oxygenation represents the efficiency of gas exchange in the lungs; lowering PVR and decreasing right ventricular afterload are important objectives when trying to increase pulmonary blood flow and correct hypoxemia in this situation. However, patients with single-ventricle anatomy represent a unique population that requires physiological interpretation of oxygenation and hemodynamics in light of the parallel nature of the circulation. In this circumstance, a single ventricle supplies both pulmonary and systemic blood flow, and lowering PVR in these patients may improve oxygenation but adversely affect hemodynamics in some circumstances.

An infant with single-ventricle physiology may have a variety of anatomical lesions, ranging from tricuspid atresia (a single left ventricle) through double-inlet left ventricle (two atrioventricular (AV) valves and one single ventricle) to mitral atresia (a single right ventricle, i.e. hypoplastic left heart). In single-ventricle lesions, both AV valves enter a single chamber and a small outflow chamber gives rise to one great artery which is usually the aorta. The AV valves may be atretic. Subpulmonary stenosis or atresia is common. Occasionally, subaortic stenosis is present at birth or develops subsequently. Despite the anatomical diagnosis, virtually all patients with effective single-ventricle hearts, as shown in Box 27.4, are amenable to a repair that corrects the physiology, i.e. the Fontan procedure. It is increasingly common to use a stage approach to promote ventricular growth in order to create a biventricular circulation in a subset of patients previously thought to have insufficient ventricular volume such as unbalanced AV canal defects [209].

It is important to note, however, that an effective parallel circulation with single ventricle physiology can exist in patients with two ventricles (Box 27.4). In these circumstances, the balance between pulmonary and systemic vascular resistance is the critical determinant of systemic perfusion and, therefore, a balanced circulation (Qp/Qs = 1). Much of the discussion here regarding maneuvers used to increase or decrease pulmonary blood flow applies in these patients as well prior to surgery. Examples include patients who have a large PDA (left-to-right shunt across the PDA from the aorta to the pulmonary artery), common ventricular outflow tract (as in truncus arteriosus), or aortic arch interruption (right-to-left flow from the pulmonary artery to the distal aorta across the PDA to maintain systemic perfusion).

Patient with a single-ventricle anatomy share a common physiological principle. Desaturated systemic venous blood returns to the heart and mixes completely with oxygenated blood returning to the same chamber from the lungs. Common mixing of systemic and pulmonary venous blood means that the aortic O_2 saturation reflects the Qp/Qs. In the absence of lung disease (pulmonary venous desaturation), the pulmonary venous blood with oxygen saturations of 95–100% will drain to the ventricle and mix with systemic venous blood having saturations of 55–60% or less, depending on the amount of oxygen extraction in the periphery. If pulmonary and systemic blood flows are equal (i.e. Qp/Qs = 1) then the resultant "mixed" O_2 saturation that emerges from the ventricle measured in the systemic artery is 75–80%. As the pulmonary blood flow rises in proportion to systemic blood flow, so, too, rises the arterial oxygenation. Consequently, an arterial oxygen saturation of 90% is achieved at the expense of excessive pulmonary blood flow (Qp/Qs >3) and a substantial volume load to the single ventricle, which is required to supply all systemic and pulmonary (three times systemic) blood flow. CHF therefore ensues. If both the pulmonary artery and aorta are anatomically related to the ventricle and unobstructed, then flow to the pulmonary and systemic beds will be partitioned according to the relative resistances of each circuit (i.e. parallel circulations). As the PVR falls below SVR during the first few hours of life, pulmonary blood flow increases relative to systemic flow and systemic arterial oxygen saturation rises above 80%. Therefore, systemic oxygen saturation is a convenient marker of Qp/Qs. The effects of alterations of Qp/Qs on systemic arterial oxygen saturation for common mixing lesions are shown in Figure 27.20.

Box 27.4: Anatomical diagnoses and surgical procedures that demonstrate parallel or balanced circulation physiology

Defects amenable to a single-ventricle repair (i.e. common mixing lesions)

- Atrioventricular valve atresia
  - Tricuspid atresia
  - Mitral atresia
- Ventricular hypoplasia
  - Hypoplastic left heart syndrome
  - Double inlet left or right ventricle
  - Unbalanced atrioventricular canal
- Outflow tract obstruction
- Aortic atresia
  - Shone's complex
  - Pulmonary atresia and small right ventricle

Defects amenable to a two-ventricle repair

- Common ventricular outflow tract
  - Truncus arteriosus
- PDA-dependent pulmonary blood flow
  - Tetralogy of Fallot and pulmonary atresia
- PDA-dependent systemic blood flow
  - Interrupted aortic arch

Postoperative single-ventricle palliation

- Norwood/Sano procedure for hypoplastic left heart syndrome
- Modified Blalock–Taussig shunt

Increased Qp/Qs

The deleterious effects of overcirculated lungs perfused at high pressure and flows, combined with the adverse effects of this volume load (particularly on the neonatal heart which is less capable of increasing stroke volume in response to increasing preload than the mature myocardium), will culminate in a picture of hyperdynamic CHF in which systemic perfusion is compromised and oxygen delivery is impaired despite the elevated arterial oxygen saturation (Fig. 27.20). The myocardium ultimately cannot provide adequate systemic flow as PVR falls and more and more of the stroke volume is inefficiently recirculated to the lungs. Treatment is

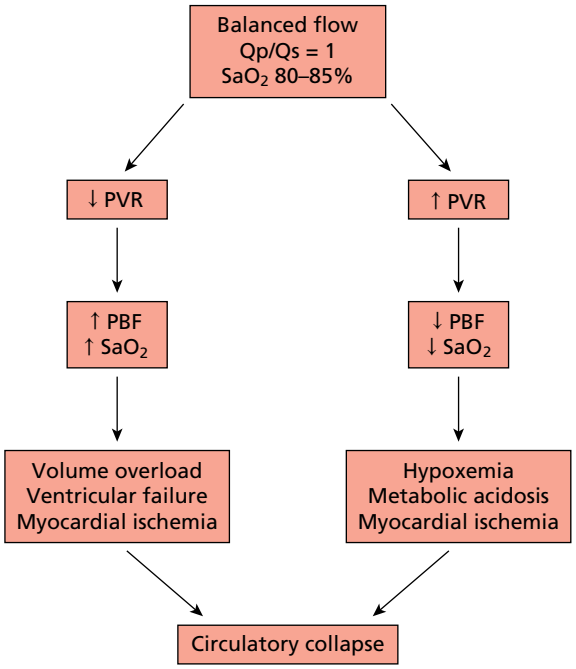


Figure 27.20 Effect of changes in PVR potentially contributing to circulatory collapse in patients with single-ventricle physiology. Qp, pulmonary blood flow; Qs, systemic blood flow; SaO_2, arterial oxygen saturation; PBF, pulmonary blood flow; PVR, pulmonary vascular resistance.

therefore directed toward raising resistance to blood flow to the lungs, balancing pulmonary and systemic blood flow ratios, and maintaining adequate systemic blood flow (Table 27.8).

Pulmonary vascular resistance can be increased with controlled mechanical hypoventilation to induce a respiratory acidosis, and with a low FiO_2 to induce alveolar hypoxia. Ventilation with room air may suffice, but occasionally a hypoxic gas mixture is necessary. This is achieved by the addition of nitrogen to the inspired gas mixture, reducing the FiO_2 to 0.17–0.19. Hypoxic gas mixtures result in lower cerebral oxygen saturation and require complex ventilation set-ups which are prone to accidental delivery of higher than intended nitrogen concentrations, and therefore are rarely used in contemporary practice [210,211]. While these maneuvers are often successful in increasing PVR and reducing pulmonary blood flow, it is important to remember that these patients have limited oxygen reserves and may desaturate suddenly and precipitously. Controlled hypoventilation in effect reduces the FRC of the lung and therefore oxygen reserve, which is also compromised by the use of a hypoxic inspired gas mixture. Inotropic support is often necessary because of ventricular dysfunction secondary to the increased volume load. Systemic afterload reduction with agents such as phosphodiesterase inhibitors may improve systemic perfusion, although they may also decrease PVR and thus not correct the imbalance of pulmonary and systemic flow. Patients who have continued pulmonary overcirculation with high SaO_2 and reduced systemic perfusion despite the above maneuvers require early surgical intervention to control pulmonary blood flow. At the time of surgery, a snare may be placed around either branch of the pulmonary artery to effectively limit pulmonary blood flow. Monitoring the SVC O_2 saturation, as a measure of mixed venous O_2 saturation and therefore cardiac output, often remains useful in patients with single-ventricle physiology. For instance, a patient with too much pulmonary blood flow may have an arterial O_2 saturation that is high (i.e. >85%), but a low SVC O_2 saturation (i.e. <50%) if systemic perfusion and cardiac output are reduced. In contrast, a patient who is hypoxic with a low arterial O_2 saturation (i.e. <75%) but has a normal arterial–SVC O_2 saturation difference of 25–30% can be assumed to have an adequate cardiac output and other causes for hypoxemia need to be evaluated. Monitoring changes in the SVC O_2 saturation during treatment is a useful guide to the adequacy of management. Early surgical repair avoids the problems associated with prolonged pulmonary overciruclation in single-ventricle neonates.

Decreased Qp/Qs

Decreased pulmonary blood flow, i.e. Qp/Qs <1, in patients with a single ventricle and parallel circulation is reflected by hypoxemia with an SaO_2 of <80%. Preoperatively this may be due to restricted flow across a small ductus arteriosus, increased PVR secondary to parenchymal lung disease, or increased pulmonary venous pressure secondary to obstructed pulmonary venous drainage or a restrictive ASD. Initial resuscitation involves maintaining patency of the ductus arteriosus with a PGE1 infusion at a rate of 0.025–0.05 μg/kg/min. Most patients require tracheal intubation and mechanical ventilation either because of apnea secondary to PGE1 or for manipulation of gas exchange to assist balancing the pulmonary and systemic flow. Systemic blood pressure, and therefore perfusion pressure across the ductus arteriosus, is maintained with the use of volume and vasopressor agents. Sedation, paralysis, and manipulation of mechanical ventilation to maintain an alkalosis may be effective if PVR is elevated. Nitric oxide as a specific pulmonary vasodilator may also be of use in this situation. Systemic oxygen delivery is maintained by improving cardiac output and red blood cell transfusions are performed to maintain a hematocrit >40%. Interventional cardiac catheterization with balloon septostomy or dilation of a restrictive ASD may be necessary; however, early surgical intervention and palliation with a systemic-to-pulmonary artery shunt are usually indicated.

Anesthesic considerations

A thorough preoperative assessment is essential to assess the balance of pulmonary and systemic flow, presence of cardiac failure, and possible end-organ injury from reduced systemic perfusion. A spontaneously breathing patient who is well balanced prior to surgery may readily become unbalanced after induction of anesthesia and when mechanically ventilated. The arterial oxygen saturation usually rises once the patient is anesthetized and paralyzed, due to a rise in mixed venous oxygen saturation from reduced peripheral O_2 extraction, and improved cardiac output secondary to reduced myocardial work and afterload on the ventricle. However, PVR may fall as well, leading to an increase in pulmonary blood flow at the expense of systemic perfusion. Hypotension and a fall in diastolic blood pressure may be evident. In this circumstance, it is important to maintain a low inspired O_2 concentration and ventilate with a low rate and tidal volume to maintain a mild respiratory acidosis. Close monitoring of the arterial blood gas is important, with the ideal being a pH of 7.40, PaO_2

Table 27.8 Parallel circulation physiology: management considerations

Clinical circumstance	Etiology	Management
Balanced flow	Qp = Qs ~1 0.	No intervention
SaO_2 80–85% and normotensive		
Overcirculated	Qp ≫ Qs	**Raise PVR**
SaO_2 > 90% and low blood pressure	Low PVR	Controlled hypoventilation
	Large aortopulmonary shunt size (PDA or B-T shunt)	Low FiO_2 (0.21)
	Clinical signs	**Increase systemic perfusion**
	Wide pulse pressure	Afterload reduction
	Poor peripheral perfusion	Inotrope support
	Congestive heart failure	Treat hypertension
	Oliguria	**Surgical intervention**
	Laboratory	Shunt revision
	Metabolic acidosis	
	Low SvO_2 saturation	
	Increased (SaO_2–SvO_2) difference	
Undercirculated	Qp < Qs	**Lower PVR**
SaO_2 <75% and normal/elevated blood pressure	High PVR	Controlled hyperventilation
	Small or occluded aortopulmonary shunt	Alkalosis
	Clinical signs	Reduce stress response
	Cyanosis	Pulmonary vasodilation
	Narrow pulse pressure	**Increase cardiac output**
	Myocardial ischemia	Raise systemic blood pressure
	Loss of murmur (late)	Inotrope support
	Laboratory	**Increase mixed venous O_2**
	Metabolic acidosis	Hematocrit >40%
	Normal (SaO_2–SvO_2) difference	Sedation/anesthesia/paralysis
		Surgical intervention
		Shunt revision
Low cardiac output	Ventricular failure	**Ventricular support**
SaO_2 <75% and hypotension	Myocardial ischemia	Maximize inotrope support
	Clinical signs	Optimize preload
	Poor peripheral perfusion	Open sternum
	Oliguria/anuria	Minimize stress response
	Narrow pulse pressure	**Surgical revision**
	Laboratory	Aortic arch and coronary anastomosis; transplantation
	Metabolic acidosis	**Mechanical support of the circulation**
	Low SvO_2 saturation	
	Increased (SaO_2–SvO_2) difference	

B-T, Blalock–Taussig; FiO_2, inspired oxygen concentration; PDA, patent ductus arteriosus; PVR, pulmonary vascular resistance; Qp, pulmonary blood flow; Qs, systemic blood flow; SaO_2, arterial oxygen saturation; SVC, superior vena cava; SvO_2, SVC oxygen saturation.

40 mmHg, and $PaCO_2$ 40 mmHg. If non-invasively monitored, an SaO_2 of 75–85% and end-tidal CO_2 of 40–45 mmHg are usually appropriate.

It is very important that patients are deeply anesthetized to minimize hemodynamic changes, in particular tachycardia, in response to surgical stimulation. If the patient is overcirculated (i.e. Qp > Qs) and has a low diastolic blood pressure, coronary perfusion may not increase sufficiently to meet the increased demand of myocardial work in response to surgical stress. Myocardial ischemia may therefore occur, usually manifest as ST segment changes on the ECG or sudden onset of dysrhythmias, in particular ventricular fibrillation.

Staged single-ventricle repair/Fontan procedure

The palliative operation for infants with single ventricles is a modified Fontan procedure. Di Donato et al [207] demonstrated in patients with tricuspid atresia that SVC blood could be directed into the lungs without passing through the heart, and Fontan and associates extended this concept to include blood returning from the IVC [212,213]. Since the original description, the Fontan procedure and subsequent modifications have been successfully used to treat a wide range of simple and complex single-ventricle congenital heart defects [214]. The repair is physiological in that the systemic and pulmonary circulations are separated, or in series, after directing the systemic venous return directly to the pulmonary artery (PA), and patients are no longer cyanosed. However, based on longer term outcome data, significant problems and complications may develop over time and the repair is viewed as palliative rather than curative.

The Fontan procedure has undergone numerous modifications since the first description [214]. The original procedure was described by Fontan in a patient with tricuspid atresia, and involved disconnecting the pulmonary arteries from each other, creating a classic Glenn shunt, connecting the right atrium (RA) directly to the left PA using a valved conduit and placing a valve at the IVC–RA junction [212]. It was believed the RA would function as a pumping chamber; however,

following improvements in echocardiography, it was apparent that the RA functioned primarily as a conduit with little pumping action contributing to pulmonary blood flow, and in the low-pressure venous system the valves remained opened. Further, this procedure was complicated in the long term by a high risk of pleuro-pericardial effusions and atrial dysrhythmias secondary to the effects of RA hypertension and distension.

An early modification involved the direct anastomosis of the RA appendage to the PA, closing the ASD and patching over the tricuspid valve, if patent [215]. This procedure, however, continued to have a high risk of complications related to RA hypertension.

Over the past 40 years, the total cavopulmonary anastomoses have become the modified Fontan procedure of preference. The SVC is anastomosed directly to the PA and a lateral tunnel created in the RA, baffling IVC flow to the SVC (Fig. 27.21A) [216]. This was associated with an improvement in mortality, although morbidity related to baffle hypertension persisted [205–207].

A significant advance was the creation of a fenestration or small hole in the intracardiac baffle, thereby creating an opportunity for a R-L shunt at the atrial level. This fenestration is created at the time of surgery using a small 4 mm punch [192]. In the event of an increase in RA or PA pressure with reduced flow across the pulmonary vascular bed, and therefore less preload to the systemic ventricle, patients are able to shunt right to left across the fenestration. While patients develop increased cyanosis, cardiac output is maintained. This proved to be very successful and has enabled patients at relatively high risk to undergo a successful modified Fontan procedure [217–220]. While the early mortality has declined further since the introduction of fenestration techniques, the most significant improvement has been in patient morbidity. The incidence of early pleuro-pericardial effusions, ascites (Fig. 27.22), and atrial dysrhythmias has been significantly reduced. The fenestration can be test balloon occluded and easily closed in the cardiac catheterization laboratory with a clamshell device later in the postoperative period.

More recently, the use of an external conduit baffling the IVC to the pulmonary circulation has been reported (Fig. 27.21B) [221]. Fenestration can be created between the external conduit and RA, if necessary. The major advantage in the immediate postoperative period is that the procedure can be completed on CPB without needing to arrest the heart. In addition, advocates of this technique have contended that it reduced the risk of atrial dysrhythmias by reducing atrial suture lines, lowering RA pressure, and avoiding suture lines

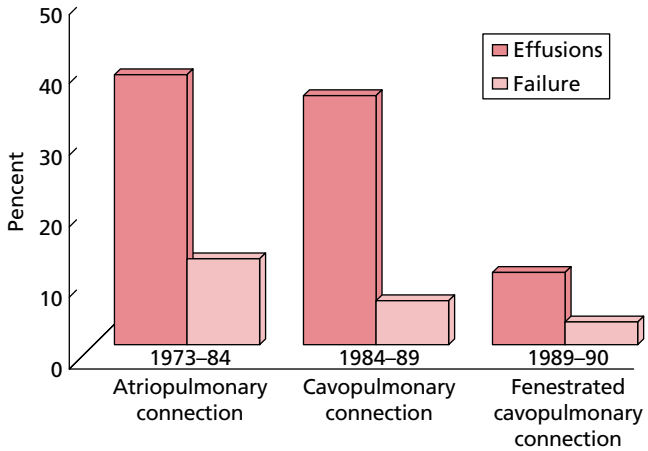


Figure 27.22 Incidence of pleural effusions and failure (i.e. take-down or mortality) during the early surgical evolution of the modified Fontan procedure at the Children's Hospital, Boston. *Source*: Reproduced from Castaneda et al [217] with permission from Wolters Kluwer.

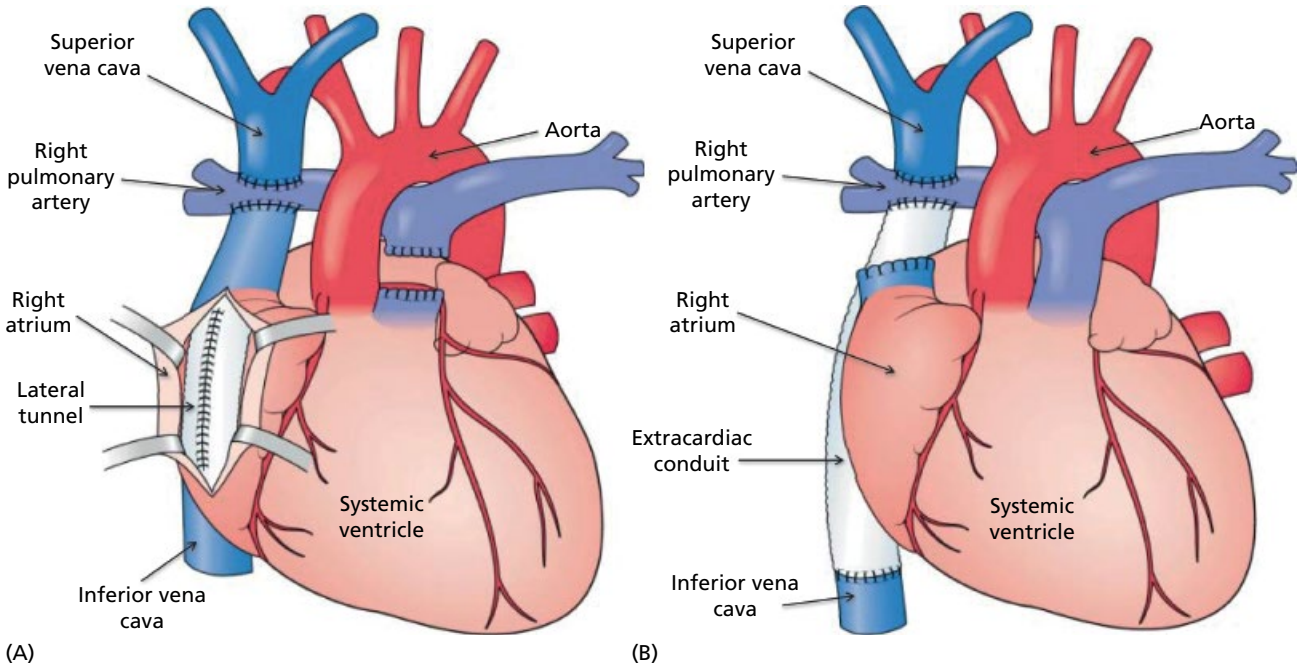


Figure 27.21 (A) Lateral tunnel Fontan total cavopulmonary connection. A polytetrafluoroethylene (PTFE) patch or tube is fashioned inside the right atrium. (B) Extracardiac conduit Fontan. The PTFE tube is anastomosed outside the heart from the detached inferior vena cava directly to the right pulmonary artery. *Source*: Reproduced from Andropoulos and Gottlieb [359] with permission from Elsevier.

near the sinoatrial node. Nonetheless, there continues to be debate as to whether the lateral tunnel or external conduit technique is the preferred shunt [222,223].

Selection crtieria

Fontan and other investigators originally listed a number of selection criteria that were considered important determinants for a successful early outcome, including age between 4 and 15 years, low PVR (<4 Wood U/m^2), mean pulmonary artery pressure <20 mmHg, systemic ventricle ejection fraction >0.6, normal sinus rhythm, normal AV valve function, and normal systemic and pulmonary venous drainage [207]. Patients with a diagnosis of tricuspid atresia who met these criteria had a mortality rate of less than 5% from this procedure [224]. Modifications to these criteria have subsequently been made over the years as experience and surgical techniques have evolved [225,226]. The modified Fontan procedure is now preferably performed in children under 2–4 years of age to enable earlier correction of chronic hypoxemia and to limit the potential longer term complications associated with prior palliation. The Fontan procedure has also been successfully performed in selected patients older than 15 years with CHD who have appropriate hemodynamics despite long-term palliation. Unobstructed flow across the pulmonary vascular bed is essential. A mean PA pressure <15 mmHg and a PVR <2 Wood U/m^2 are preferable, as they have been associated with a lower early mortality [227]. Diastolic dysfunction of the ventricle with an elevated end-diastolic pressure (e.g. >12 mmHg) secondary to increased myocardial mass or outflow obstruction is an important consideration which could increase postoperative risk; a higher SVC and PA pressure are necessary to maintain the transpulmonary gradient and therefore pulmonary blood flow in this situation.

Bidirectional cavopulmonary (Glenn) shunt

The benefits of a series circuit in patients with single-ventricle physiology include improved systemic oxygenation and a reduction in the obligatory diastolic load borne by the ventricle that simultaneously fills systemic and pulmonary circuits (parallel circulation). The compensatory ventricular dilation that must occur in a parallel circuit places the ventricle at an unfavorable position on the Starling curve and over time will lead to progressive ventricular dysfunction. As previously noted, the increase in ventricular end-diastolic volume, and eventually end-diastolic pressure, may significantly compromise the Fontan physiology and effective pulmonary blood flow [228]. Therefore, early palliation and relief of any volume load from the systemic ventricle is an important interim step in the staged management of patients with single-ventricle physiology. For most patients, this can be achieved by performing a bidirectional cavopulmonary connection or bidirectional Glenn procedure during infancy, commonly around 3–6 months of age. The volume and pressure load is partially relieved from the systemic ventricle and effective pulmonary blood flow is maintained and the chance of a successful conversion to a complete cavopulmonary anastomosis or modified Fontan procedure is improved.

After a bidirectional Glenn procedure, the Qp/Qs is reduced as the source of pulmonary blood flow is from the SVC only. At the time of surgery, the azygous vein is usually ligated to prevent decompression of venous drainage from the SVC to veins below the diaphragm and the IVC, which could contribute to a lower arterial oxygen saturation. Following the procedure, the arterial oxygen saturation should be in the 80–85% range, and preload to the systemic ventricle is maintained by mixing of pulmonary venous blood with systemic venous blood returning via the IVC to the common atrium. As the volume output of the ventricle must meet only the demands of the systemic circulation, the end-diastolic volume (EDV) is therefore substantially reduced. As the EDV decreases, an alteration in ventricular geometry takes place. In some children, the resulting small, hypertrophic ventricle exhibits diastolic dysfunction that was not present at higher EDV [228,229]. In other children, subaortic obstruction may appear across a bulboventricular foramen that was unobstructed in the preoperative state.

The bidirectional Glenn procedure is usually performed on CPB using mild hypothermia with a beating heart. The complications related to CPB and aortic cross-clamping are therefore minimal, and patients can be weaned and extubated in the early postoperative period. Systemic hypertension is common following the procedure. The etiology remains to be determined, but possible factors include improved contractility and stroke volume after the volume load on the ventricle is removed, and brainstem-mediated mechanisms secondary to the increased systemic and cerebral venous pressure. Treatment with vasodilators may be necessary. The cerebral vascular response (vasodilation) to elevated CO_2 over-rides the pulmonary vascular response (vasoconstriction) so mild hypercarbia increases cerebral and pulmonary blood flow, and postoperative permissive hypercarbia enhances systemic oxygen delivery [230].

Ideal physiology immediately after the Fontan procedure

The maintenance of effective pulmonary blood flow and cardiac output following the Fontan procedure depends on the pressure gradient between the pulmonary artery and the pulmonary venous atrium. The factors contributing to a successful cavopulmonary connection are shown in Table 27.9. A systemic venous pressure of 10–15 mmHg and a left atrial pressure of 5–10 mmHg, i.e. a transpulmonary gradient of 5–10 mmHg, are ideal.

Intravascular volume must be maintained and hypovolemia treated promptly. Venous capacitance is increased and as patients rewarm and vasodilate following surgery, a significant volume requirement is common. If the stated selection criteria are followed, patients undergoing a modified Fontan procedure will have a low PVR without labile pulmonary hypertension. Therefore, vigorous hyperventilation and induction of a respiratory and/or metabolic alkalosis to further reduce PVR are often of little benefit in this group of patients; conversely, the increase in mechanical ventilation requirements to induce a respiratory alkalosis may have an adverse effect on pulmonary blood flow. A normal pH and $PaCO_2$ of 40 mmHg should be the goal and, depending on the amount of R-L shunt across the fenestration, the arterial oxygen saturation is usually in the 80–90% range. However, PVR may increase following surgery, particularly secondary to an acidosis, hypothermia, atelectasis, hypoventilation, vasoactive drug infusions, and stress response.

Table 27.9 Management considerations following a modified Fontan procedure

	Aim	Management
Baffle pressure 10–15 mmHg	Unobstructed venous return	→ or ↑ preload Low intrathoracic pressure
Pulmonary circulation	PVR <2 Wood units/m^2 Mean PAp <15 mmHg	Avoid increases in PVR, such as from acidosis, hypo- and hyperinflation of the lung, hypothermia, and excess sympathetic stimulation
	Unobstructed pulmonary vessels	Early resumption of spontaneous respiration
Left atrium pressure 5–10 mmHg	Sinus rhythm Competent AV valve Ventricle: Normal diastolic function Normal systolic function No outflow obstruction	Maintain sinus rhythm, → or ↑ HR to increase CO → or ↓ afterload → or ↑ contractility PDE inhibitors useful because of vasodilation, inotropic and lusitropic properties

AV, atrioventricular; CO, cardiac output; HR, heart rate; PAp, pulmonary artery pressure; PDE, phosphodiesterase; PVR, pulmonary vascular resistance; →, maintain/normal; ↑, increase; ↓, decrease.

Any acidosis must be treated promptly. If the cause is respiratory, ventilation must be adjusted. A metabolic acidosis reflects poor cardiac output, and while correction with bicarbonate may be necessary in the short term to reduce the associated increase in PVR, treatment should be directed at the potential causes, including reduced preload to the systemic ventricle, poor contractility, increased afterload, and loss of sinus rhythm.

The beneficial effect of spontaneous ventilation on the hemodynamics of Fontan patients has been largely overstated [231]. While large instantaneous increases in pulmonary blood flow are seen in Fontan patients with normal inspiration, the incremental improvement in flow associated with normal inspiration is quite modest when considered over the entire respiratory cycle. In fact, in adult total cavopulmonary connection (TCPC) patients, approximately 30% of systemic venous flow to the pulmonary arteries is respiratory dependent as compared with 15% in normal two-ventricle patients. Furthermore, while inspiration augments pulmonary flow in TCPC patients, aortic blood flow (cardiac output) is actually higher during expiration. This is identical to the response seen in normal two-ventricle patients. In two-ventricle patients interventricular dependence results in the inspiratory increase in RV EDV and stroke volume, simultaneously reducing LV EDV and stroke volume. In TCPC patients in whom interventricular dependence is not a factor, a decrease in aortic blood flow is due to the pulmonary vasculature serving as a large-volume reservoir.

Given the effects of negative intrathoracic pressure on pulmonary blood flow, the effects of positive pressure ventilation on Fontan hemodynamics are of concern. Unfortunately, the effects on Fontan hemodynamics of positive pressure ventilation as compared with spontaneous ventilation have never been systematically evaluated. However, because pulmonary blood flow occurs throughout the respiratory cycle, employing a ventilation strategy that minimizes mean airway pressure is a rational, physiologically based approach. Available evidence suggests that a near-linear inverse relationship exists between mean airway pressure and cardiac index. The use of PEEP continues to be debated. The beneficial effects of PEEP include an increase in FRC, maintenance of lung volume, and redistribution of lung water and need to be balanced against the possible detrimental effect of an increase in mean intrathoracic pressure. A PEEP of 3–5 cmH_2O, however, rarely has hemodynamic consequences or substantial effects on effective pulmonary blood flow [231–236]. Early tracheal extubation after the Fontan operation, often in the operating room prior to ICU transfer, can be performed safely and the early hemodynamic advantages of spontaneous ventilation may facilitate rapid recovery [237].

Non-specific pulmonary vasodilators such as sodium nitroprusside, nitroglycerin, PGE1, and prostacyclin have been used to dilate the pulmonary vasculature in an effort to improve pulmonary blood flow after a Fontan procedure. Results have been variable. While PVR may fall, pulmonary blood flow could also increase as a result of reduced ventricular end-diastolic pressure and improved ventricular function secondary to the fall in systemic afterload. The response to inhaled nitric oxide is also variable and the improvement may relate to changes in ventilation/perfusion matching rather than a direct fall in PVR.

An elevated left atrial pressure may reflect systolic or diastolic ventricular dysfunction, AV valve regurgitation or stenosis, and loss of sinus rhythm with cannon "a" waves that raise left atrial pressure. Afterload stress is poorly tolerated after a modified Fontan procedure because of the increase in myocardial wall tension and end-diastolic pressure. Although pulmonary blood flow is phasic to a certain extent, a substantial proportion of flow occurs during diastole as well. The diastolic or relaxation characteristics of the ventricle play a significant role in the volume of pulmonary blood flow and, hence, the preload accepted by the ventricle. Therefore, low cardiac output usually accompanies diastolic dysfunction.

Therapeutic manipulations are not always successful in reversing diastolic dysfunction. Right-sided filling pressure must be increased to maintain the transpulmonary gradient, and treatment with inotropes and vasodilators is initiated; however diastolic relaxation may be impaired with high doses of inotropic medications, and cardiac output may worsen. One should scrupulously maintain or augment circulating volume to avoid additional reductions in EDV. The phosphodiesterase inhibitor milrinone is particularly beneficial. Besides being a weak inotrope with pulmonary and systemic vasodilating properties, its lusitropic action will

assist by improving diastolic relaxation and lowering ventricular end-diastolic pressure, thereby improving effective pulmonary blood flow and cardiac output. If a severe low output state with acidosis persists, take-down of the modified Fontan operation and conversion to a bidirectional Glenn anastomosis or other palliative procedure can be life saving.

Early postoperative complications after the Fontan procedure

Not all patients require a fenestration for a successful, uncomplicated Fontan operation. Those with ideal preoperative hemodynamics often maintain adequate pulmonary blood flow and cardiac output without requiring a R-L shunt across the baffle. Similarly, not all Fontan patients who have received a fenestration will use it to shunt right to left in the immediate postoperative period. These patients are fully saturated following surgery, and may have an elevated right-sided filling pressure, but nevertheless maintain an adequate cardiac output. The problem is predicting which patients are at risk for low cardiac output after a Fontan procedure, and who will benefit from placement of a fenestration. Patients with ideal preoperative hemodynamics may manifest a significant low-output state after surgery. Because of this, essentially all patients have a fenestrated Fontan procedure at the Boston Children's Hospital. Premature closure of the fenestration may occur in the immediate postoperative period, leading to a low cardiac output state with progressive metabolic acidosis and large chest drain losses from high right-sided venous pressures. Patients may respond to volume replacement, inotrope support, and vasodilation; however, if hypotension and acidosis persist, cardiac catheterization and removal of thrombus or dilation of the fenestration may need to be urgently undertaken (Table 27.10) [238].

Arterial O_2 saturation levels may vary substantially following a modified Fontan procedure. Common causes of persistent arterial O_2 desaturation <75% include a poor cardiac output with a low mixed venous O_2, a large R-L shunt across the fenestration, or additional leak in the baffle pathway producing more shunting. An intrapulmonary shunt and venous admixture from decompressing vessels draining either from the PA to the systemic venous circulation or systemic vein to the pulmonary venous system are additional causes [239]. Re-evaluation with echocardiography and cardiac catheterization may be necessary.

The incidence of recurrent pleural effusions and ascites has decreased since introduction of the fenestrated Fontan baffle [240]. Nevertheless, for some patients this remains a major problem with associated respiratory compromise, hypovolemia, and possible hypoproteinemia [241]. The cause is usually related to persistently elevated systemic venous pressure, and cardiac catheterization may be indicated.

Atrial flutter and/or fibrillation, heart block, and, less commonly, ventricular dysrhythmia may have a significant impact on immediate recovery, as well as long-term outcome. Sudden loss of sinus rhythm initially causes an increase in left atrial and ventricular end-diastolic pressure, and a fall in cardiac output. The SVC or PA pressure must be increased, usually with volume replacement, to maintain the transpulmonary gradient. Prompt treatment with antiarrhythmic drugs, pacing, or cardioversion is necessary.

Anesthetic considerations after a Fontan procedure

There are no prospective studies that have evaluated the effects of specific anesthetic techniques and drugs in patients with Fontan physiology. Anesthetic management will vary on a case by case basis according to the functional and clinical status of each patient, and the specific complications unique

Table 27.10 Circumstances, etiology, and treatment strategies for patients with low cardiac output immediately following the Fontan procedure.

Circumstance	Etiology	Treatment
Increased TPG		
Baffle >20 mmHg	Inadequate pulmonary blood flow and preload to left atrium:	Volume replacement
LAp < 10 mmHg	Increased PVR	Reduce PVR
TPG increased >>10 mmHg	Pulmonary artery stenosis	Correct acidosis
Clinical state:	Pulmonary vein stenosis	Inotrope support
High SaO_2/low SvO_2	Premature fenestration closure	Systemic vasodilation
Hypotension/tachycardia		Catheter or surgical intervention
Poor peripheral perfusion		
SVC syndrome with pleural effusions and increased chest tube drainage		
Ascites/hepatomegaly		
Metabolic acidosis		
Normal TPG		
Baffle >20 mmHg	Ventricular failure:	Maintain preload
LAp >15 mmHg	Systolic dysfunction	Inotrope support
TPG normal 5–10 mmHg	Diastolic dysfunction	Systemic vasodilation
Clinical state:	AV valve regurgitation and/or stenosis	Establish sinus rhythm or AV synchrony
Low SaO_2/low SvO_2	Loss of sinus rhythm	Correct acidosis
Hypotension/tachycardia	Afterload stress	Mechanical support
Poor peripheral perfusion		Surgical intervention, including takedown to BDG and transplantation
Metabolic acidosis		

AV, atrioventricular; BDG, bidirectional Glenn anastomosis; LAp, left atrial pressure; PVR, pulmonary vascular resistance; SaO_2, systemic arterial oxygen saturation; SVC, superior vena cava; SvO_2, SVC oxygen saturation; TPG, transpulmonary gradient.

to the Fontan procedure. An increasing hazard function for failure or reintervention, a late decline in functional status, and a 15-year survival between 60% and 73% have been reported on intermediate to late follow-up [242–244]. However, these figures include patients operated upon in the earlier surgical years; with improved surgical techniques and patient selection subsequent survival figures have improved [245,246].

Arrhythmias, in particular atrial flutter, sick sinus syndrome, and heart block, have been reported in 20% or more of survivors 10 years following the Fontan procedure. The probability of freedom from atrial flutter has been reported as about 40% at 15 years post Fontan procedure, although these data include patients from different surgical eras [247]. Predisposing factors include surgery involving the atrium with extensive suture lines, disrupted sinoatrial node blood supply, and chronic atrial distension. In addition, older age at Fontan operation, longer duration of follow-up, and type of surgical procedure are associated with an increased incidence of atrial flutter after the operation. Patients with recurrent arrhythmias are often treated with long-term antiarrhythmic drugs, often present for repeat cardioversions, and may undergo radiofrequency ablation of re-entrant flutter pathways [194,248,249]. There are no recommendations at this time for prophylactic antiarrhythmic drugs, such as digoxin or amiodarone, prior to anesthesia for non-cardiac surgery, but it is important that equipment for immediate external cardiac pacing or cardioversion is readily available in the operating room for these patients.

There is an increased incidence of thromboembolism in patients who have undergone the Fontan procedure, but the routine use of long-term anticoagulation remains controversial. The actual incidence of thromboembolism is difficult to determine because of the heterogeneous patient population. The prevalence of thromboembolic complications after a Fontan operation has ranged from 5% to 33% in mixed cohorts of pediatric and adult patients with different rhythm status [250,251]. The nature of the Fontan circulation with increased venous pressure and stasis of flow through the right atrial baffle, atrial dysrhythmias, alterations in pro- and anticoagulant factors, and possible increased resting venous tone in this population of patients, are all contributing factors [252,253]. The role and efficacy of prophylactic anticoagulant therapy in congenital heart disease in general, and the Fontan population in particular, is poorly defined. Antiplatelet therapy with aspirin is commonly used in the immediate and early postoperative period, although the benefit of long-term use is equivocal [254]. In high-risk patients and those who have had previous thrombus formation, coumadin therapy for an extended period is often utilized. Patients with Fontan physiology may be at increased risk for deep venous thrombosis, or thrombus formation within the Fontan baffle or atrial appendage following non-cardiac surgery. Prophylactic subcutaneous heparin should be considered for older Fontan patients undergoing non-cardiac procedures, and patients should be kept well hydrated and mobilized early after surgery.

Protein-losing enteropathy has been reported in 3–14% of Fontan patients on long-term follow-up [255]. The precise incidence is unknown largely because there is wide variability in the application of laboratory (serum albumin, serum protein, fetal α1-antitrypsin) and clinical criteria to define it [256]. Patients frequently have limited hemodynamic reserve with increased systemic venous pressure, decreased cardiac index, and increased end-diastolic ventricular pressure.

Most patients with stable single-ventricle physiology subjectively report that they are able to lead relatively normal lives with moderate exercise tolerance. Nevertheless, deterioration in function according to New York Heart Association classification has been reported over longer follow-up. Objective evaluation with exercise testing demonstrates the limited cardiorespiratory reserve of many Fontan patients [257,258]. The implications of these findings for subsequent anesthetics have not been studied, but the response to exercise testing may be useful for assessing a patient's ability to tolerate the stress of anesthesia and surgery. Compared with normal control subjects, those with Fontan physiology frequently demonstrate a reduced maximal exercise workload and less endurance, take longer to recover after stopping exercise, and have a lower anaerobic threshold and maximal oxygen consumption. A fall in arterial oxygen saturation and an increase in arteriovenous oxygen saturation difference is common because of the suboptimal increase in cardiac index [259]. The inability to increase effective pulmonary blood flow and stroke volume during strenuous exercise underscores the importance of the pulmonary vascular bed in determining ventricular filling and the dependence upon heart rate to increase cardiac output.

Intraoperative monitoring during major surgery needs careful planning in patients with Fontan physiology. Placement of a central venous line into the SVC will enable monitoring of systemic venous return, pulmonary artery pressure, and mixed venous oxygen saturation. An important consideration, however, is the risk of thrombosis and obstruction to venous return. Cardiac catheterization may be indicated prior to surgery if there has been a change in symptoms or deterioration in function. Performing a hemodynamic study in stable patients prior to major surgery may be beneficial if significant fluid shifts are anticipated. Besides being able to assess baseline hemodynamics, a balloon-tipped catheter can be wedged in a pulmonary capillary to measure the transpulmonary gradient. Positioning the catheter using pressure waveforms alone is difficult because there is no pulsatile arterial pressure waveform and the balloon may not readily float out to a lung segment. Placement under direct vision using fluoroscopy is preferable. Attempted measurement of cardiac output using thermodilution will also be inaccurate.

Tetralogy of Fallot

Pathophysiology

Tetralogy of Fallot (TOF) is a cyanotic heart defect where right ventricular outflow tract (RVOT) obstruction shunts systemic venous blood across a VSD into the aorta producing arterial desaturation (Fig. 27.23). The primary embryological event in TOF is the anterior and cephalad deviation of the conal septum. This causes multilevel RVOT obstruction and a VSD with aortic over-ride. The tetrad is completed by the presence of right ventricular hypertrophy that is secondary to right ventricular hypertension, RVOT obstruction, and the VSD.

In TOF with pulmonary stenosis, there is anterograde flow through the RVOT but it is reduced by fixed infundibular narrowing. Dynamic obstruction is caused by hypertrophied

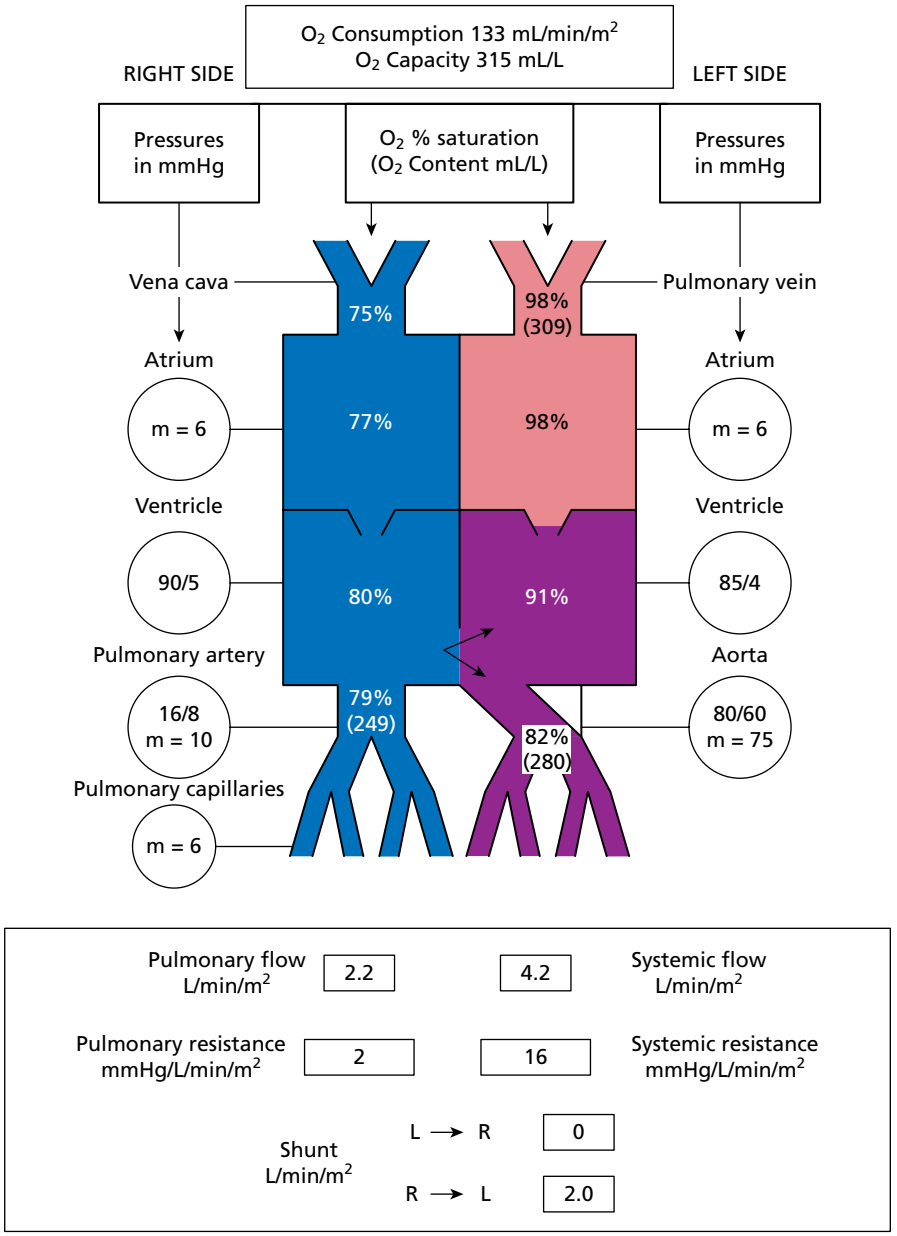


Figure 27.23 Catheterization findings in a patient with tetralogy of Fallot. m, mean pressure. *Source*: Reproduced from Nadas and Fyler [357] with permission of Elsevier.

muscles of the outlet septum, the right ventricular free wall, and the septomarginal trabeculations. The pulmonary valve is usually small and stenotic and branch pulmonary artery obstruction can occur and is usually proportional to the amount of antegrade pulmonary blood flow. Pulmonary artery pressures are normal or low and have little impact on the degree of shunting. The VSD is subarterial and usually perimembranous with fibrous continuity to the aortic and tricuspid valve, but other types of VSDs can also be present. The VSD is large and non-restrictive so the amount of blood that shunts from right to left is dependent on the amount of fixed and dynamic RVOT obstruction. The degree of dynamic obstruction is dependent on the diameter of the RVOT which is affected by the sympathetic tone of the hypertrophied muscles of the RVOT and the preload of the RV.

Hypercyanotic or Tet spells usually occur when infundibular muscle spasms increase RVOT obstruction or SVR is decreased by systemic vasodilation. Hypoxemia worsens when more systemic venous blood is shunted across the VSD to the aorta. Such spells can occur at any time before surgical correction of the anomalies and can be life threatening. Treatment is outlined below. Because the morbidity associated with recurrent hypercyanotic spells is significant, many physicians consider recurrent episodes of hypercyanosis to be an indication for corrective surgery at any age.

Anesthetic management

Tetralogy of Fallot is surgically corrected by relieving the RVOT obstruction and repairing the VSD. Delaying the primary repair for at least 3 months makes a transatrial approach to the VSD and a transpulmonary artery approach to the RVOT technically feasible [260]. Excellent outcomes have been achieved with this approach and the need for a transpulmonary valve annulus outflow patch (transannular patch) at

the time of surgery is reduced. More recently, aggressive efforts to preserve the RVOT and RV pulmonary valve have been used, given the long-term consequences of pulmonary regurgitation and arrhythmogenic scar tissue in the RVOT in this population [261]. In approximately 8% of patients, abnormalities in the origin and distribution of the coronary arteries preclude placement of the right ventricular outflow patch [262,263], making it necessary to bypass the stenosis by placing an external conduit from the body of the RV to the pulmonary artery.

Younger symptomatic patients are first palliated with an aortopulmonary shunt or a stent placed in the RVOT. Some argue for an early complete repair of TOF regardless of symptoms, citing the risks of cyanosis and the potential complications related to palliative aortopulmonary shunts [264]. This may be performed in the neonate or young infant depending upon the degree of obstruction and arterial oxygen saturation level. Complete repair in neonates and young infants more often requires a transventricular approach to close the VSD, with pericardial augmentation of the RVOT. A ventriculotomy is performed in the RVOT and is frequently extended distally through the pulmonary valve annulus and beyond any associated pulmonary artery stenosis. The outflow tract is then enlarged with pericardium or synthetic material, and obstructing muscle bundles are resected to relieve the outflow tract obstruction. Pulmonary regurgitation results after a transannular incision and patch. This combined with the ventriculotomy may compromise ventricular function in the postoperative period.

Anesthetic management of these patients should maintain systemic vascular resistance, minimize pulmonary vascular resistance, and avoid myocardial depression. Hypercyanotic spells in non-anesthetized children are traditionally treated initially with 100% oxygen by facemask, a knee–chest position, and morphine sulfate. This regimen usually causes the dynamic infundibular stenosis to relax while maintaining systemic resistance. Deeply cyanotic and lethargic patients are given IV crystalloid infusions to augment the circulating blood volume and reduce RVOT obstruction by increasing the diameter of the RVOT. Continued severe hypoxemia is treated with a vasopressor (e.g. phenylephrine 1–2 μg/kg) to increase SVR, and sometimes by judicious use of IV propranolol or esmolol to slow the heart rate; the latter allows more filling time and relaxes the infundibulum. If a hypercyanotic spell persists despite treatment, immediate surgical correction of the anomaly is indicated. The child can be anesthetized with IV opioids and hypnotics but anesthetic agents that predominantly decrease SVR should be used with caution. The pattern of mechanical ventilation is critical as excessive inspiratory pressure or short expiratory times will increase the mean intrathoracic pressure and further reduce antegrade flow across the RV outflow.

Patients usually separate from CPB with a satisfactory blood pressure and atrial filling pressures <10 mmHg on inotrope support, such as dopamine 5–10 μg/kg/min. The aim of therapy is to support right ventricular function and minimize afterload on the RV. This is particularly important following repair in neonates or small infants. Systolic dysfunction of the RV may occur following neonatal ventriculotomy, but restrictive physiology reflecting reduced RV compliance and diastolic function is more common [265,266]. Factors contributing to diastolic dysfunction include ventriculotomy, lung and myocardial edema following CPB, inadequate myocardial protection of the hypertrophied ventricle during aortic cross-clamp, coronary artery injury, residual outflow tract obstruction, volume load on the ventricle from a residual VSD, or pulmonary regurgitation and dysrhythmias. A low cardiac output status may occur in neonates in the first 6–16 h after repair, characterized by increased right-sided filling pressures from diastolic dysfunction. Continued sedation and muscle relaxation are usually necessary for the first 24–48 h to minimize the stress response and the associated increase in myocardial work. Preload must be maintained despite elevation of the RA pressure. In addition to high right-sided filling pressures, pleural effusions and/or ascites may develop. Significant inotrope support is often required, and a phosphodiesterase inhibitor, such as milrinone is beneficial because of its lusitropic properties. Because of the restrictive defect, even a relatively small volume load from a residual VSD or pulmonary regurgitation is often poorly tolerated in the early postoperative period. It may take 2–3 days before RV compliance improves following surgery and cardiac output increases. While the patent foramen ovale or any ASD is usually closed at the time of surgery in older patients, it is beneficial to leave a small atrial communication following neonatal repair. In the face of diastolic dysfunction and increased RV end-diastolic pressure, a R-L atrial shunt will maintain preload to the left ventricle and therefore cardiac output. Patients may be desaturated initially following surgery because of this shunting. As RV compliance and function improve, the amount of shunt decreases and both antegrade pulmonary blood flow and arterial oxygen saturation increase.

Arrhythmias following repair include heart block, ventricular ectopy, and junctional ectopic tachycardia. It is important to maintain sinus rhythm to avoid additional diastolic dysfunction and an increase in end-diastolic pressure. Atrioventricular pacing may be necessary for heart block. Complete right bundle branch block is typical on the postoperative ECG.

Most patients recover systolic ventricular function postoperatively. However, there is a small group of patients, especially those repaired at older ages, in whom significant ventricular dysfunction remains. Pulmonary valve insufficiency may contribute to residual ventricular systolic dysfunction [267]. The most common cause of systolic dysfunction immediately after repair of TOF is a residual or unrecognized additional VSD which causes a volume load on the left ventricle and pressure load on the hypertrophied right ventricle, leading to right ventricular failure and poor cardiac output [268,269]. A residual VSD combined with a residual right ventricular outflow obstruction is particularly deleterious. Suprasystemic pressure may occur in the right ventricle particularly if the PAs are hypoplastic or stenotic. In some cases, this can be ameliorated by partially opening the VSD to allow an intracardiac R-L ventricular shunt. This shunt unloads the compromised right ventricle but results in systemic hypoxemia.

Anesthetic considerations after right ventricle outflow reconstruction

Reconstruction of the RVOT may lead to significant problems that affect RV function and the risk for arrhythmias over time. While most of the long-term outcome data pertain to patients

following TOF repair, similar complications and risks are also likely for those who have undergone an extensive RV outflow reconstruction, such as placement of a conduit from the right ventricle to the pulmonary artery for correction of pulmonary atresia or truncus arteriosus, and the Rastelli procedure for transposition of the great arteries with pulmonary stenosis.

Complete surgical repair of TOF has been successfully performed for over 40 years, with recent studies reporting a 30–35-year actuarial survival of about 85%. Many patients report leading relatively normal lives, but RV dysfunction may progress after repair and may only be evident on exercise stress testing or echocardiography. Continued evaluation is necessary because these patients have an increased risk of ventricular dysrhythmias and late sudden death. Factors that may adversely affect long-term survival include older age at initial repair, initial palliative procedures, and residual chronic pressure and/or volume load such as from pulmonary insufficiency or stenosis [270,271]. A spectrum of problems may develop, ranging from a dilated RV with systolic dysfunction to diastolic dysfunction from a poorly compliant RV (Table 27.11). These problems need to be thoroughly evaluated preoperatively.

Both RV and LV systolic dysfunction secondary to a residual volume load from pulmonary regurgitation after tetralogy repair are predictors of late morbidity [270,271]. There is also an association between RV dilation from pulmonary regurgitation and the risk of ventricular tachycardia (VT) and sudden death [272]. The consequences of chronic pulmonary regurgitation are reflected by cardiomegaly on chest x-ray, an increase in RV EDV by echocardiography, and on exercise testing as a reduction in anaerobic threshold, maximal exercise performance, and endurance [273]. Preoperative exercise testing may provide some insight into hemodynamic reserves. Patients who have significant pulmonary regurgitation and reduced RV function are at potential risk of a fall in cardiac output during anesthesia, particularly as positive pressure ventilation may increase RV afterload and the amount of pulmonary regurgitation. Once again, it is difficult to predict those patients who are more likely to have instability during anesthesia for non-cardiac surgery; nor is it possible to formulate a "recipe" for anesthesia that will be suited to all patients.

Table 27.11 Long-term follow-up considerations after tetralogy of Fallot repair: right ventricular function

Circumstance	Clinical
Systolic dysfunction: "non-restrictive"	RV dilation: cardiomegaly Significant pulmonary regurgitation Volume overload: ↑ RVEDV, ↓ RV ejection fraction ↓ Maximal exercise capacity and endurance ↑ Risk for ventricular arrhythmias and possibly sudden death
Diastolic dysfunction: "restrictive"	↓ RV compliance: cardiomegaly less likely Limited pulmonary regurgitation ↑ RVEDP, contractility maintained Improved exercise capacity Lower risk for ventricular dysrhythmias

RV, right ventricle; RVEDP, right ventricle end-diastolic pressure; RVEDV, right ventricle end-diastolic volume; ↑, increased; ↓, decreased.

Some patients have restrictive physiology or diastolic dysfunction secondary to reduced ventricular compliance. These patients usually do not have cardiomegaly and demonstrate better exercise tolerance, and the risk for ventricular dysrhythmias is possibly decreased. Although the RV is hypertrophied, function is generally well preserved on echocardiography with minimal pulmonary regurgitation [273].

The incidence of significant RV outflow obstruction developing over time is low. Residual obstruction contributes to early mortality within the first year after surgery, but is well tolerated in the long term. A gradient more than 40 mmHg across the RV outflow is uncommon and the pressure ratio between the RV and LV is usually less than 0.5. The gradient may become more significant with time, but as the progression is usually slow, RV dysfunction occurs late.

A wide variation in the incidence of ventricular ectopy has been reported in numerous follow-up studies, including up to 15% of patients on routine ECG and up to 75% of patients on Holter monitor. Multiple risk factors including an older age at repair, residual hemodynamic abnormalities, and duration of follow-up have all been considered important [194,259,272]. In common with these factors is probable myocardial injury and fibrosis from chronic pressure and volume overload, and cyanosis. While ventricular ectopy is common in asymptomatic patients during ambulatory ECG Holter monitoring and exercise stress testing, it is often low grade and has not identified those patients at risk for sudden death. Electrophysiological induction of sustained VT, especially when monomorphic, is suggestive of the presence of a reentrant arrhythmic pathway [274]. Although dependent on the stimulation protocol used to induce VT, the presence of monomorphic VT in a symptomatic patient with syncope and palpitations is significant and indicates treatment with radiofrequency ablation, surgical cryoablation, antiarrhythmic drugs, or placement of an implantable cardioversion-defibrillator (ICD) [194,249,263]. The risk for ventricular dysrhythmias during anesthesia is unknown. While preoperative prophylaxis with antiarrhythmic drugs is not recommended, a means of external defibrillation and pacing must be readily available.

Tetralogy of Fallot with absent pulmonary valve

The absence of a functioning pulmonary valve gives rise to *in utero* pulmonary regurgitation resulting in the aneurysmal dilation of the main and branch pulmonary arteries. Tracheobronchial compression can result such that the pathophysiology of TOF is complicated by symptoms of an anterior mediastinal mass. These patients are usually positioned on their sides even when mechanically ventilated. Prior to repair, the patient is kept in the lateral position and returned supine immediately prior to incision and CPB is intiated expeditiously.

Pulmonary atresia

Pathophysiology

The intracardiac anatomy of TOF with pulmonary atresia is similar to that of simple TOF, but the RVOT is atretic. All systemic venous return moves right to left across the VSD. Therefore, complete mixing of pulmonary and systemic venous return occurs in the left ventricle and aorta, producing arterial hypoxemia. When antegrade flow is established from

the right ventricle into the main pulmonary artery by a reparative procedure, the L-R shunt via collateral flow will impose a diastolic load on the left ventricle. Preoperative occlusion of these collateral vessels can be accomplished by interventional techniques in the cardiac catheterization laboratory but may leave the child more cyanotic in the hours before operation. The most effective temporizing therapy is to reduce oxygen consumption (e.g. anesthesia, mechanical ventilation) and to increase the systemic perfusion pressure across other systemic-to-pulmonary communications.

Atresia of the pulmonary valve or main pulmonary artery forms a spectrum of cardiac defects, the management of which depends on the extent of atresia, size of the RV and tricuspid valve, presence of a VSD and collateral vessels, surface area of the pulmonary vascular bed, and coronary artery anatomy. At birth, pulmonary blood flow is derived either from a PDA or from other aortopulmonary collateral blood vessels. These collaterals, which arise from the descending aorta and supply both lungs, may be extensive. The RV is usually hypertrophied, and a restrictive physiology is common during initial postoperative recovery.

Critical pulmonary stenosis may exist with a variable degree of hypoplasia of the right ventricle, tricuspid valve, and pulmonary artery. There is no VSD. A pinhole orifice is present in the pulmonic valve, but the right ventricle is generally less hypoplastic than with pulmonary atresia. A fixed obligatory shunt of all systemic venous return occurs from the right to the left atrium, where blood mixes completely with pulmonary venous blood. Some blood may flow into the right ventricle, but because there is no outlet, blood regurgitates back across the tricuspid valve and eventually reaches the left atrium and left ventricle. Pulmonary blood flow is derived exclusively or predominantly from a PDA. These patients usually do not have extensive aortopulmonary collateral blood flow; consequently, they often become cyanotic when the PDA closes after birth. Critical pulmonary valve stenosis can be effectively treated by balloon dilation in the catheterization laboratory. Antegrade flow across the RV outflow may not improve immediately, but gradually increases over days as RV compliance improves.

Pulmonary valve atresia or short-segment main pulmonary artery atresia, with a VSD and normal-sized tricuspid valve, RV, and branch pulmonary arteries, is completely repaired in the neonate, usually involving placement of a pericardial patch to reconstruct the outflow tract. If there is long-segment pulmonary artery atresia, a homograft conduit is necessary to reconstruct the RV outflow. Conduits may be extrinsically compressed or kinked at the time of sternal closure, causing partial RV outflow obstruction or direct compression of a coronary artery leading to ischemia.

Patients with pulmonary atresia, a VSD, and small RV and tricuspid valve may not tolerate a complete initial repair. The RV may be unable to cope with the entire cardiac output, resulting in a low output state and RV failure (see later). Alternative management strategies therefore include initial palliation with a shunt and/or RV outflow patch to improve pulmonary blood flow, or a repair of the outflow tract with fenestration of the VSD patch to enable a R-L shunt at that level. Two-ventricle repair may ultimately be limited by growth of the tricuspid valve. If the right ventricle subsequently grows, the shunt and the patent foramen ovale ASD and VSD can be closed surgically.

Patients with pulmonary atresia and an intact ventricular septum usually have a small RV and tricuspid valve, which in general makes them unsuitable for a two-ventricle repair in the long term. Initial palliation with an aortopulmonary shunt is necessary; reconstruction of the RV outflow with a pericardial patch or conduit may also be considered if the RV is of a sufficient size such that a two-ventricle repair could be considered. Prior to surgery, the coronary anatomy should be determined, usually by cardiac catheterization. A large conal branch or aberrant left coronary artery across the RVOT may restrict the size of a ventriculotomy and placement of a patch or conduit. Patients with pulmonary atresia, a hypoplastic RV, and intact ventricular septum may have numerous fistulous connections between the small hypertensive RV cavity and the coronary circulation [275,276]. A significant proportion of the myocardium may therefore be dependent upon coronary perfusion directly from the RV. If, in addition, there is proximal coronary artery stenosis or even atresia restricting coronary perfusion from the aortic root, then decompression of the RV following reconstruction of the RVOT can lead to myocardial infarction.

Severe pulmonary atresia may be associated with a hypoplastic RV and diminutive pulmonary arteries that are not suitable for primary repair [277]. A palliative procedure with a B-T or central shunt is usually necessary at first to improve pulmonary blood flow, followed by staged single-ventricle repair (see section "Anesthetic considerations for patients following a Fontan procedure"). Multiple aortopulmonary collateral arteries may be present, supplying some or all segments of the lung. They can be associated with a large L-R shunt, contributing to volume overload and pulmonary hypertension. RV to diminutive pulmonary artery continuity is established in the operating room. Larger collateral vessels supplying significant portions of the lung can be anastomosed or unifocalized to the native pulmonary arteries, with the ultimate aim being to establish full antegrade pulmonary blood flow. Smaller vessels to some segments of lung can be coiled in the cardiac catheterization laboratory, provided there is antegrade flow from the native pulmonary arteries to those lung segments. Cyanosis may occur after collateral vessels are occluded in the cardiac catheterization laboratory. Therapy is aimed at lowering PVR and improving pulmonary blood flow.

It is important to establish early antegrade flow from the right ventricle to the pulmonary artery when pulmonary arteries are diminutive to promote growth and establish a pathway to the pulmonary arteries for subsequent balloon dilation. A B-T shunt may be necessary to provide sufficient pulmonary blood flow if the pulmonary arteries and right ventricle are small. Initially, the VSD can be left open, and postoperative management of cyanosis or CHF will be determined by the size of and the resistance offered by the pulmonary circuit.

Postoperatively, fully saturated hemoglobin in the aorta with elevated pulmonary artery oxygen saturation and left atrial pressure can signify a L-R shunt through a developing VSD. This will produce a volume load on the left ventricle which, if not tolerated, may require VSD closure or revision. When the patient is not fully saturated in the aorta but is suffering from a volume-loaded left ventricle with low cardiac output and high left atrial pressure postoperatively, excessive

systemic-to-pulmonary collateral flow may be the cause, and occlusion of the vessels in the catheterization laboratory or immediate reoperation may be necessary.

Anesthetic management

Anesthetic management of patients with pulmonary atresia is similar to that for TOF, but hypercyanotic spells related to indundibular spasm do not occur. Maintaining the patency of the ductus for the perioperative treatment of neonates with pulmonary atresia and critical pulmonary stenosis is essential. If the right ventricle is sufficiently well developed and the main pulmonary artery is present, it may be possible to perform a pulmonary valvotomy and provide adequate pulmonary blood flow without a supplemental systemic-to-pulmonary artery shunt. The goal of therapy is to improve oxygenation and decrease right ventricular afterload. Because the underdeveloped right ventricle is non-compliant and requires high filling pressures, there may be substantial R-L shunting through the foramen ovale, making these infants hypoxemic during the immediate postoperative period. With growth and improved compliance of the right ventricle, the R-L shunting diminishes and the infant's oxygenation improves substantially. If hypoxemia persists, a PGE1 infusion should be started to increase pulmonary blood flow through the ductus arteriosus while arrangements are made to surgically create a pulmonary-to-systemic artery shunt.

In patients with long-segment pulmonary atresia, the need for a conduit to bridge the gap between the right ventricle and the pulmonary artery complicates the repair. Again, right ventricular failure may occur postoperatively, especially when there is a residual VSD or an outflow obstruction. The conduit may obstruct acutely during chest closure, further elevating pressure in the right ventricle.

After the VSD is closed and blood flow is from the right ventricle to the pulmonary arteries, there may be excessive pulmonary blood flow (Qp/Qs >1) owing to the combined flow into the pulmonary arteries from the right ventricle and from aortopulmonary collaterals. If this occurs, the patient develops CHF and requires intraoperative inotropic support of the heart and an extended period of postoperative mechanical ventilation. With large collateral flows, the pulse pressure is large and diastolic pressure low. The patients may require surgery to ligate the collateral vessels or embolization in the catheterization laboratory.

Anesthetic considerations after repair

Patients with TOF and pulmonary atresia are subject to the same late problems and complications as patients with TOF alone. In addition, they may develop progressive conduit obstruction after surgery.

Tricuspid atresia

Pathology

In this condition, an imperforate tricuspid valve and hypoplasia of the right ventricle are present, often accompanied by a VSD of variable size and by pulmoniary stenosis (Fig. 27.24). A fixed obligatory shunt of all systemic venous return occurs from the right atrium through the patent foramen ovale or ASD into the left atrium, where complete mixing takes place. The degree of hypoxemia depends on the amount of pulmonary blood flow, which is regulated by the severity of the pulmonary stenosis. The common presentation is characterized by significant hypoxemia caused by the decreased pulmonary blood flow induced by either a restrictive VSD or a severe pulmonary stenosis.

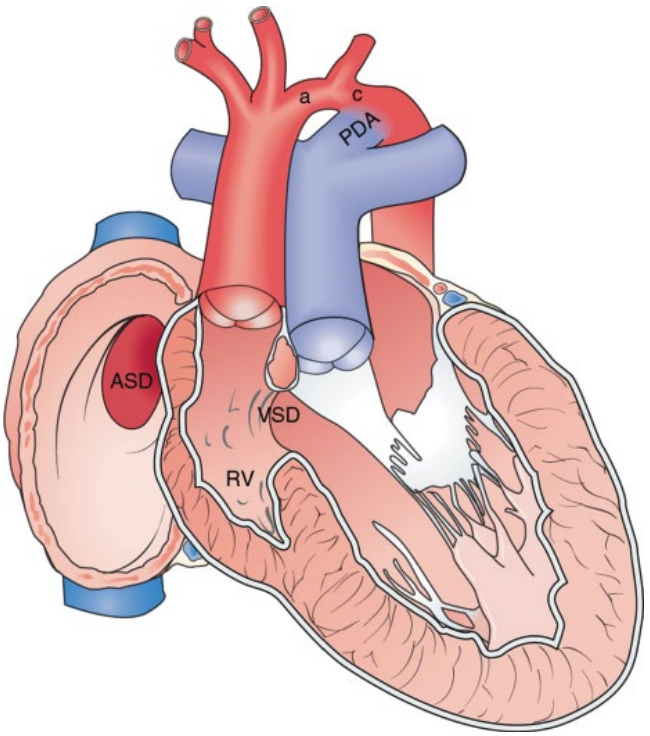


Figure 27.24 Tricuspid atresia. A plate-like obstruction exists in place of the tricuspid valve. This variant is type IIc (see text for details): transposition of the great vessels with no pulmonary stenosis. ASD, atrial septal defect; VSD, ventricular septal defect; RV, right ventricle; PDA, patent ductus arteriosus; a, hypoplastic transverse aortic arch; c, coarctation of the aorta. *Source*: Reproduced from Andropoulos and Gottlieb [359] with permission of Elsevier.

Anesthetic management

The reparative operation of choice for tricuspid atresia is a modified Fontan procedure, but a palliative procedure may initially be required to improve pulmonary blood flow. A pulmonary artery band may be needed if the pulmonary blood flow is increased, or a shunt may have to be created for the severely hypoxemic child with decreased pulmonary blood flow. The anesthetic management and complications are those discussed in the sections on shunts, banding, and modified Fontan procedures (see earlier in this chapter). Complications of chronic hypoxemia and cyanosis are also present.

Transposition of the great arteries

Pathophysiology

With transposition of the great arteries, the right ventricle gives rise to the aorta (Fig. 27.25). Transposition physiology is characterized by pulmonary artery saturation that is greater than aortic saturation. Almost 50% of patients with this anomaly have a VSD, and some of them have a variable degree of subpulmonary stenosis (Fig. 27.25). Oxygenated pulmonary venous blood returns to the left atrium and is recirculated to the pulmonary artery without reaching the systemic

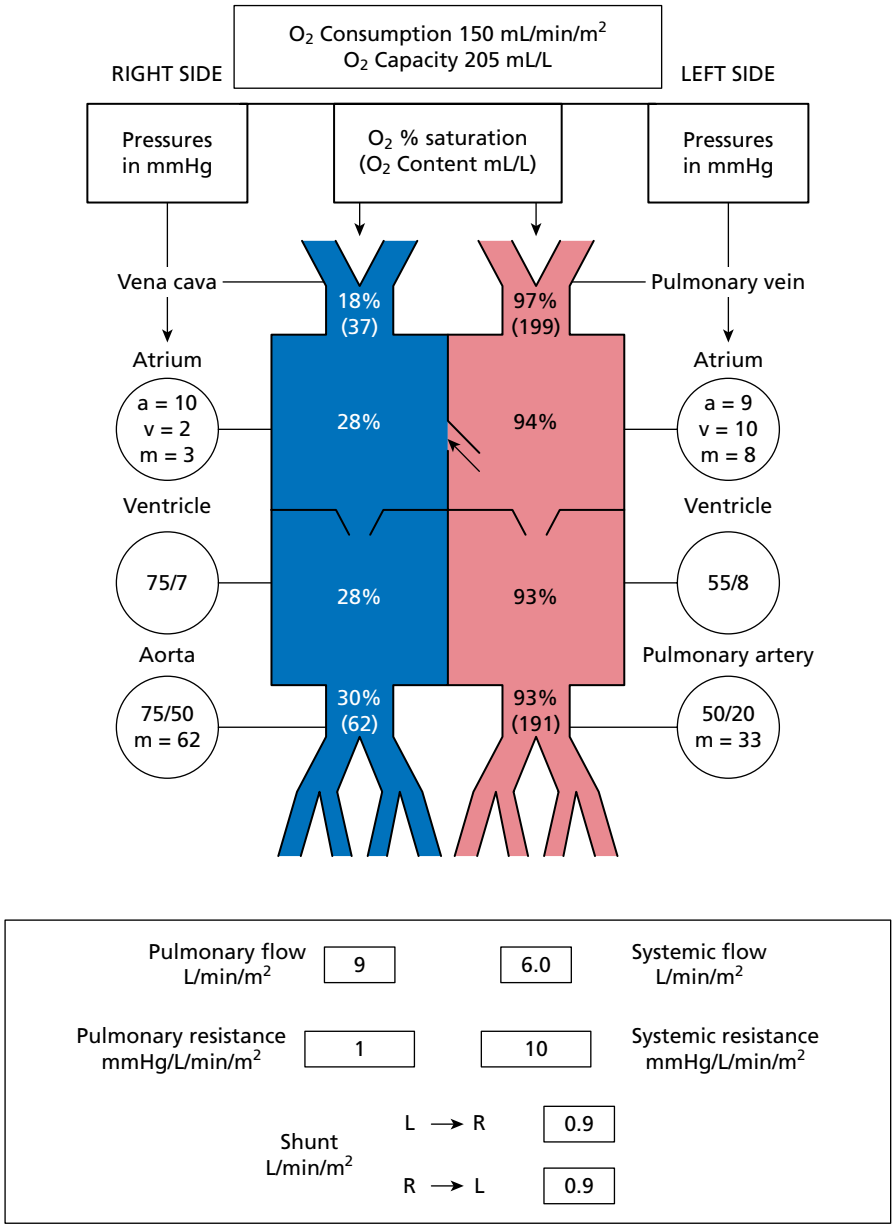


Figure 27.25 Catheterization findings in a patient with d-transposition of the great arteries and restricted pulmonary flow. a, arterial pressure; m, mean pressure; v, venous pressure. *Source*: Reproduced from Nadas and Fyler [357] with permission of Elsevier.

circulation. Similarly, systemic venous blood returns to the right atrium and ventricle and is ejected into the aorta again. This arrangement is incompatible with life unless there is some mixing of pulmonary and systemic venous blood via a patent ductus arteriosus or an opening in the atrial or ventricular septum at birth. The physiological disturbance in these patients is one of inadequate mixing of pulmonary and systemic blood rather than one of inadequate pulmonary blood flow.

Mixing of blood at the atrial level can be improved by balloon atrial septostomy. If dangerous levels of hypoxemia persist after the septostomy and metabolic acidosis ensues, an infusion of PGE1 can maintain the patency of the ductus arteriosus, increase pulmonary blood flow (by increasing L-R shunting across the PDA), and thereby increase the volume of oxygenated blood entering the left atrium. The volume-overloaded left atrium is likely to shunt part of its contents into the right atrium and thereby improve the oxygen saturation of aortic blood. Unlike the kinetics with other lesions, increased shunting of blood during anesthesia improves arterial oxygen saturation before correction of the transposition.

Depending on the particular anatomy and the presence of a VSD or pulmonary stenosis, one of three corrective procedures is used. The intraoperative and postoperative problems encountered differ with each type of procedure.

Atrial baffle procedure (Mustard and Senning)

An atrial-level partition or baffle is created to redirect pulmonary venous blood across the tricuspid valve to the right ventricle and thus to the aorta [278]. Systemic venous return is directed across the atrial septum to the mitral valve, into the left ventricle, and out into the pulmonary artery. Although the pulmonary and systemic circuits are then connected serially instead of in parallel, this arrangement leaves the patient with

a morphological right ventricle and tricupsid valve in continuity with the aorta. Thus, the morphological right ventricle must work against systemic arterial pressure and resistance.

One problem with atrial baffles is that they can obstruct systemic and pulmonary venous return [279]. When this occurs, the patient manifests signs and symptoms of systemic venous obstruction, as evidenced by SVC syndrome or other signs of systemic venous hypertension. When the pulmonary venous pathway is obstructed, pulmonary venous hypertension may be manifested by respiratory failure, poor gas exchange, and pulmonary edema (seen on chest radiograph). Severe pulmonary venous obstruction is manifested in the operating room by the presence of copious amounts of bloody fluid in the endotracheal tube, low cardiac output, and frequently poor oxygenation. Residual interatrial shunts also may cause intra- or postoperative hypoxemia. Long-term rhythm disturbances, along with functional and long-term limitations of the morphological right ventricle and atrioventricular valve in the systemic position have made this operation nearly obsolete. The Mustard and Senning procedures have not been performed regularly since the 1980s, but rare anatomical variants may require this approach, and adults with these repairs may present for cardiac or non-cardiac procedures.

Arterial switch procedure

The arterial switch operation (ASO) to correct dextro-transposition of the great arteries (d-TGA) is one of the major advances in congenital heart surgery over the past 40 years. Jatene and others explored whether anatomical correction of this lesion by dividing both great arteries and reattaching them to the opposite, anatomically correct, ventricle, would improve survival [280,281]. This procedure is now performed in virtually all patients who do not have outflow tract obstruction. It requires excision and reimplantation of the coronary arteries to the neo-aorta (formerly the proximal main pulmonary artery). Virtually all coronary artery patterns are amenable to the ASO (Fig. 27.26).

The success of the arterial switch procedure depends on maintaining adequate function of the morphological left ventricle before repair and successful transfer of the coronary arteries to the pulmonary artery. Anatomical correction of transposition of the great vessels is done during the neonatal period when PVR (afterload of the morphological left ventricle) and left ventricular pressures are still high, preserving the function of both ventricles. Left ventricular mass decreases progressively after birth as the PVR falls. If left ventricular function is misjudged preoperatively, the child may develop severe left ventricular failure postoperatively and require inotropic support and afterload reduction to provide normal cardiac output.

Infants with d-TGA who are more than a few weeks of age and have an intact ventricular septum may have decreased left ventricular pressure and mass. In such cases, the left ventricle may not tolerate the work required to perfuse the systemic vessels. Banding the pulmonary artery increases the afterload of the left ventricle and prepares it to function as a systemic ventricle by increasing and remodeling ventricular muscle mass. Pulmonary blood flow might need to be augemented with a modified B-T shunt if banding results in unacceptable cyanosis. The ASO can usually be accomplished 1 week later after hypertrophy and hyperplasia of the ventricle have occurred [282]. However, during this interval, these patients are cyanotic, with a volume-loaded right ventricle and a pressure-loaded left ventricle, and they may require considerable pharmacological support [283]. Infants with d-TGA and a non-restrictive VSD have a left ventricle that is

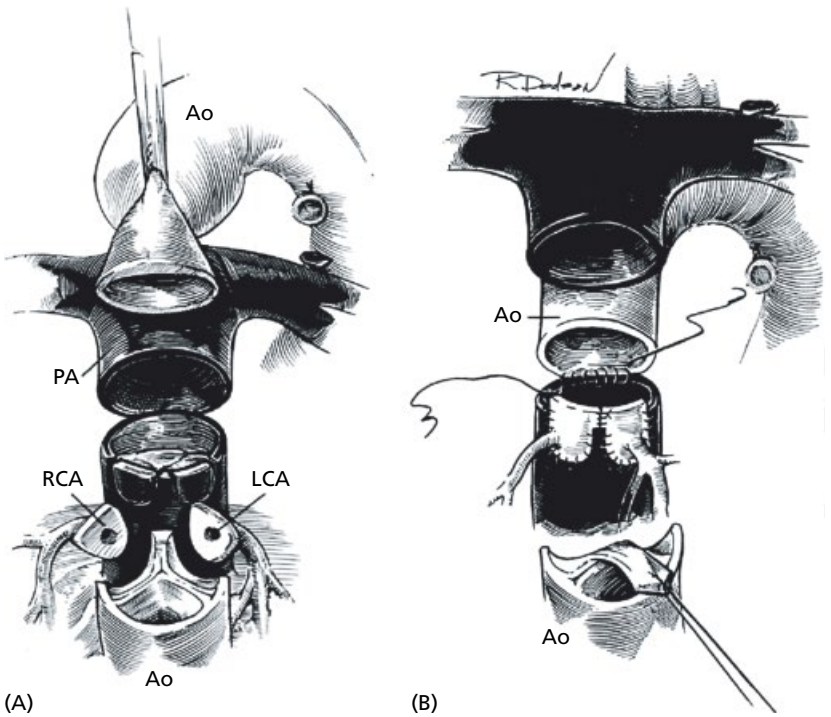


Figure 27.26 Arterial switch operation. (A) The aorta (Ao) and pulmonary artery (PA) are transected and translocated. (B) Coronary arteries are excised with surrounding tissue "buttons" and reimplanted in the neo-aorta site. LCA, left coronary artery; RCA, right coronary artery. *Source*: Reproduced from Castaneda et al [360] with permission of Elsevier.

accustomed to high pressure and may tolerate the increase in workload after the arterial switch operation at any age.

In experienced centers, the incidence of mortality for neonatal repair for d-TGA is now less than 3% and may be less than 2% for most anatomical arrangements of coronary arteries if the aortic arch is normal [284–286]. Midterm follow-up of these patients shows excellent outcome. Alternative operations are reserved almost exclusively for patients with particularly difficult coronary anatomy or pulmonic (neo-aortic) stenosis.

Myocardial ischemia or infarction may occur after mobilization and reimplantation of the coronary arteries, especially if they are stretched or twisted. This may occur if the left atrium becomes distended. Inotropic support, maintenance of coronary perfusion pressures, control of heart rate, and treatment with vasodilators may be particularly useful, as in adult patients with myocardial ischemia. Postoperative bleeding and tamponade occur more commonly with this operation because there are multiple arterial anastomoses.

Ventricular switch (Rastelli procedure)

Patients with a large VSD and severe subpulmonary stenosis can have the VSD closed obliquely to direct left ventricular flow to the aorta. The pulmonary valve is oversewn and the right ventricle connected to the pulmonary artery with a conduit [287]. Complications of the Rastelli procedure include obstruction of left ventricular outflow due to narrowing of the subaortic region by the VSD patch. The conduit also may obstruct during or after the immediate postoperative period. There is a small but significant incidence of heart block in these patients, which can be a difficult postoperative problem. In order to reduce the incidence of these complications, alternative surgical procedures involving biventricular outflow tract reconstruction such as aortic root translocation (Nikaidoh) and réparation à l'etage ventriculaire (the REV or Lecompte procedure) have been developed and modified [288,289].

Anesthetic considerations after repair

Patients who have a morphological right ventricle remaining as the systemic ventricle (as in patients who underwent an atrial switch procedures) have a physiologically corrected but anatomically incorrect functional two-ventricle repair. Actuarial survival figures at 20 years have been quoted up to 80%, but significant long-term functional deterioration is likely with increasing risk of right heart failure, sudden death, and dysrhythmias [290–293]. This situation is evidenced by systemic (right) ventricular dysfunction and tricuspid valve regurgitation long after the repair [294,295].

The development of arrhythmias later in life continues to be a problem following atrial switch procedures. There is a progressive postoperative increase in the incidence of non-sinus rhythm following both the Mustard and Senning operations. Actuarial analysis of several series revealed that by 10 years postoperation, only about 60–70% of patients will be in sinus rhythm at rest and by 20 years this will decrease to 40–50% [296–300]. In one series, only 7% of patients who underwent a Senning procedure for d-TGA with VSD were in sinus rhythmn at 15 years [290]. The majority of patients not in sinus rhythm will be in a junctional rhythm without the necessity for a pacemaker. Atrial flutter is present in 8% of patients at 5 years and in 27% at 20 years [300]. Late development of atrial flutter/fibrillation may be a surrogate marker for ventricular dysfunction and as such may put the patient at risk for VT and sudden death [301].

The exercise response of patients who have undergone an atrial switch procedure is abnormal with RV dysfunction, chronotrophic impairment, failure to augment ventricular filling and stroke volume, deconditioning, and impaired lung function all playing a role. Failure to augment ventricular filling is the consequence of diastolic pathology and poor atrial transport across reconstructed intra-atrial pathways [302–305].

Postoperative concerns of the ASO include the long-term patency and growth potential of the reimplanted coronary arteries. Fortunately, these problems have not materialized on a large scale. The overwhelming majority (95%) of patients have normal-sized, patent coronary arteries. A more recent study of a large cohort demonstrated that the incidence of adverse cardiovascular events was 93% at 25 years [306]. Patients with complex preoperative coronary anatomy are at increased risk of late occlusion [307].

After repair, the native pulmonary valve becomes the neo-aortic valve. Aortic insufficiency occurs in approximately 50% of patients at long-term follow-up with the majority (93%) graded as trivial or mild [294,308]. Time has shown aortic insufficiency to be a rare source of morbidity or indication for reoperation following the ASO [284,285].

In contrast to the atrial switch procedures, electrophysiological abnormalities are uncommon after the ASO. The most common abnormalities noted at midterm and long-term follow-up are rare asymptomatic atrial and ventricular premature beats [308–310].

Supravalvar pulmonary artery stenosis was an early complication, but is now less common with surgical techniques that extensively mobilize, augment, and reconstruct the pulmonary arteries. The incidence of supravalvular stenosis severe enough to require reoperation (generally a gradient greater than 50–60 mmHg) is approximately 10% [284,285]. There continue to be refinements in surgical technique to further reduce the incidence of this complication [311].

Assessment of myocardial performance using echocardiography, cardiac catheterization, and exercise testing following the ASO has demonstrated function identical to age-matched controls [312]. Based upon the currently available clinical, functional, and hemodynamic data, a patient who has undergone a previous ASO with no evidence of subsequent problems should be treated as for any patient with a structurally normal heart when presenting for non-cardiac surgery.

Total anomalous pulmonary venous connection

Pathophysiology

Patients with total anomalous pulmonary venous connection are cyanotic and have pulmonary veins connected to a systemic vein. The venous connection may be above the level of the heart (e.g. to the SVC, innominate, or azygos vein), directly to the right atrium, or below the level of the heart and the diaphragm (e.g. to the hepatic veins) (Fig. 27.27). Patients with this anomaly must have a patent foramen ovale or an ASD that allows blood flow to the left side of the heart. A subset of patients may have varying degrees of pulmonary venous obstruction.

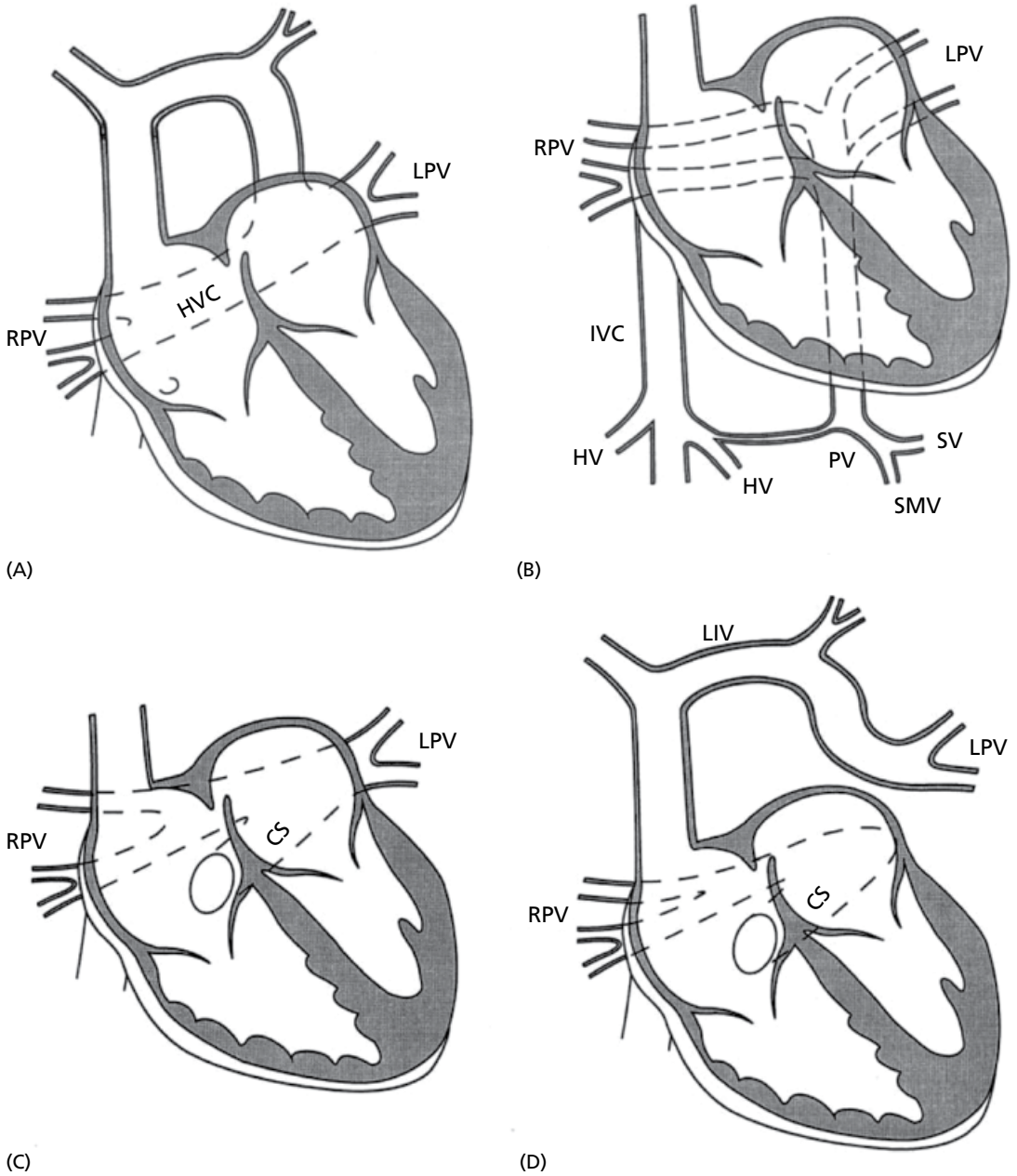


Figure 27.27 Four major subtypes of total anomalous pulmonary venous return (see text for further explanation): (A) supracardiac, (B) infracardiac, (C) cardiac, and (D) mixed. RPV, right pulmonary vein; HVC, horizontal pulmonary venous confluence; LPV, left pulmonary vein; CS, coronary sinus; IVC, inferior vena cava; HV, hepatic vein; PV, portal vein; SMV, superior mesenteric vein; SV, splenic vein; LIV, left innominate vein. *Source*: Reproduced from Allen et al [361] with permission of Wolters Kluwer.

This anatomical arrangement provides complete mixing of all systemic and pulmonary venous blood in the right atrium. The mixed venous blood is partially shunted across the atrial communication to the left arium and systemic circulation. Most of this right atrial blood passes through the right ventricle into the pulmonary artery, which increases pulmonary blood flow. If pulmonary venous return is significantly inhibited, there is increased pulmonary venous congestion and decreased pulmonary blood flow.

Anesthetic management

These patients may be very ill, with hypoxemia, severe pulmonary edema, and pulmonary artery hypertension. Patients are resuscitated with mechanical ventilation, use of PEEP, and inotropic support, and then undergo early surgical intervention to relieve the pulmonary venous obstruction. Although the patients are hypoxemic, their primary pathology is caused by obstructed venous return from the lungs. Therapy that increases pulmonary blood flow (e.g. PGE1) must be avoided. Surgical repair of total anomalous pulmonary venous connection requires attachment or redirection of the pulmonary venous confluence to the left atrium [313].

Intraoperative and postoperative problems are often related to residual or recurrent stenosis of the pulmonary veins. The pulmonary vascular bed is highly reactive in patients who had pulmonary venous hypertension preoperatively. This reactivity may produce high pulmonary artery pressures and poor right ventricular function after bypass and during the

early postoperative period. Anesthetic management of these patients after completion of the repair should emphasize inotropic support of the right ventricle, avoidance of myocardial depressant drugs, and minimization of pulmonary vascular resistance. Early extubation of the trachea is usually not feasible. Mechanical ventilation with hyperventilation and other postoperative therapy to decrease PVR are required. Use of inhaled nitric oxide has been particularly useful in this population.

Anesthetic considerations after repair

Other than the potential for late development of recurrent pulmonary venous obstruction, these patients generally do well and have good cardiovascular reserve once recovery from the surgery is complete [314]. The size of the pulmonary veins at birth may be a predictor of late complications with recurrent pulmonary vein stenosis [315].

Atrial septal defects

Pathophysiology

There are three anatomical varieties of ASD (Fig. 27.28). The most common is the secundum ASD, which is a deficit in the septum primum, the membrane that usually covers the region of the foramen ovale. The ASD primum is a deficit of the inferior portion of the atrial septum (endocardial cushion) and is usually accompanied by a cleft in the anterior leaflet of the mitral valve. Sinus venosus defects are located near the junction of the right atrium and the superior or inferior vena cava and are are frequently associated with a partial anomalous pulmonary venous connection where the two right-sided veins connect directly to the SVC.

ASDs are functionally characterized as simple L-R shunts that cause a low-pressure volume load to the right ventricle. Pulmonary blood flow is increased, but not enough to make these patients symptomatic during early childhood. Later in life, the left ventricle becomes less compliant and the left atrial pressure increases. Left-to-right shunting across the ASD and volume loading increase and symptoms of CHF may occur. Rarely does the long-standing increase in pulmonary blood flow cause development of precapillary pulmonary hypertension.

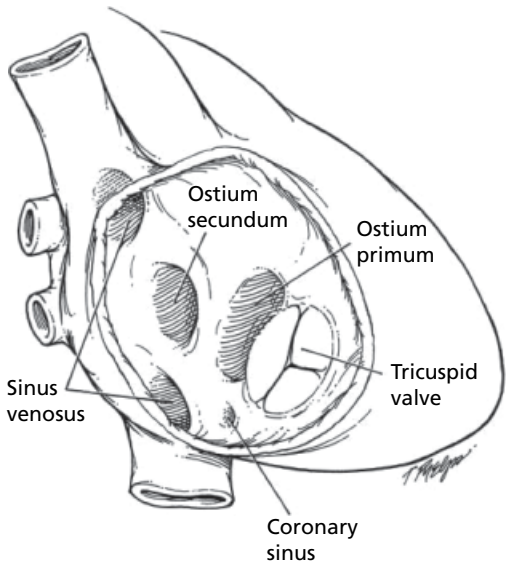


Figure 27.28 Types of atrial septal defects. *Source*: Reproduced from Redmond and Lodge [362] with permission of Elsevier.

Anesthetic management

Secundum ASDs can sometimes be closed using a minimally invasive transcatheter device in the catheterization laboratory. Large or multiple defects, as well as those with inadequate atrial borders to anchor a transcatheter device, require direct closure using sutures or a patch made of autologous or synthetic material. Sinus venosus defects associated with partial anomalous pulmonary venous connection require a more extensive patch that also directs the partial anomalous pulmonary venous return into the left atrium.

Patients with ASDs are usually easy to manage in the prebypass period and short bypass times make the patient amenable to early tracheal extubation in the ICU or operating room. Cardiovascular function and reserve are usually normal in the postoperative period, and inotropic support is rarely required. Atrial arrhythmias, including atrial flutter and atrial fibrillation, are unusual. Mitral regurgitation may occur in patients who have undergone repair of an ASD primum. Residual ASDs are uncommon, but occasionally failure to recognize partial anomalous pulmonary venous return results in a residual L-R shunt.

Ventricular septal defects

Pathophysiology

Defects in the ventricular septum occur at several locations in the muscular partition dividing the ventricles (Fig. 27.29). Simple shunting occurs across the ventricular septum. The magnitude of pulmonary blood flow is determined by the size of the VSD and the PVR (Fig. 27.30) [316]. With a non-restrictive defect, high left ventricular flows and pressures are transmitted to the pulmonary artery. Therefore, surgical repair is indicated within the first 2 years of life to prevent the progression of pulmonary vascular occlusive disease. In patients with established pulmonary vascular disease, the pulmonary arteriolar changes may not recede when the defect is closed. The growth and development of the pulmonary vascular bed are significant factors in the patient's ability to normalize pulmonary vascular hemodynamics after surgery [317]. When PVR approaches or exceeds systemic vascular resistance, R-L shunting occurs through the VSD and patients develop progressive hypoxemia (Eisenmenger syndrome) [318,319]. Closing the VSD in this circumstance may require management of acute right heart failure.

Anesthetic management

The defects are closed during CPB. The most common septal defect, the membranous defect, is frequently repaired through a right atriotomy and the tricuspid valve. However, lesions in the inferior apical muscular septum or those high in the ventricular outflow tract may require a left or right ventriculotomy. If so, the postoperative ventricular function may be impaired.

Before repair, measures that decrease PVR may appreciably increase L-R shunting in patients with a non-restrictive defect and may increase the degree of CHF. Postoperative right or left ventricular failure may be a manifestation of the preoperative status of the myocardium, a result of the ventriculotomy

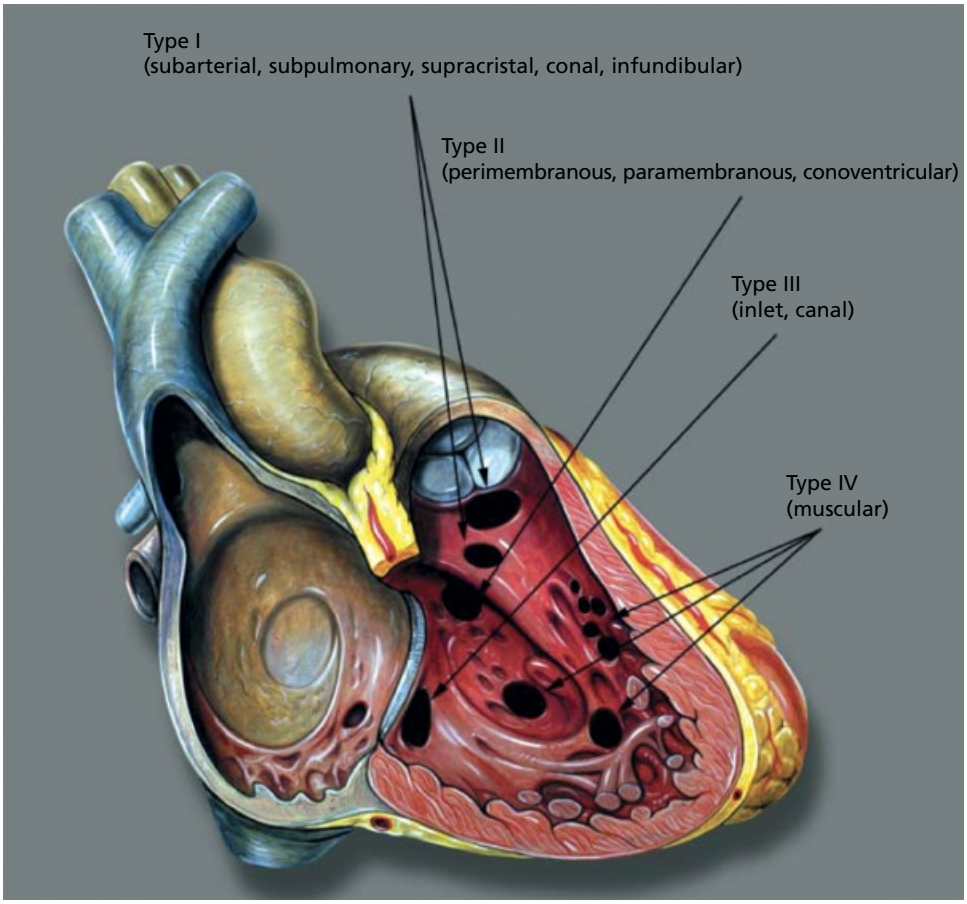


Figure 27.29 Types of ventricular septal defect. *Source*: https://commons.wikimedia.org/wiki/File:Heart_right_vsd.jpg. Licensed under CCBY 2.5.

and CPB, or both. Small infants who fail to thrive, who are malnourished, and who have significant CHF preoperatively may have excessive lung water and may require prolonged mechanical ventilation postoperatively. Such infants may have limited intraoperative tolerance for anesthetics that depress the myocardium or for maneuvers that increase pulmonary blood flow.

Persistent CHF and an audible murmur postoperatively, evidence of low cardiac output, or the need for extensive inotropic support intraoperatively suggest that a residual or previously unrecognized VSD is continuing to place a volume and pressure load on the ventricles. When PVR is increased preoperatively, the increase in right ventricular afterload caused by closure of the VSD may be poorly tolerated, leading to the need for inotropic support of the heart and measures to decrease PVR. Occasionally, ventricular outflow tract obstruction is caused by placement of the septal patch. Aortic regurgitation caused by prolapse of one of the aortic valve cusps can develop in subaortic or subpulmonic VSDs. In addition, heart block may occur after closure of VSDs with a patch. A pacemaker may be needed to maintain an adequate heart rate and cardiac output.

Anesthetic considerations after repair

Most patients regain normal myocardial function after repair, particularly when the VSD is repaired early. Residual VSDs, outflow tract obstruction, and heart block are known postoperative complications that will prolong recovery. A small percentage of patients, especially those who have had a large defect repaired late in childhood, will have persistent ventricular dysfunction and pulmonary hypertension.

Atrioventricular canal defects

Pathophysiology

The endocardial cushion defect, complete common AV canal, consists of defects in the atrial and ventricular septa and the AV valvular tissue. All four chambers communicate and share a single common AV valve. The atrial and ventricular shunts communicate volume and systemic pressures to the right ventricle and pulmonary artery. The ventricular shunt orifice is usually non-restrictive (simple shunt); therefore, PVR governs the degree of excess pulmonary blood flow. Mitral regurgitation and direct left ventricular-to-right atrial shunting may further contribute to atrial hypertension and total L-R shunting.

Anesthetic management

Surgical repair of this lesion consists of division of the common AV valve and closure of the atrial and ventricular septal defect with a single patch, modified single-patch, or two-patch technique [320]. In addition, the mitral valve (and sometimes the tricuspid valve) requires suture approximation and resuspension of the separated portions.

Preoperatively, these patients have large L-R shunts with excessive pulmonary blood flow that may progress to CHF with the eventual development of pulmonary hypertension. Myocardial depressants and therapies that decrease PVR may

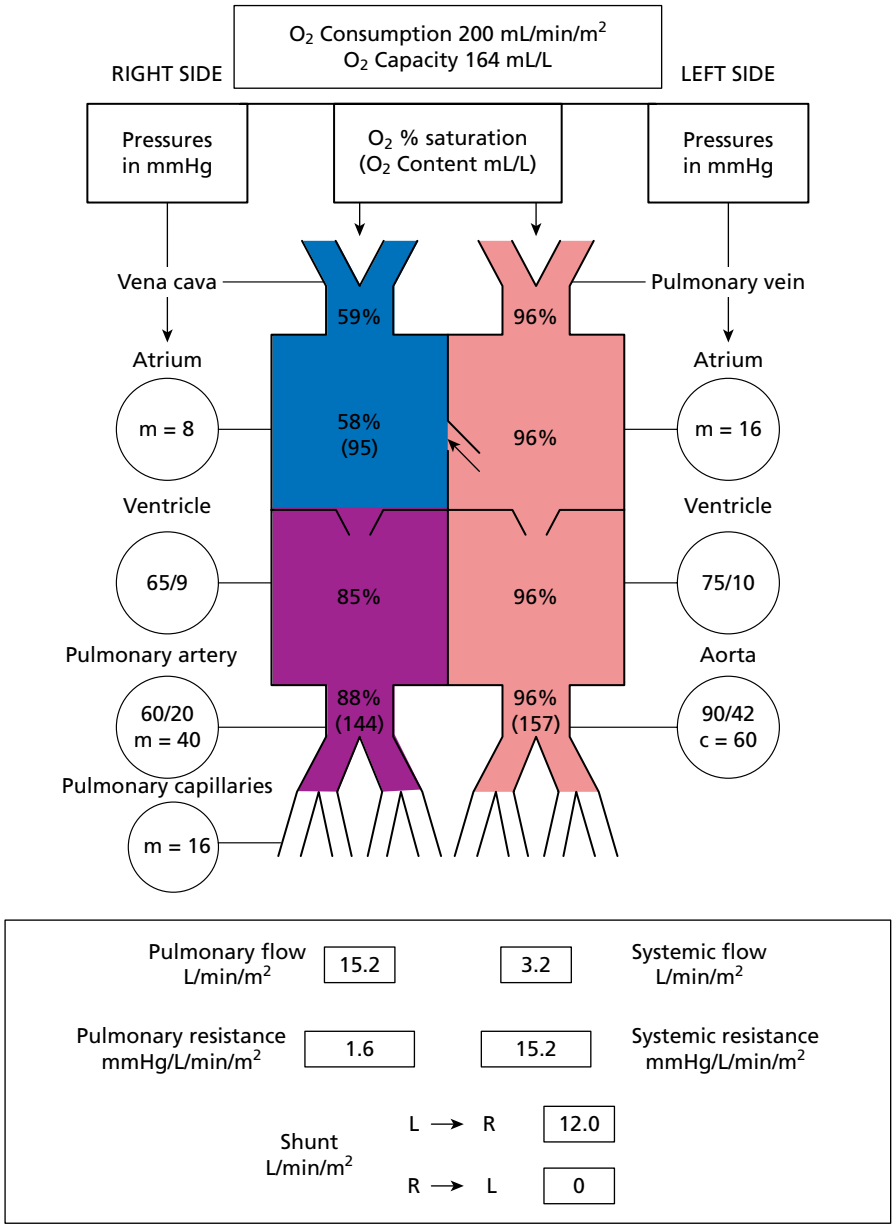


Figure 27.30 Catheterization findings in a patient with a VSD and pulmonary artery hypertension. m, mean pressure. *Source*: Reproduced from Nadas and Fyler [357] with permission of Elsevier.

be poorly tolerated. Some patients, especially older children, may have obstructive pulmonary vascular disease. All of the potential complications of ASD and VSD closures are seen in these patients. In addition, the mitral valve may be regurgitant [321]. Inotropic support for the failing heart, afterload reduction for mitral regurgitation, and measures to decrease PVR may be required intraoperatively and following repair [322].

Patients with Down syndrome frequently have an associated complete AV canal defect. Prolonged ventilatory support and therapies to decrease PVR following repair are sometimes necessary as these patients may have reactive airways and pulmonary vascular beds. The usual perioperative concerns of patients with Down syndrome exist, including macroglossia, upper airway obstruction, and difficult vascular access, but Down syndrome is not a risk factor for cardiac mortality, and early postoperative problems in Down syndrome patients are non-cardiac [323].

Patent ductus arteriosus

Pathophysiology

The ductus arteriosus is a fetal vascular communication between the main pulmonary artery at its bifurcation and the descending aorta below the origin of the left subclavian artery. When patent, it provides a simple shunt between the systemic and pulmonary arteries. The magnitude and direction of flow between the systemic and pulmonary vessels are determined by the relative resistances to flow in the two vascular beds and the diameter (resistance) of the ductus itself. Pulmonary blood flow is excessive and there is a large volume load on the left heart when the ductus is non-restrictive and the PVR is low. Pulmonary steal occurs when blood flows to the low-resistance lungs during systole and diastole at the expense of perfusing the systemic tissue beds. In addition, overcirculated lungs and elevated left atrial pressure increase the work of breathing.

Anesthetic management

Although the PDA of premature infants can often be closed medically with indomethacin or ibuprofen, contraindications to the use of these agents (e.g. intracranial hemorrhage, renal dysfunction, and hyperbilirubinemia) may require that the defect be closed surgically [324]. Thoracotomy and surgical ligation of the ductus arteriosus is the standard approach in infants and children, but some centers now occlude the ductus with a percutaneously inserted coil or occlusion device [325] or by using video-assisted thoracoscopic surgery (VATS) [326]. Advantages of VATS compared with open thoracotomy include decreased postoperative pain, shorter hospital stay, and decreased incidence of chest wall deformity [327].

Healthy asymptomatic patients can emerge from anesthesia in the operating room, but premature infants with severe lung disease may require mechanical ventilation for protracted periods of time after ligation of the ductus arteriosus. Fentanyl, a muscle relaxant, oxygen, and air constitute a common anesthetic regimen for this procedure in these sick premature infants. Anesthetic management of the premature infant in the operating room requires special considerations of gas exchange, hemodynamic performance, temperature regulation, metabolism, and drug and oxygen toxicity. Thoracotomy and lung retraction usually decrease lung compliance and increase oxygen and ventilatory requirements. A transient rise in systemic blood pressure with ligation of the ductus arteriosus may increase left ventricular afterload or elevate cerebral perfusion pressure, potentially precipitating heart failure or an intracranial hemorrhage in a premature infant. Inadvertent ligation of the left pulmonary artery or descending aorta has occurred because the ductus arteriosus is often the same size as the descending aorta.

Ligation of an isolated ductus arteriosus generally results in a decrement in left ventricular efficiency within 24 h due to the marked increase in afterload but recovers to preoperative levels after 2–4 days.

Truncus arteriosus

Pathophysiology

Truncus arteriosus is characterized by failure of the embryonic truncus to separate normally into the two great arteries, resulting in a single great artery that leaves the heart and gives rise to the coronary, pulmonary, and systemic circulations (Fig. 27.31). The truncus straddles a large VSD and receives blood from both ventricles.

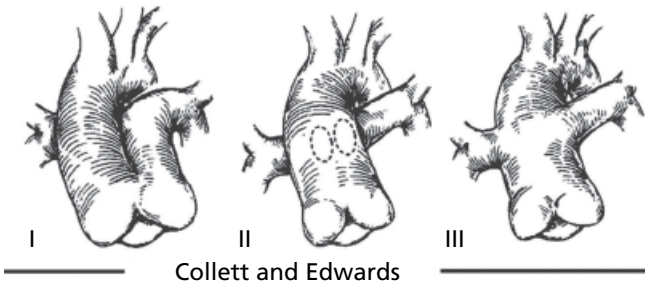


Figure 27.31 Truncus arteriosus – Collett and Edwards classification. In type I, the main pulmonary artery arises from the truncus (70% of patients). In type II, there are separate left and right pulmonary artery origins from the posterior truncus (30%). In type III, there are separate left and right pulomary artery origins from the lateral truncus (<1%). *Source*: Reproduced from Jacobs [363] with permission of Elsevier.

There is complete mixing of systemic and pulmonary venous blood in the single great artery, causing mild hypoxemia. One or two pulmonary arteries may originate from the ascending truncus with orifices that are seldom restrictive. The resulting simple shunt produces excessive pulmonary blood flow early in life as the pulmonary vascular resistance decreases, and pulmonary steal may develop compromising systemic blood flow. Net systemic oxygen transport decreases and lactic acidosis develops. Children with truncus arteriosus are at risk for developing early pulmonary vascular obstructive disease. Regurgitation of blood through the truncal valve may place an additional volume load on the ventricles [328].

Anesthetic management

Complete repair of this lesion should be performed in the neonatal period before the development of irreversible pulmonary vascular changes. The VSD is closed with a synthetic patch and the pulmonary arteries are detached from the truncus. Continuity is established between the right ventricle and the pulmonary arteries with a valved conduit. The truncal systemic valve may require valvuloplasty if a significant amount of blood regurgitates through it.

Anesthetic management centers around control of pulmonary blood flow and supporting ventricular function. Pulmonary blood flow may increase further with induction of anesthesia, hyperventilation, alkalosis, and oxygen administration, resulting in hypotension, decreased coronary perfusion, and acute ventricular failure. If measures to increase PVR do not decrease pulmonary flow, occlusion of one branch of the pulmonary artery with a tourniquet limits pulmonary flow and restores systemic perfusion pressure until CPB can be instituted. These patients are frequently in high-output CHF so myocardial depressants should be used with caution.

Persistent pulmonary artery hypertension and right ventricular failure may need to be addressed following the repair. Aggressive measures should be taken to normalize myocardial function and lower the PVR. A residual VSD adds an additional volume and pressure load on both ventricles and should be suspected in patients with poor hemodynamics and oxygenation after repair. Truncal valve regurgitation or stenosis may induce left ventricular failure early during the postoperative period.

Anesthetic considerations after repair

Obstruction of the pulmonary conduit and accompanying right ventricular hypertension may occur early or late during the postoperative course. The late development of truncal (systemic) valve regurgitation is possible, as is residual pulmonary hypertension, particularly in patients who underwent repair later in infancy or childhood.

Coarctation of the aorta

Pathophysiology

Patients with coarctation of the aorta have a narrowing of the descending aorta near the insertion of the ductus arteriosus into the aorta (Fig. 27.32). Coarctation of the aorta is sometimes associated with hypoplasia of the aortic isthmus proximal to the coarctation. Aortic and mitral valve abnormalities, as well as VSDs, may also be present.

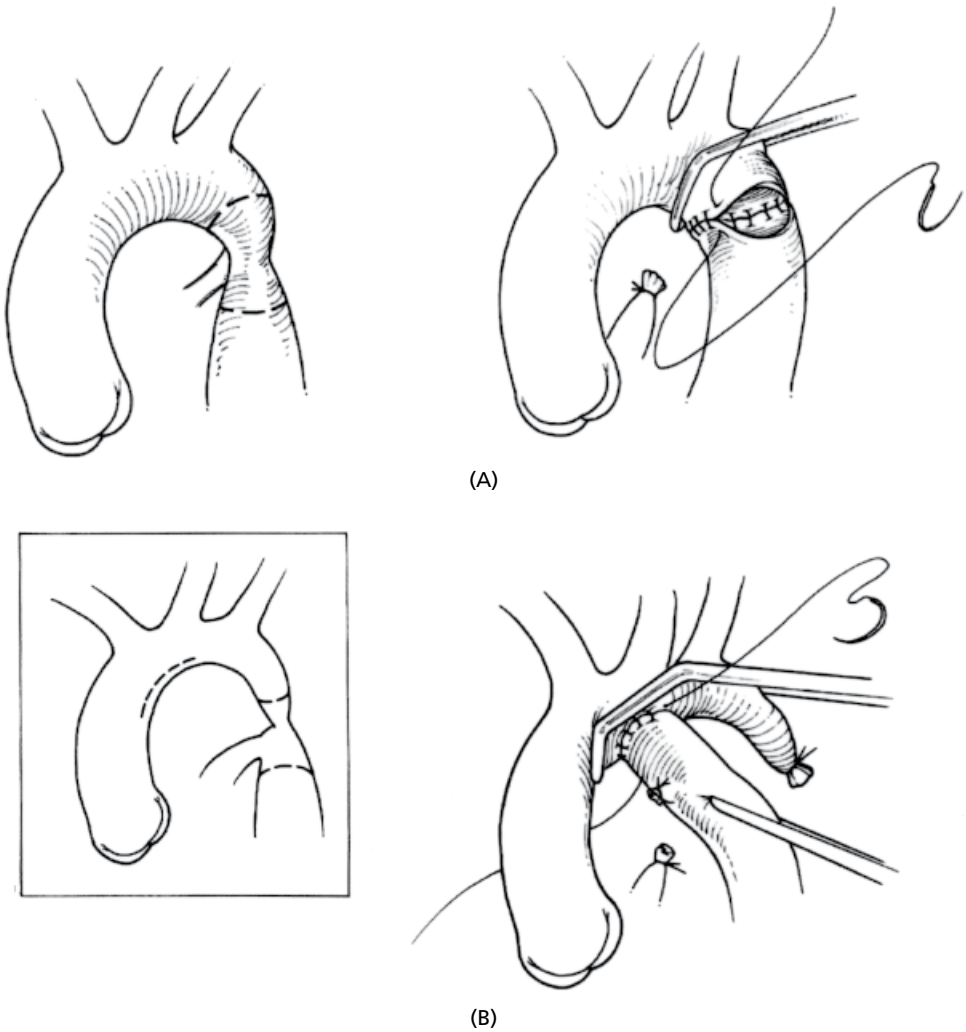


Figure 27.32 Two surgical approaches for repair of coarctation of the aorta. (A) Resection of coarctation with end-to-end anastomosis. (B) End-to-side or aortic arch advancement technique. *Source*: Reproduced from Chang et al [364] with permission of Wolters Kluwer.

Inadequate systemic perfusion caused by obstruction of blood flow in the descending aorta causes profound metabolic acidosis. Increases in left ventricular afterload are usually poorly tolerated by the neonatal heart, and elevated left ventricular end-diastolic pressure may cause pulmonary artery hypertension. Systemic flow distal to the coarctation is provided by right-to-left flow from the right ventricle and pulmonary artery through the ductus arteriosus. Maintaining or re-establishing duct flow can be accomplished with PGE1 infusion, which also reduces the left ventricular afterload.

Less severe coarctation of the aorta may be compensated for by the development of collateral circulation to the lower body and by increasing left ventricular muscle mass. Upper extremity hypertension and left ventricular hypertrophy noted later in childhood may be the only manifestation of the coarctation.

Anesthetic management

The optimal treatment for neonates, infants, and children with aorta coarctation is usually complete excision of the area of coarctation and surrounding ductal tissue with end-to-end anastomosis (Fig. 27.32A). Alternatively, a reverse subclavian patch repair can be undertaken. In this technique, the left subclavian artery is ligated and transected with the proximal portion of the artery used as a flap to augment the area of coarctation. Following this procedure, left arm pulses will be weak or absent. This technique is no longer used in modern surgical practice; an aortic arch advancement technique where the descending thoracic aorta is anastomosed to the underside of the aortic arch is an effective technique (Fig 27.32B). Dacron patch aortoplasty following resection of the posterior coarctation ridge has also been used, but this technique is associated with late development of hypertension and aneurysm formation as compared with end-to-end anastomosis [329].

All approaches require 10–25 min of aortic cross-clamping above and below the area of coarctation. Acidosis, hypertension, and spinal cord ischemia can occur during this period. Paraplegia is an extremely rare but tragic complication of the procedure. Upper body hypertension may compromise left ventricular function and decrease cardiac output, especially to the lower body, and must be treated. If the elevated arterial pressure in the head is transmitted to the cerebrospinal fluid (CSF), the CSF pressure may be elevated. Elevated pressures are transmitted to the CSF below the level of the coarctation so net spinal cord perfusion pressure is decreased [330]. Alternatively, if upper body hypertension is overtreated with vasodilators during cross-clamping of the aorta, the arterial pressure may be inadequate in the vasodilated lower half of the body, which is supplied by collaterals. If this occurs, spinal

cord or renal ischemia may result. Development of abdominal pain and bowel ischemia during the postoperative period may be related to insufficient flow in the mesenteric artery

These complications are not so much related to changes in proximal aortic pressure or distal CSF pressure as they are to distal perfusion pressures, adequacy of arterial collaterals, and duration of cross-clamping. Monitoring of arterial pressures in the lower extremities may be helpful but impractical during the cross-clamp period. Hyperthermia to 38°C and 40°C during cross-clamping is associated with an increased incidence of paraplegia and transient renal failure [331]. Therefore, mild hypothermia (32–34°C) is used in some centers during aortic cross-clamping as a possible prophylaxis for these rare but tragic problems.

Rebound hypertension after the cross-clamp is removed and later when the patient emerges from the anesthetic may be problematic. The etiology of this persistent hypertension is multifactorial. Reduced compliance of the left ventricle in systole, as well as stiffness of the perfused arteries, have been implicated [332]. Propranolol and hydralazine may be useful for treating moderate forms of postoperative hypertension, the more severe forms are best treated with sodium nitroprusside and esmolol during the first few hours after surgery.

The geometry of the aortic arch following coarctation and distal aortic arch repair is also a determinant of subsequent upper body vascular responses, pulse wave velocity, and left ventricular mass. Anatomy with a high arch height to width ratio (Gothic arch) is associated with impaired vascular response, increased pulse wave velocity, central aortic stiffness, and increased LV mass as compared to anatomy with a lower arch height to width ratio (Crenel and normal Romanesque arch anatomy) [333,334]. Abnormalities in baroreceptor reflexes and in the renin–angiotensin–aldosterone system have also been implicated as factors in persistent hypertension following successful coarctation repair. Recent evidence suggests that abnormalities in cardiovascular reflexes are already present in neonates with coarctation prior to repair [335–337].

Anesthetic considerations after repair

Persistent hypertension and left ventricular hypertrophy may be problems for anesthetic management in as many as one-third of patients after adequate repair of coarctation of the aorta [338]. If the left subclavian artery was used for the repair, the left arm cannot be used for accurate blood pressure measurements. Restenosis of the coarctation is routinely balloon dilated in the interventional catheterization laboratory.

Interrupted aortic arch

Pathophysiology

In some patients, the aorta is completely interrupted at one or more points along the aortic arch (Fig. 27.33). A PDA and VSD are nearly always present. Flow distal to the aortic interruption is supplied entirely by blood shunted right to left through the ductus arteriosus with L-R flow through the VSD. The L-R shunt through the VSD may cause excessive pulmonary blood flow and respiratory insufficiency. In addition, left ventricular outflow obstruction may be present. Ductal closure eliminates blood flow to the lower body and leads to metabolic acidosis. Patency of the ductus arteriosus is re-established with PGE1.

Anesthetic management

Repair of this lesion in neonates consists of patch closure of the VSD and a direct anastomosis of the descending aorta to the underside of the transverse arch. Alternatively, a palliative approach may be taken where the aortic arch is repaired, the pulmonary artery is banded, and the VSD is closed when the patient has grown. In the presence of significant left ventricular outflow tract obstruction, alternative procedures such as a Ross–Konno or Yasui procedure are considered [339].

The introduction of PGE1 has substantially improved the preoperative resuscitation and perioperative morbidity, and the PGE1 infusion should be continued until CPB is initiated. The residual effects of protracted poor perfusion distal to the interruption may complicate the intra- and postoperative course of these patients. Circulatory problems after CPB that require inotropic support may be caused by a significant residual VSD, by obstruction of blood flow in the aorta, or by subaortic stenosis aggravated by the VSD closure and a narrow subaortic region.

Late problems are related to obstruction of the descending aorta with subsequent growth of the child. These problems are similar to those seen with coarctation of the aorta. Subaortic stenosis may also develop and presents considerable surgical challenges to adequate relief of obstruction.

Critical aortic stenosis

Pathophysiology

The aortic valves in patients with critical aortic stenosis are thickened and rigid and have some degree of fusion of the valvar commissures. Patients have various degrees of fusion of the valvular commissures. In the newborn, the valve appears amorphous. There also may be evidence of endocardial

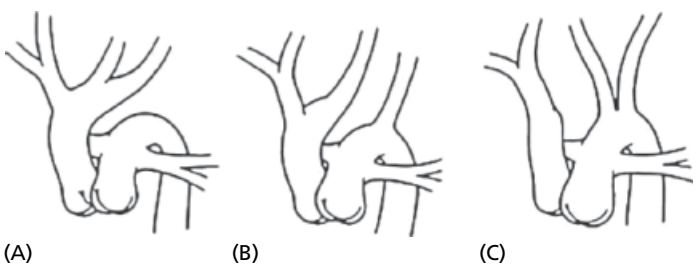


Figure 27.33 Interrupted aortic arch. (A) Type A: interruption between the left subclavian artery and the ductus arteriosus. (B) Type B: interruption between the left carotid and left subclavian arteries. (C) Type C: interruption at the proximal aortic arch between the innominate and left carotid arteries. *Source*: Reproduced from Chang et al [364] with permission of Wolters Kluwer.

fibroelastosis of the left ventricle and functional or anatomical abnormalities of the mitral valve.

Left ventricular outflow tract obstruction is poorly tolerated in the neonate because it causes left ventricular failure, poor systemic perfusion, hypotension, and pulmonary congestion. Myocardial perfusion is often borderline because the coronary perfusion pressure is relatively low and intraventricular pressure is high. Ventricular fibrillation may occur with surgical manipulation of the heart. In severe cases of criticial aortic stenosis, systemic blood flow may be partly supported from the right ventricle by R-L flow through the ductus arteriosus, provided that there is atrial septal communication. Stabilization of the patient's condition can be aided by infusion of PGE1 to increase systemic perfusion.

Anesthetic management

The treatment options for isolated critical aortic stenosis in the neonate are percutaneous balloon angioplasty and surgical valvotomy [340]. Myocardial depressants and rapid heart rates are poorly tolerated during either procedure. A defibrillator should be available for immediate use. Preoperative resuscitation and optimization of the left ventricle is imperative. Inadequate relief of the obstruction and persistence of left ventricular failure can complicate and prolong the postprocedure course. Residual stenosis or other added hemodynamic burdens further reduce myocardial performance. Mitral regurgitation may continue intraoperatively, and aortic regurgitation may occur after the valvotomy. Myocardial ischemia is not generally a problem after valvotomy. If the obstruction is adequately relieved, afterload reduction and inotropic agents may improve the poor myocardial function often evident postoperatively, especially when there is some degree of aortic regurgitation. In some patients, associated hypoplasia of the left ventricle or mitral valve may inhibit recovery and dictate a therapeutic approach to hypoplastic left heart.

Hypoplastic left heart syndrome

Pathophysiology

Hypoplastic left heart syndrome (HLHS) is the most severe form of obstructive left heart lesion and results in single-ventricle physiology (Fig. 27.34). There is an anatomical spectrum of disease. In its most severe and common presentation there is atresia or marked hypoplasia of the aortic and mitral valves with critical underdevelopment of the left atrium, left ventricle, and ascending aorta. A 1 or 2 mm ascending aorta gives rise to the coronary circulation and the head vessels before converging with the ductus arteriosus, where the aorta becomes larger and supplies the circulation to the lower body. Pulmonary venous return arrives in the diminutive left atrium and cannot cross the atretic mitral valve; therefore, it is directed to the right atrium and right ventricle, where common mixing occurs with the systemic venous return and all blood is ejected into the pulmonary artery. Systemic blood flow is then supplied from the pulmonary artery, right to left, across the PDA. As the PDA constricts in the neonatal period, systemic blood flow decreases and all ventricular output is directed to the lungs. The Qp/Qs ratio approaches infinity as Qs nears zero. Therefore, one has the paradoxical presentation of high PO_2 (70–150 mmHg) and profound metabolic acidosis. When the ductus arteriosus is reopened with PGE1, systemic perfusion is re-established, the acidosis resolves, and the PO_2 returns to the 40–60 mmHg range, representative of a Qp/Qs ratio of between 1 and 2.

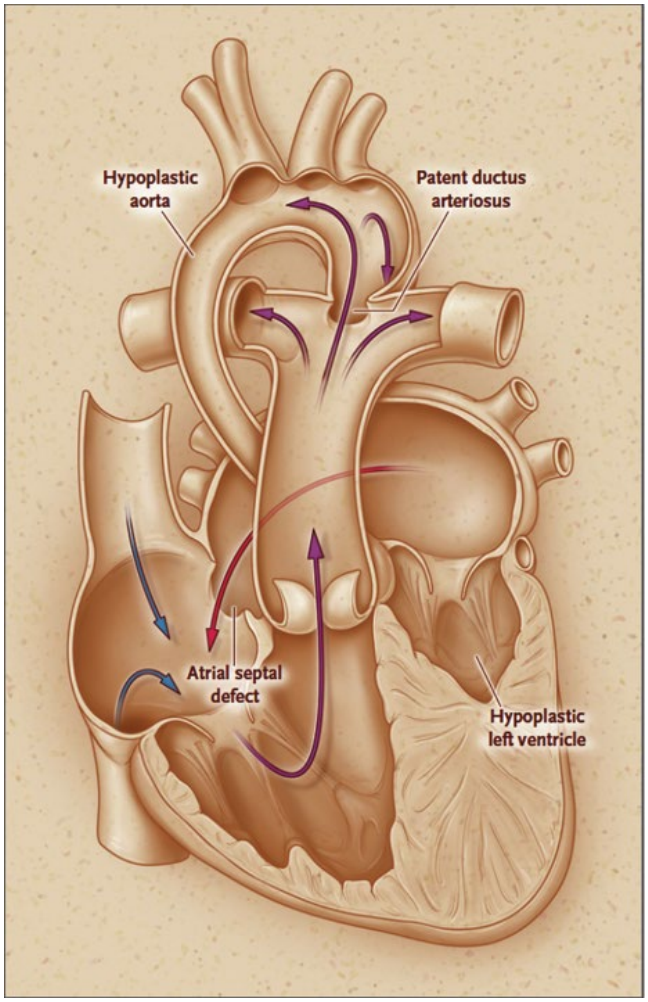


Figure 27.34 Hypoplastic left heart syndrome (HLHS). HLHS involves a single right systemic ventricle. Oxygenated blood from the pulmonary veins enters the left atrium, passes through an atrial septal defect to the right atrium, where it mixes with systemic venous blood returning through the vena cavae. The blood passes into the right ventricle, and is ejected out of the pulmonary artery. From the pulmonary artery, a portion of the blood flows to the lungs, and a portion of the blood flows through the patent ductus arteriosus to supply the lower body through the descending aorta, and the upper body, brain, and coronary arteries via retrograde blood flow. In cases of aortic atresia, there is no antegrade blood flow across the aortic valve; in severe aortic stenosis there is a minimal level of antegrade flow. *Source*: Reproduced from Ohye et al [344] with permission of NEJM.

HLHS is a uniformly fatal disease if left untreated and debate continues over staged palliation versus neonatal transplantation versus comfort care [341–343]. The results of surgical management vary between institutions, and are clearly dependent upon expertise and experience, as well as the clinical condition of the neonate at presentation and degree of hypoplasia of left heart structures [344]. In recent years, the trend has continued toward stage I palliation, where the hypoplastic aorta is reconstructed using the pulmonary valve and artery, and pulmonary blood flow is created using a systemic-to-pulonary artery shunt, or RV to PA conduit (Fig. 27.35) [344]. The stage I palliation for HLHS has now become the most commonly performed neonatal surgery in

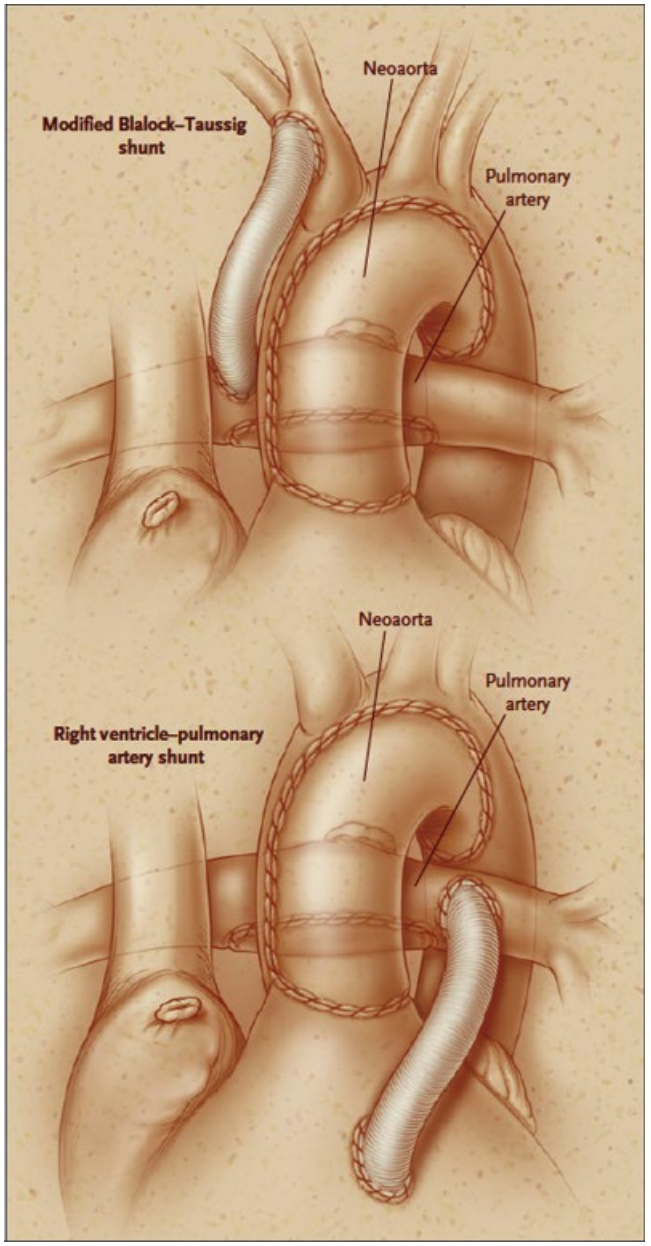


Figure 27.35 The Norwood stage I palliation with modified Blalock–Taussig shunt (A) or right ventricle-to-pulmonary artery shunt (B). *Source*: Reproduced from Ohye et al. [344] with permission of NEJM.

the Society for Thoracic Surgeons' Congenital Heart Surgery database of over 115 congenital heart surgery programs, mostly in the USA and Canada, accounting for 11.2% of neonatal operations in 2013–2016. Immediate postoperative survival is now over 80% in most centers [345].

Anesthetic management

Adequate preoperative resuscitation with PGE1 and correction of metabolic acidosis and end-organ dysfunction is crucial to the anesthetic preparation and management of patients with HLHS. Resuscutation is facilitated by judicious use of inotropic agents, which can optimize cardiac output and blood flow to systemic organs. Delays in surgical intervention will result in a gradual reduction in pulmonary vascular resistance over days, with excessive pulmonary blood flow and inadequate systemic perfusion.

The surgical palliative approach to this lesion currently entails three operations, with the goal of having a reconstructed aortic arch and Fontan type of circulation for single-ventricle physiology in as early as the first 2–3 years of life. In the first stage of the reconstruction (Norwood operation), the pulmonary artery is transected at the bifurcation and an anastomosis is performed to the ascending aorta, which has been surgically incised so that the aortic and pulmonary arterial confluences arise together from the single right ventricle as the neo-aorta, which is extended into the remaining native aorta using homograft material. Pulmonary blood flow is established with either a 3.5 or 4 mm modified B-T shunt or a 5 or 6 mm unvalved RV–PA conduit (Sano shunt). The atrial septum is excised to ensure free flow of pulmonary venous return over to the tricuspid valve. In addition to HLHS, the Norwood operation is also used to repair other complex single-ventricle defects with systemic outflow obstruction or hypoplasia [346,347].

The anesthetic considerations are the same as those outlined in detail for patients with single-ventricle physiology. The intraoperative and postoperative management requires careful manipulation of PVR and SVR to provide adequate but not excessive pulmonary blood flow and oxygen delivery while maintaining sufficient systemic and coronary artery perfusion. The precarious nature of the coronary os, which may be extremely small and closely approximated to the suture lines, means that even small variations in hemodynamics may compromise myocardial blood flow. Myocardial depressants are poorly tolerated, and ventricular failure and tricuspid (systemic) valve regurgitation can inhibit recovery.

The physiology of the modified B-T shunt and the RV–PA conduit as a source of pulmonary blood flow differs. A B-T shunt carries systemic arterial blood in systole and diastole to the pulmonary circulation, where an RV–PA conduit carries blood from the RV to the pulmonary circulation before it has entered the systemic arterial circulation (much like a double-outlet RV). As a result, for a given cardiac output and Qp/Qs, the pulse pressure is narrower and the aortic diastolic blood pressure is higher in patients with an RV–PA conduit. The higher diastolic blood pressure obtained with the RV–PA conduit shunt may provide better cerebral, coronary, and splanchnic perfusion. However, the RV–PA conduit requires creation of a small right ventriculotomy. The long-term functional consequences of this ventriculotomy in the systemic ventricle are unknown. The RV–PA conduit is usually valveless, resulting in some pulmonary insufficiency. The volume load on the RV induced by this is small and probably offset by the fact that RV–PA conduit patients have a slightly lower Qp/Qs and volume load than modified B-T shunt patients.

After CPB in the Norwood palliation procedure, the PVR may be transiently elevated and the B-T shunt or RV–PA conduit may not be adequate to sustain pulmonary blood flow and achieve adequate oxygenation without hyperventilation with 100% oxygen, alkalosis, and inotropic support to support systemic blood pressue. PVR usually falls in minutes to hours, myocardical function is restored, and pulmonary blood flow may become excessive. Hypoventilation with room air and the use of systemic vasodilators are not always effective at reversing the pulmonary steal phenomenon in this circumstance. More drastic measures, such as ventilation with hypoxic gas mixtures or ventilation with added CO_2, have

been advocated by some centers but have largely been abandoned over the years due to a lack of efficacy and deleterious effects on the distribution of blood flow away from the splanchnic bed [348–350].

The stage 1 hybrid procedure for HLHS is an alternative to the Norwood stage 1 procedure. The procedure (Fig. 27.36) involves off-pump placement of a bare metallic stent in the ductus arteriosus, bilateral pulmonary artery banding, and dilation/stenting of the intra-atrial septum. The hybrid procedure does not require CPB and the associated use of either DHCA or ACP in the neonatal period. This procedure must be done in a location that provides full cardiac catheterization infrastructure, including biplane cardio-angiography, in a sterile operating room environment. Whether hybrid strategies should be applied to select subsets of patients and whether they are a lower risk alternative to Norwood operations overall remains to be determined [351,352]. The balloon atrial septostomy is generally performed prior to discharge from the hospital unless there is obstruction of pulmonary venous blood delivery to the right ventricle and pulmonary venous hypertension detected earlier. The physiological burden associated with CPB and DHCA or ACP avoided in the first stage is then incurred at the time of the comprehensive stage 2 procedure (bidirectional Glenn shunt, Stansel anastomosis, aortic arch reconstruction, and definitive atrial septectomy) performed at 3–6 months of age.

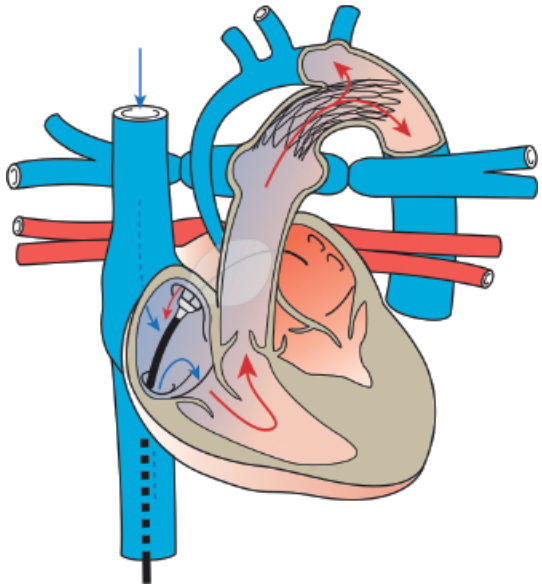


Figure 27.36 Hybrid palliation in a neonate with hypoplastic left heart syndrome. Note the stent in the patent ductus arteriosus and bilateral pulmonary artery banding.

KEY POINTS: SPECIFIC LESIONS AND PROCEDURES

- In the past several decades emphasis on complete repair of congenital heart defects in early infancy, where possible, has changed the congenital heart surgery population dramatically
- The neonatal arterial switch operation for transposition of the great arteries, and stage I palliation for hypoplastic left heart syndrome, together comprise about 20% of neonatal congenital heart surgeries
- Single-ventricle patients comprise almost 20% of patients having congenital heart surgery; almost all of these will undergo three stages of repair: neonatal surgery, bidirectional cavopulmonary connection at 3–6 months, and Fontan completion at 2–4 years of age
- Older children, teenagers, and adults with CHD who had previous operations with older approaches are increasingly presenting for subsequent surgery to revise or repair residual defects

CASE STUDY

The patient is a term 3-month-old male weighing 4.0 kg s/p stage I palliation on day 3 of life for HLHS with mitral and aortic atresia. He presents now for percutaneous endoscopic gastrostomy tube placement. The parents request that a circumcision be performed during the same anesthetic. The patient is poorly tolerant of oral feeds, has demonstrated poor weight gain and somatic growth (25th percentile for height and weight), and has medically managed gastroesophageal reflux. Oral medications are: 0.5 baby aspirin qd, furosemide 8 mg tid, digoxin 0.02 mg bid, captopril 1 mg tid, and ranitidine 8 mg bid.

Echocardiogram done 1 week ago reveals a patent Damus–Kaye–Stansel (DKS) anastomosis, non-restrictive atrial septum, a patent right modified Blalock–Taussig shunt without pulmonary stenoses, and a narrowed aorta at the junction of the isthmus and descending aorta with a peak Doppler-derived gradient of 30 mmHg without evidence of continuous flow in the abdominal aorta. There is mild to moderate tricuspid regurgitation and mild to moderate global right ventricular dysfunction.

Blood pressure is 70/30 mmHg in the left arm, heart rate is 165 bpm in sinus rhythm, and the SaO_2 is 75% on room air. Chest x-ray reveals an enlarged cardiac silhouette with some increase in pulmonary vascular markings.

Questions

1. What is your assessment of this child's cardiovascular status? What is the significance of the tricuspid regurgitation and right ventricular dysfunction in the setting of residual arch obstruction? What is the likely mechanism of the tricuspid regurgitation (TR)? Are the increased pulmonary vascular markings due to ventricular dysfunction, a high Qp/Qs or both?
2. Could better medical management of this child's heart failure obviate the need for a feeding tube?
3. Should this infant undergo an arch dilation in the cardiac catheterization laboratory prior to the proposed surgery?

Should this patient be considered for an early bidirectional Glenn as a means of decreasing the volume load on his RV and improving the TR?

4. Which a.m. medications will you have the parents give and which if any should be held? Is this infant an appropriate a.m. admission case or should he be admitted the night prior to surgery? Is the ICU necessary postoperatively?
5. What premedication will you administer? How will you induce and maintain anesthesia? What monitoring is necessary?

Induction of anesthesia proceeds smoothly and the anesthesia is maintained with remifentanil 0.5 μg/kg/min and isoflurane 0.7% in 100% O_2. During introduction of the endoscope ST segment depression is noted in V_5. Blood pressure is 60/25 mmHg, heart rate is 170 bpm, end-tidal CO_2 is 35 mmHg, and SaO_2 is 75%.

Questions

6. How will you adjust the ventilator (rate, tidal volume, PEEP, FiO_2)?
7. Is a fluid bolus warranted? Should inotropic support be initiated? Which inotrope?
8. How will you assess the adequacy of systemic oxygen delivery?
9. What is the mechanism of myocardial ischemia?
10. Once hemodynamics are stabilized and the ischemia resolves, should the case continue?

Discussion

The primary goal in the management of patients with single-ventricle physiology is optimization of systemic oxygen delivery and perfusion pressure. This is necessary if end-organ (myocardial, renal, hepatic, splanchnic) dysfunction and failure are to be prevented. This goal is achieved by balancing the systemic and pulmonary circulations. The term "balanced circulation" is used because both laboratory and clinical investigations have demonstrated that maximal systemic oxygen delivery (the product of systemic oxygen content and systemic blood flow) is achieved for a given single-ventricle output when Qp/Qs is at or just below 1:1. This relationship is illustrated in the graphs (Figs 27.37–27.41). Increases in Qp/Qs in excess of 1:1 are associated with a progressive decrease in systemic oxygen delivery because the subsequent increase in systemic oxygen content is more than offset by the progressive decrease in systemic blood flow (Fig. 27.37). Decreases in Qp/Qs just below 1:1 are associated with a precipitous decrease in systemic oxygen delivery because the subsequent increase in systemic blood flow is more than offset by the dramatic decrease in systemic oxygen content.

Since Qp/Qs is not a readily measurable parameter in a clinical setting, pulse oximetry is commonly used as a surrogate method of assessing the extent to which a balanced circulation exists. An arterial saturation of 75–80% is felt to be indicative of a balanced circulation (Fig. 27.38). It is important to point out, however, that an arterial saturation of 75–80% is indicative of a Qp/Qs at or near 1:1 only if the pulmonary venous saturation is 95–100% and the mixed

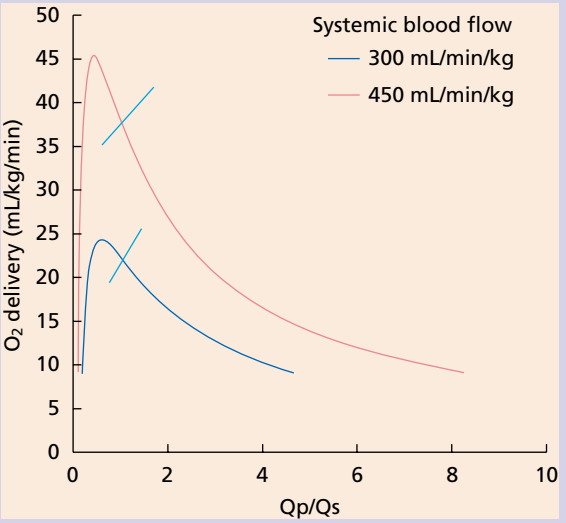


Figure 27.37 Pulmonary/systemic blood flow ratio versus systemic oxygen delivery.

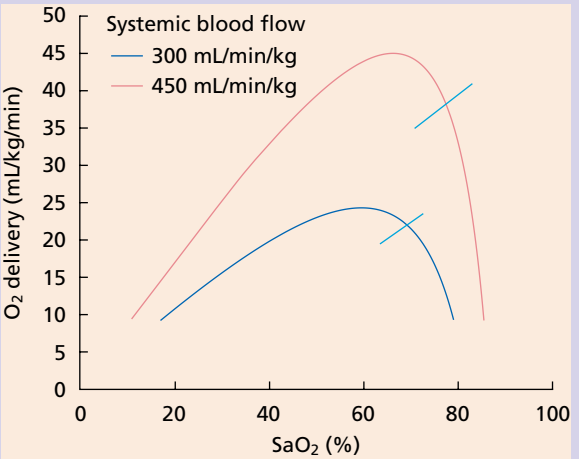


Figure 27.38 Systemic arterial oxygen saturation (SaO_2) versus systemic oxygen delivery.

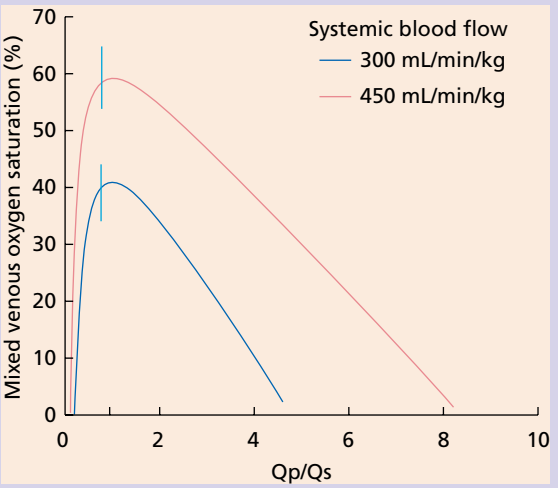


Figure 27.39 Pulmonary/systemic blood flow ratio versus mixed venous oxygen saturation (Ssvc%).

venous (SVC) saturation is 55–60% (Fig. 27.39). In fact, based on these assumptions, the equation used to calculate Qp/Qs in patients with univentricular physiology (SaO_2 – $SsvcO_2$)/$SpvO_2$ – SaO_2) can be simplified to: 25/(95 – SaO_2). In this simplified equation, $SpvO_2$ is assumed to be 95% and the AV O_2 saturation difference is assumed to 25%. Use of this simplified equation requires that the FIO_2 be at or near 21% in order that the dissolved O_2 content of the pulmonary venous blood can be ignored and an $SpvO_2$ of 95% used. Unfortunately, an arterial saturation of 75–80% can exist at the extremes of Qp/Qs depending on pulmonary and systemic venous saturation (Fig. 27.40). Specifically, in the presence of a high Qp/Qs it is possible for there to be inadequate systemic oxygen delivery (systemic venous desaturation, a wide AV O_2 difference, metabolic acidosis) in the presence of what is considered to be an adequate arterial saturation of 75–80%. In addition, clinically unrecognized episodes of pulmonary venous desaturation ($SpvO_2$ <90%) further confound assessment of Qp/Qs based on SaO_2.

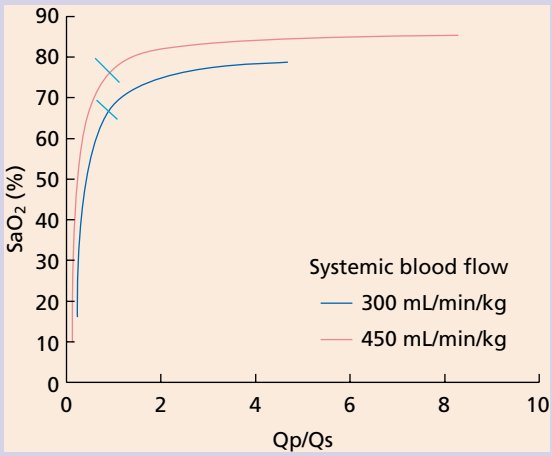


Figure 27.40 Pulmonary/systemic blood flow ratio versus systemic arterial oxygen saturation (SaO_2).

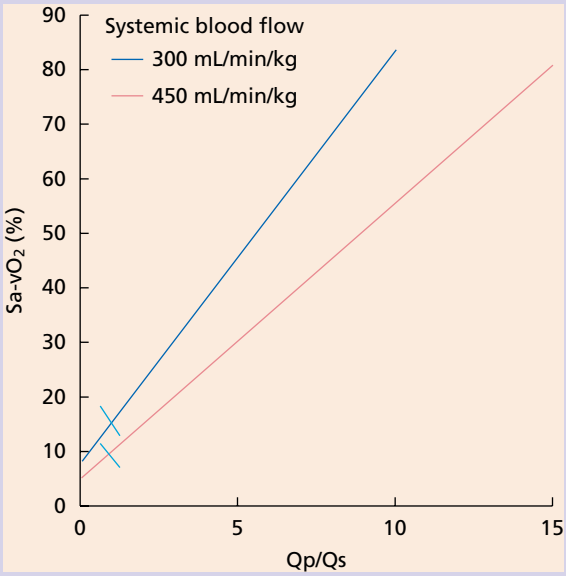


Figure 27.41 Pulmonary/systemic blood flow ratio versus arteriovenous oxygen difference (Sa-vO_2).

Mathematical modeling of univentricular physiology reveals that systemic O_2 delivery is a complex function of cardiac output (CO), pulmonary venous O_2 content, systemic O_2 consumption, and Qp/Qs. In fact, SaO_2 correlates poorly with Qp/Qs and the measurement of $SpvO_2$ and $SsvcO_2$ substantially improves estimation of Qp/Qs. Regression analysis demonstrates that SaO_2 accounts for 8% of the error in estimating Qp/Qs while $SsvcO_2$ and $SpvO_2$ contribute 48% and 44%, respectively. The figures illustrate the effect of CO (systemic blood flow 450 mL/min/kg versus 300 mL/min/kg) on O_2 delivery, SvO_2, SaO_2, and Sa-vO_2 as Qp/Qs varies with $SpvO_2$ = 95% and O_2 consumption = 9 mL/min/kg. It is clear that while SaO_2 remains satisfactory over a wide range of Qp/Qs, O_2 delivery and $SsvcO_2$ decrease precipitously outside a narrow range of Qp/Qs near 1.0. By the time a SaO_2 of 80% is reached, O_2 delivery is precipitously on the decline. Furthermore, Sa-vO_2 increases linearly with increasing Qp/Qs. Any combination of variables that produces a $SsvcO_2$ <30% is likely to result in the development of anaerobic metabolism. It is also clear that a higher CO allows maintenance of satisfactory O_2 delivery and $SsvcO_2$ over a wider range of Qp/Qs.

Debate continues as to the most efficacious method of manipulating the balance of SVR and PVR. Methods to elevate PVR include use of inspired N_2 to reduce alveolar O_2, use of intentional alveolar hypoventilation to achieve mild hypercarbia and a slightly acidotic pH, or use of inspired CO_2 to achieve mild hypercarbia and a slightly acidotic pH while maintaining normal minute ventilation.

Patients with congenital heart disease are more at risk for the development of subendocardial ischemia than is commonly appreciated. In some congenital lesions, abnormalities in the coronary circulation predispose to the development of myocardial ischemia but in many others ischemia occurs in the presence of normal coronary arteries secondary to myocardial oxygen supply/demand imbalance.

Subendocardial perfusion is largely determined by coronary perfusion pressure, that is the mean aortic diastolic pressure minus the ventricular end-diastolic pressure. In addition, the time interval available for perfusion (predominantly diastole) is critical. As a result, the relationship between heart rate, diastolic blood pressure, and ventricular end-diastolic pressure will determine whether subendocardial ischemia occurs.

- Aortic diastolic pressure that is normally low in neonates and infants is further compromised in single -ventricle physiology lesions because these lesions promote diastolic run-off of aortic blood into the lower resistance pulmonary circuit.
- Subendocardial pressure is elevated and subendocardial perfusion is compromised in the presence of an elevated ventricular end-diastolic pressure. Elevated ventricular end-diastolic pressure occurs as the result of the ventricular volume overload, which accompanies single-ventricle lesions, lesions with a high Qp/Qs, and regurgitant atrioventricular and semi-lunar valve lesions.

- The duration of diastole diminishes geometrically as heart rate increases while the duration of systole remains relatively constant. As a direct consequence of this, the time available for diastolic coronary artery perfusion, or diastolic perfusion time, falls geometrically as heart rate increases. Consequently, a higher diastolic pressure is necessary to maintain subendocardial perfusion at higher heart rates. The obvious corollary is that subendocardial perfusion is more likely to be maintained in the presence of a low diastolic blood pressure if the heart rate is slower. In an infant with HLHS and an aortic diastolic pressure of 25 mmHg, a heart rate of 130–140 bpm may well be tolerated without evidence of subendocardial ischemia whereas it is unlikely that a heart rate of 170–180 bpm will be tolerated at the same diastolic pressure.

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A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 28

Anesthesia for Non-cardiac Surgery in Patients with Congenital Heart Disease

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Introduction

The incidence of congenital heart disease (CHD) in the USA is eight per 1000 live births, and it is estimated that congenital heart defects affect a minimum of 40,000 infants in the USA per year [1]. Major non-cardiac anomalies are found in approximately 25% of newborns with CHD [2]. Patients with CHD have an increased risk of anesthetic morbidity and mortality. Recognition of high-risk lesions, a thorough understanding of the anatomy and physiology of congenital heart lesions, and the ability to develop a detailed perioperative management plan are important to achieve the best possible anesthetic outcomes.

This chapter presents the anesthetic/perioperative management of lesions associated with the highest risk of perioperative morbidity and mortality, as well as management of patients who have undergone repair of CHD who are undergoing non-cardiac surgery. Procedural or operative conditions such as laparoscopy, otolaryngological airway assessment, and diagnostic imaging requiring anesthesia or sedation are also considered. Logistical concerns surrounding care of this complex population including risk stratification, anesthetic care providers, location, and current recommendations for bacterial endocarditis prophylaxis are reviewed.

Congenital heart disease and perioperative risk

Patients with CHD undergoing procedures requiring anesthesia are at an increased risk of perioperative morbidity and mortality. According to the Pediatric Perioperative Cardiac Arrest (POCA) Registry data, 34% of anesthesia-related pediatric cardiac arrests occurred in patients with heart disease. In addition, the mortality associated with perioperative pediatric cardiac arrest was higher in patients with cardiac disease (33% versus 23%) [3]. The increased risk of anesthetizing children with CHD exists in all anesthetizing locations including cardiac operating rooms, the cardiac catheterization laboratory, general operating rooms and procedural suites, and radiology locations [4–7].

Published data demonstrate that certain cardiac diagnoses are at higher risk of perioperative morbidity and mortality. Recognition of such patients and careful planning is essential for decreasing the anesthetic risk. Cardiac diagnoses demonstrated to be at higher risk include a single functional ventricle, left-to-right shunt lesions, left ventricular outflow tract obstruction, cardiomyopathy, and pulmonary hypertension (Table 28.1) [3,8,9]. The likelihood of mortality after perioperative cardiac arrest is also associated with diagnosis, with the highest mortality seen in patients with aortic stenosis (62%) and cardiomyopathy (50%) [3].

Young age is also a risk factor for perioperative morbidity and mortality in cardiac patients undergoing non-cardiac surgery. The POCA Registry data suggest that children less than 2 years of age are at higher risk [3]. Baum et al report a two-fold increase in mortality in neonates and infants with cardiac disease undergoing non-cardiac surgery [4].

As the patient groups at higher risk for perioperative morbidity and mortality undergo better definition, risk stratification scores and strategies are being developed to predict anesthetic risk in children with cardiac disease undergoing non-cardiac procedures. The purpose of risk stratification is to aid in determining in what locations patients should be cared for, what anesthesiologist training and experience is appropriate, the location of postanesthetic care, and occasionally whether the risks of the anesthetic and procedure outweigh the benefits [10–13].

It is also important to note that the number of adults with CHD has increased dramatically. It is estimated that there were 800,000 adults living with congenital heart defects in the

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

Table 28.1 Cardiac lesions conferring greatest mortality and morbidity risk with anesthesia

Cardiac lesion	Pathophysiological considerations	Anesthetic goals	Risk of cardiac arrest with anesthesia	Reference
Suprasystemic pulmonary artery hypertension	Calecholamine release from light anesthesia, hypercarbia, hypoxemia, acidosis, or systemic hypotension lead to elevated pulmonary artery pressure, right ventricular failure, low cardiac output, and hypoxemia	Maintain oxygenation, ventilation, coronary perfusion pressure, and adequate depth of anesthesia, and administer pulmonary vasodilators including nitric oxide	1.1–5.7% of anesthetics in severe pulmonary hypertension	[9]
Left ventricular outflow tract obstruction: subvalvar, valvar, or supravalvar aortic stenosis (e.g. Williams syndrome)	Tachycardia, hypovolemia, systemic hypotension, excessive myocardial depression, or hypercontractility reduce stroke volume, lead to coronary ischaemia, and low cardiac output	Maintain ventricular filling, systemic vascular resistance, normal to slow heart rate, and normal myocardial contractility	16% of POCA Registry	[2]
Infant with single functional ventricle and systemic to pulmonary artery shunt	Systemic and pulmonary output both ejected by single functional ventricle; pulmonary-to-systemic vascular resistance ratio determines systemic cardiac output	Avoid hyperoxygenation/ hyperventilation and maintain ventricular function	19% of POCA Registry	[2]
Dilated cardiomyopathy	Very increased ventricular volume, ejection fraction 5–25%, cardiac output maintained by near normal stroke volume and tachycardia, very limited reserve for decreased systemic vascular resistance, contractility, and preload	Avoid any decrease in myocardial contractility; maintain preload and systemic vascular resistance	13% of POCA Registry; 1.7% of anesthetics with dilated cardiomyopathy	[2,13]

POCA, Pediatric Perioperative Cardiac Arrest.
Source: Reproduced from Gottlieb and Andropoulos [37] with permission of Wolters Kluwer.

USA in 2000 [1]. Adults with CHD are also at higher risk of perioperative morbidity and mortality when undergoing non-cardiac surgery, and it is often challenging to determine the best location and care team for delivery of optimal care in this patient group. Adults with CHD may be cared for in adult hospitals lacking anesthesiologists, cardiologists, and intensivists with expertise in CHD. Alternatively, these adult patients may be cared for in pediatric hospitals with expertise in CHD, but without access to adult specialists [14–17]. Ideally, these patients should be cared for in an adult hospital with an adult CHD team.

KEY POINTS: CHD AND PERIOPERATIVE RISK

- Recognizing high-risk patients is key to decreasing morbidity and mortality; it allows care at the right place with the right resources
- Cardiac lesions associated with cardiac arrest include left-to-right shunt lesions, left ventricular outflow tract obstruction, single ventricle lesions, and cardiomyopathy
- Pulmonary hypertension is also associated with perioperative morbidity and mortality, especially systemic or suprasystemic pulmonary hypertension

High-risk lesions

Left-to-right shunt

Left-to-right shunt lesions can occur at the atrial level, the ventricular level, and the level of the great arteries (Fig. 28.1). Although patients with left-to-right shunt lesions have been reported to have the highest percentage of perioperative cardiac arrest, they also have the lowest mortality after perioperative cardiac arrest [3]. The ratio of pulmonary to systemic blood flow (Qp:Qs) is often used to describe the magnitude of a left-to-right shunt. Patients with a high Qp:Qs are often described as "overcirculated," meaning they have excessive pulmonary blood flow.

In any patient with a communication between the left and right sides of the heart, meticulous care should be taken to avoid the introduction of air bubbles into the circulation. Air bubbles can cross into the systemic circulation and enter the coronary arteries causing ischemia, or go to the brain causing a stroke.

Atrial septal defects are usually not hemodynamically significant, and patients can tolerate them for many years. The degree of shunting depends on the difference between right and left atrial pressures. Over many years, the increased flow in the right heart may lead to pulmonary hypertension; this typically does not occur until the patient is over 40–50 years of age.

Ventricular septal defects (VSDs) vary in clinical significance according to size. Small, pressure-restrictive VSDs are usually not hemodynamically significant. Large or multiple VSDs can be hemodynamically significant due to the large amount of flow through the defects. These VSDs present early in life and are associated with signs of congestive heart failure from excessive pulmonary blood flow. These patients are often classified as "failing to thrive," with poor growth due to the high energy expenditure with increased total cardiac output and work of breathing from pulmonary overcirculation.

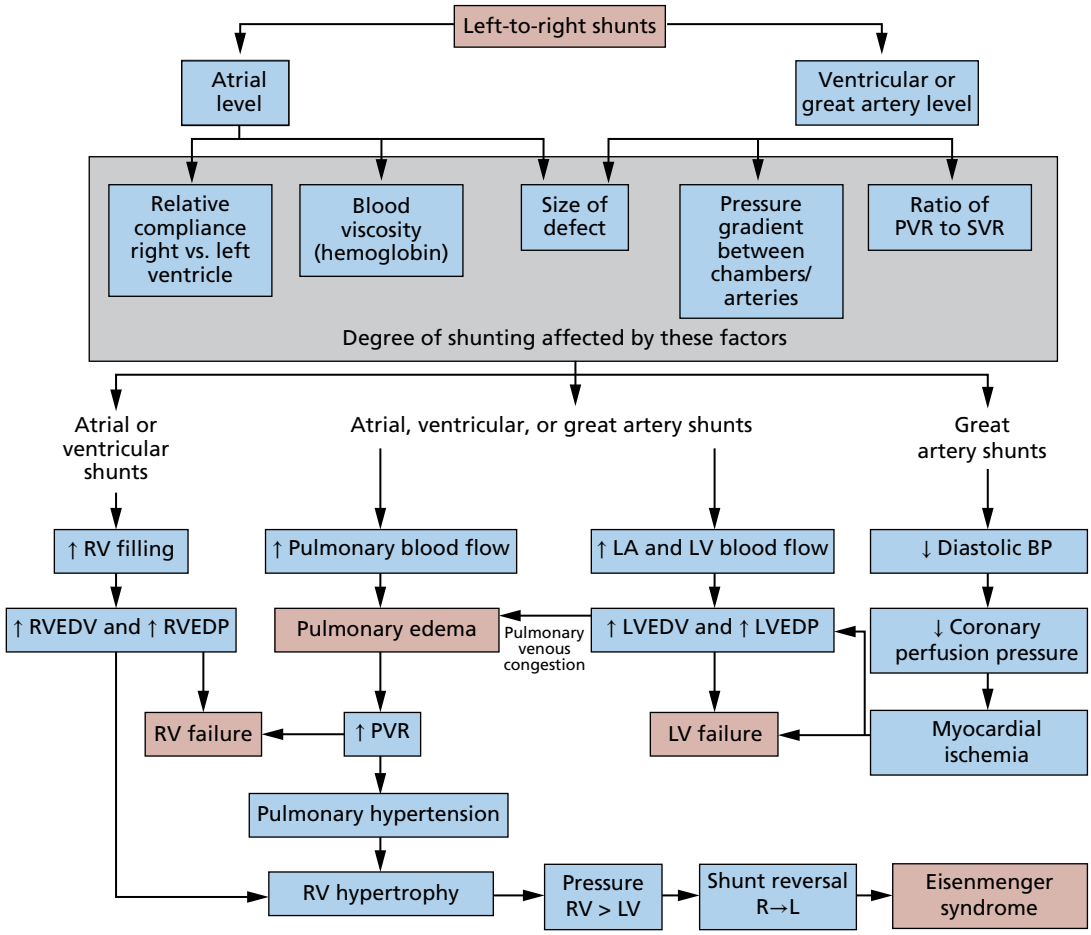

Figure 28.1 Pathophysiology of left-to-right shunting lesions. The flow diagram depicts factors that affect left-to-right shunting at the atrial, ventricular, and great artery level and the pathophysiology produced by these shunts. A large shunt will result in left ventricle (LV) failure, right ventricle (RV) failure, and pulmonary edema. Increased pulmonary blood flow and pulmonary artery pressures lead to pulmonary hypertension and eventually Eisenmenger syndrome. These final common outcomes are highlighted in bold lettering. See text for detailed discussion. BP, blood pressure; LA, left atrium; LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; PVR, pulmonary vascular resistance; RVEDP, right ventricular end-diastolic pressure; RVEDV, right ventricular end-diastolic volume; SVR, systemic vascular resistance.

These infants are underweight and experience diaphoresis and fatigue with feeding. They are often managed with diuretics prior to repair of the VSD. When these patients present for non-cardiac procedures, recognition of the degree of pulmonary overcirculation is important, and interventions to control pulmonary blood flow are instituted. To limit Qp:Qs in patients with pulmonary overcirculation, maneuvers to increase pulmonary vascular resistance should be undertaken. These include using a low fraction of inspired oxygen (FiO_2) and avoiding hyperventilation. Maintaining a low FiO_2 <0.30 and end-tidal CO_2 of 40–45 mmHg is sufficient for many patients.

Left-to-right shunts at the level of the great arteries include truncus arteriosus, aortopulmonary window, and patent ductus arteriosus (PDA). Patients with truncus arteriosus and aortopulmonary window are usually repaired in the early neonatal period because of severe pulmonary overcirculation, but they can require non-cardiac surgery before the cardiac repair. The Qp:Qs in these patients needs to be managed carefully. Unregulated pulmonary blood flow can lead to systemic hypoperfusion, coronary ischemia, and cardiac arrest. Care should be taken to increase pulmonary vascular resistance (PVR) and decrease Qp:Qs by avoiding high FiO_2 and hyperventilation. If the PVR is well maintained and diastolic hypotension persists, vasopressin or phenylephrine can increase diastolic blood pressure and avoid coronary ischemia. In addition, increasing the hematocrit to 40–45% can improve the pathophysiology by increasing the viscosity of the blood and decreasing the pulmonary blood flow. Although it is not an option during most non-cardiac procedures, the placement of a temporary pulmonary artery band can mechanically improve hemodynamics by restricting the pulmonary blood flow.

KEY POINTS: LEFT-TO-RIGHT SHUNT

- Left-to-right shunt lesions can be at the level of the atria, the ventricles, or the great arteries
- Patients with left-to-right shunt lesions at the level of the great arteries are at risk for developing diastolic hypotension and myocardial ischemia
- Maneuvers to increase pulmonary vascular resistance include using a low FiO_2 and hypoventilation to a $PaCO_2$ of 40–50 mmHg

Left ventricular outflow tract obstruction

There are a number of disease states, lesions, and syndromes that are associated with left ventricular outflow tract obstruction (LVOTO). They are characterized by obstruction at the subaortic, aortic valve, or supravalvar aortic levels. In some instances, such as Shone complex, the obstruction to left ventricular outflow occurs at multiple levels. According to the data from the POCA Registry, 16% of the perioperative cardiac arrests in children with heart disease were in children with left ventricular obstructive lesions [3]. Unfortunately, patients with this diagnosis are notoriously difficult to resuscitate; aortic stenosis patients with perioperative cardiac arrest had a mortality of 62%. The etiology of most cardiac arrests in patients with LVOTO is myocardial ischemia due to the imbalance between myocardial oxygen supply and demand. Thus, with the known difficulty in resuscitating patients with these lesions, the best approach is to avoid cardiac arrest and to have a plan in place if an arrest occurs.

Subaortic stenosis can be an isolated lesion or can exist as part of multilevel LVOTO or with another lesion such as complete atrioventricular (AV) canal. The interventricular septum can also cause dynamic LVOTO in systole in hypertrophic obstructive cardiomyopathy (HOCM). Aortic stenosis occurs at the level of the valve, and can be categorized as mild, moderate, severe, or critical depending on the pressure gradient across the valve.

Supravalvar aortic stenosis (SVAS) related to elastin arteriopathy can present as part of a syndrome (Williams syndrome), familial and non-syndromic, or sporadic cases. All varieties can be associated with sudden death and cardiac arrest in the perioperative period. Patients with Williams syndrome have a distinctive appearance and personality, and have an aptitude for music. Cardiac manifestations of elastin arteriopathies include SVAS, peripheral pulmonary stenosis, and coronary artery abnormalities. There are multiple case reports and series describing cardiac arrest related to anesthesia in patients with SVAS [18–20], and it is important that every pediatric anesthesiologist understands the pathophysiology of the disease and the causes of cardiac arrest. The tenuous balance between myocardial oxygen supply and demand is easily upset with the effects of anesthesia and surgery [21]. Due to coronary abnormalities and the loss of aortic distensibility due to reduced elastin, myocardial oxygen supply is already marginal in many SVAS patients. The decrease in systemic vascular resistance (SVR) associated with anesthetics such as propofol and inhalational agents reduces the coronary perfusion pressure that is necessary to maintain oxygen supply to the at-risk ventricles that are hypertrophied, with high end-diastolic pressures and high myocardial oxygen demand. It should be noted that surgical factors such as blood loss can also upset this tenuous balance. Hemodynamic effects associated with the procedure can lead to cardiac arrest. For example, anaphylaxis related to contrast for computed tomography imaging has been reported as the cause of cardiac arrest (and death) in a patient with Williams syndrome [22]. The hemodynamic effects associated with laparoscopy have also been implicated as a cause of cardiac arrest in this patient population. The decrease in afterload and preload associated with the release of pneumoperitoneum can lead to myocardial ischemia and arrest in patients with SVAS [23]. Steps to reduce the impact of the hemodynamic change, such as an intentional slow release of the pneumoperitoneum, should be considered. Anticipation of and preparation for procedure-related changes in afterload and preload can prevent morbidity in these patients.

Matissoff et al developed a risk assessment tool to guide perioperative care of patients with Williams syndrome (Table 28.2) [24], and Collins et al have provided a very complete review of and strategies for reducing periprocedural risk [25]. These recommendations should likely be applied to all patients with elastin arteriopathy and supravalvar aortic stenosis.

Prevention of cardiac arrest is critically important because if cardiac arrest occurs, resuscitation is difficult. Of note, the availability of extracorporeal membrane oxygenation (ECMO) support has decreased the mortality associated with perioperative cardiac arrest in patients with LVOTO. For this reason, it is suggested that anesthesia and sedation of patients with significant LVOTO should be performed at institutions where rapid cannulation for ECMO is possible [26].

KEY POINTS: LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

- Patients with LVOTO are not candidates for office-based anesthesia or ambulatory surgical centers
- Prolonged preoperative fasting should be avoided as it can lead to instability on induction; intravenous fluids should be started if the patient cannot take clear fluids
- Goals for induction include maintaining SVR and avoiding tachycardia
- It is difficult to resuscitate patients with LVOTO after cardiac arrest

Table 28.2 Classification of risks of Williams syndrome

Low risk	Moderate risk	High risk
Normal ECG	Mild stenosis of a branch of the pulmonary artery	Severe SVAS (>40 mmHg)
Normal echocardiogram	Hypertension	Symptoms or ECG signs consistent with ischemia
Minimal extracardiac anomalies	Mild-to-moderate SVAS (<40 mmHg)	Coronary disease demonstrated in imaging
	Other mild cardiac anomalies (e.g. ventricular septal defect)	Severe left ventricular hypertrophy
	Repaired SVAS or SVPS without residual gradients	Biventicular outflow tract disease
	Mild left venticular hypertrophy	Prolonged QTc on ECG
	Mild to moderate SVPS in isolation	
	Significant extracardiac disease such as difficult airway or severe gastroesophageal reflux	

ECG, electrocardiogram; SVAS, supravalvar aortic stenosis; SVPS, supravalvar pulmonary stenosis.
Source: Reproduced from Matissoff et al [24] with permission of John Wiley and Sons.

Single ventricle lesions

Patients with single ventricle (SV) physiology are another group of pediatric patients with cardiac disease who are at an increased risk of morbidity and mortality when undergoing non-cardiac procedures. According to the data from the POCA Registry, SV lesions made up 19% of the congenital heart lesions associated with a perioperative cardiac arrest [3]. It is also clear that the stage of SV palliation is an important consideration. Of the 24 SV patients experiencing cardiac arrest, 17 had not yet undergone the second stage procedure for SV palliation (bidirectional Glenn operation or superior cavopulmonary anastomosis). Two had undergone the Glenn operation, and five patients had undergone the third stage procedure (Fontan operation or total cavopulmonary anastomosis). Christensen et al reported a 15% incidence of adverse events in patients with hypoplastic left heart syndrome (all stages included) undergoing non-cardiac surgery. Of note, those who were pre-superior cavopulmonary anastomosis (pre-SCPA) had a 40% incidence of instability [27]. In a retrospective study of pre-SCPA SV patients undergoing non-cardiac surgery, Brown et al reported an 11.8% incidence of major adverse events [28]. To reduce the perioperative risk, the anesthesiologist providing care for patients with a SV lesion should have a thorough understanding of each stage of palliation, the ability to plan an appropriate anesthetic, and the capacity to rapidly assess and treat hemodynamic instability. These patients may need a non-cardiac procedure at any stage, from just after birth to after the Fontan operation, or anytime in between.

Prior to surgical/catheter-based procedure

Lesions with single ventricle physiology include tricuspid atresia, pulmonary atresia, double-inlet left ventricle, unbalanced atrioventricular canal defect, hypoplastic left heart syndrome (HLHS), and double-outlet right ventricle. After birth, the sources of systemic and pulmonary blood flow should be determined. Lesions with aortic obstruction like HLHS may require prostaglandin E1 (PGE1) to maintain ductal patency for systemic blood flow. Others like pulmonary atresia require PGE1 to maintain ductal patency for pulmonary blood flow. Other lesions may have unrestricted systemic and pulmonary blood flow [29].

Patients with a SV lesion who require anesthesia for a non-cardiac procedure prior to addressing the cardiac disease are at substantial risk of morbidity and mortality. The types of procedures that may need to be addressed at this time include tracheo-esophageal fistula/esophageal atresia (TEF/EA), congenital diaphragmatic hernia, anal atresia, intestinal atresia, myelomeningocele repair, colostomy, exploratory laparotomy for necrotizing enterocolitis, and others. Although good outcomes have been reported [30,31], there are also many reports of adverse outcomes with patients not surviving to cardiac repair [32–35]. In patients with CHD undergoing TEF/EA repair, those with PDA-dependent lesions had a 57% chance of not surviving compared with 10% in patients with non-PDA-dependent lesions. Of note, all of the patients with TEF/EA without CHD survived [32]. Among SV patients with congenital diaphragmatic hernia, only 16% survived to discharge and only 5% had their cardiac disease addressed [33].

Anesthetic care for patients with a SV lesion for non-cardiac surgery requires preparation and anticipation of instability. Because this is a diverse group of lesions, it is imperative to understand the cardiac anatomy. For patients with PDA-dependent lesions, the PGE1 infusion must be continued intraoperatively. For most procedures, general anesthesia is required, although regional anesthesia has been described [35]. Many of these patients have excessive pulmonary blood flow (high Qp:Qs), which can be exacerbated by intubating the trachea and controlling ventilation. A reasonable goal for most SV patients for oxygenation is a pulse oximeter reading of 85%. To avoid pulmonary overcirculation, PVR should be increased by achieving a FiO_2 as low as possible, while allowing the end-tidal CO_2 to increase to 40–45 mmHg. This maneuver will reduce pulmonary blood flow and augment systemic blood flow. Not uncommonly, despite these maneuvers, the peripheral oxygen saturation (SpO_2) is still in the mid-90% range, and the systemic blood pressure is low. In patients with PDA-dependent pulmonary blood flow, the diastolic blood pressure maybe extremely low due to diastolic run-off. Hypotension, especially diastolic hypotension, can lead to myocardial ischemia. It is helpful to monitor the invasive arterial blood pressure, cerebral and somatic oximetry by near-infrared spectroscopy (NIRS), and the electrocardiogram with ST segment monitoring. If the blood pressure and NIRS are low despite efforts to increase PVR with low FiO_2 and hypoventilation, other steps can be taken. Packed red blood cell transfusion to a hematocrit of 40–45% will increase oxygen-carrying capacity and blood viscosity, which can decrease left-to-right shunt flow. In addition, an infusion of vasopressin (0.01–0.02 units/kg/h), epinephrine (0.02–0.04 μg/kg/min), or calcium chloride (10 mg/kg/h) will increase systemic blood pressure. Arterial blood gases and lactate levels should be assessed frequently to manage oxygenation, ventilation, and systemic perfusion. Postoperative disposition in an intensive care unit (ICU) is almost always required, and a conservative approach to postoperative ventilation, by not extubating the trachea in the operating room, is often prudent.

After first palliative procedure

Many of these patients will require a cardiac intervention in the neonatal period. Patients with HLHS are managed with an operative stage I palliation (Norwood operation) with the creation of either a Blalock–Taussig (B-T) shunt (systemic arterial to pulmonary artery) or a Sano shunt (right ventricle to pulmonary artery conduit) or the hybrid procedure for HLHS, which includes a PDA stent, bilateral pulmonary artery bands, and an atrial septal stent (Fig. 28.2) [36]. Patients with PDA-dependent pulmonary blood flow (e.g. pulmonary atresia) will need a stable source of pulmonary blood flow, either a surgical systemic to pulmonary artery shunt (e.g. modified B-T shunt or central aortopulmonary shunt) or a PDA stent placed percutaneously in the cardiac catheterization laboratory. Patients with PDA stents, central shunts, or B-T shunts are at risk for coronary hypoperfusion from diastolic run-off into the pulmonary circulation. For this reason, the physiology is fragile and can easily be perturbed. Other patients with unrestricted pulmonary blood flow may require a pulmonary artery band placement in the operating room to help reduce pulmonary blood flow until the second stage procedure [29,37].

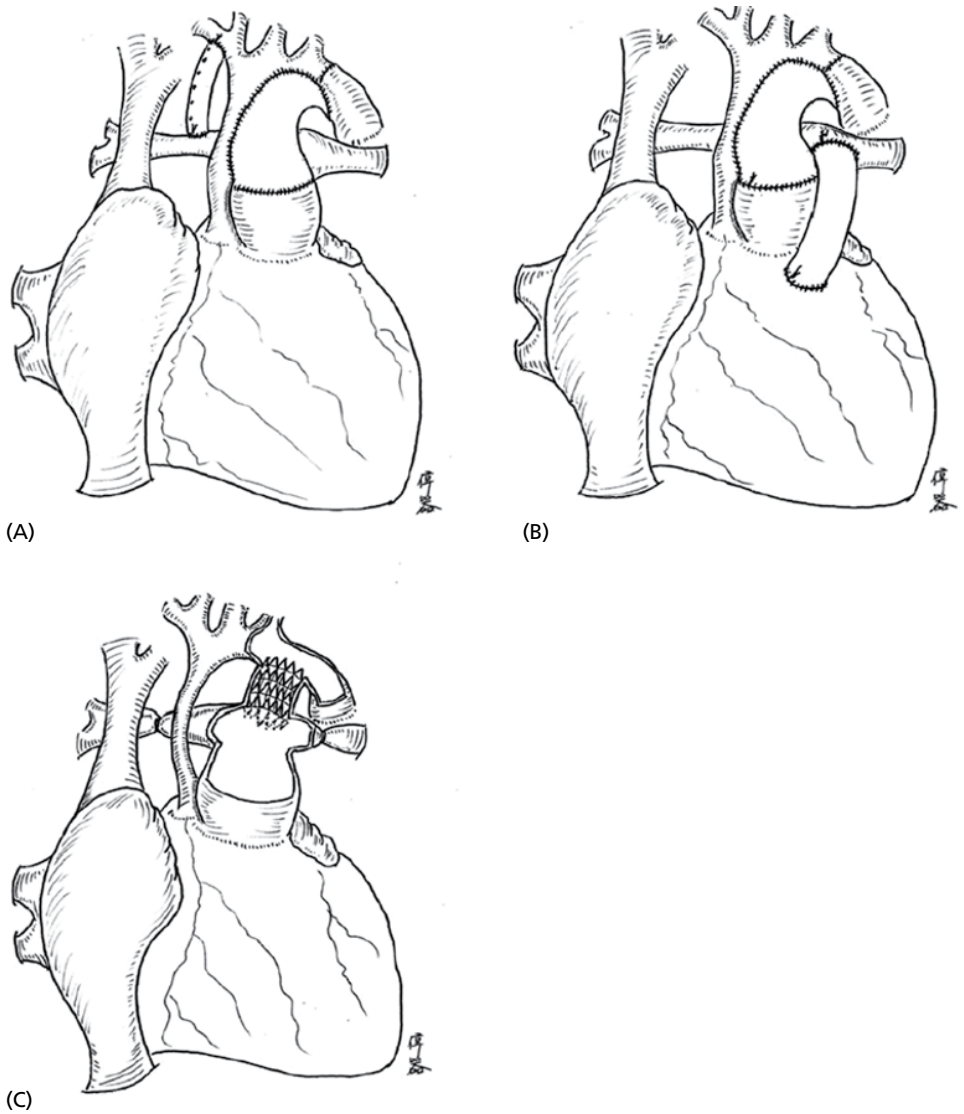

Figure 28.2 Hypoplastic left heart syndrome following the Norwood operation. (A) A demonstration of the standard Norwood procedure, with a right modified Blalock–Taussig shunt from the right subclavian artery to the right pulmonary artery. (B) A representation of the modified Norwood procedure where a right ventricle to pulmonary artery conduit (so-called "Sano") is placed to provide pulmonary blood flow. (C) A representation of the hybrid Norwood, wherein the pulmonary blood flow is controlled with bilateral restricting bands, and the ductus arteriosus is stented to provide unobstructed systemic blood flow. *Source*: Reproduced from Petit [36] with permission of John Wiley and Sons.

The patient with a shunt or PDA stent has a fragile physiology and may need to undergo non-cardiac surgery or imaging prior to the superior cavopulmonary anastomosis operation. Many agree that elective procedures should be postponed until after the SCPA operation due to increased stability of the circulation [27,29,37,38] and the removal of shunt/ductal occlusion as a risk factor [39]. These patients are at risk for periprocedural complications including heomodynamic instability and cardiac arrest [27–29,37,40–43].

Anticipation of and preparation for hemodynamic instability, coronary steal, and/or acute shunt or PDA stent occlusion will reduce these risks. Preoperative strategies include encouraging clear fluid ingestion until 2 h prior to the procedure or even hospital admission the evening before the procedure for an observed nil per os period with intravenous fluid administration [5,37]. Preoperative angiotensin-converting enzyme inhibitors have been associated with hypotension at anesthesia induction, and some institutions discontinue these drugs for 24 h preoperatively [28,41]. Management strategies for these patients undergoing non-cardiac procedures that have been successful include maintaining the hematocrit at 40–45%, monitoring invasive arterial pressure, increasing PVR by decreasing minute ventilation and allowing the $PaCO_2$ to increase, using the minimum FiO_2 to maintain baseline oxygen saturations, checking frequent arterial blood gases, monitoring NIRS, using low insufflation pressures (8–12 mmHg) with laparoscopic procedures, postoperative mechanical ventilation, and recovering the patient in the ICU [29,40,44,45]. In the event of excessive pulmonary blood flow and diastolic hypotension with possible myocardial ischemia, infusions of vasopressin, epinephrine, and calcium should be prepared [29,40].

Acute shunt or PDA stent occlusion is catastrophic and can occur during non-cardiac procedures and imaging [46]. Signs of partial or total occlusion include worsening hypoxemia despite supplemental oxygen administration, expansion of

the intravascular volume, and increasing systemic blood pressure. End-tidal CO_2 levels may drop precipitously as well. Cardiac arrest may follow and immediate resuscitation should commence. The lungs should be auscultated to exclude right mainstem bronchial intubation or another cause of decreased ventilation, and auscultation for the shunt or PDA stent murmur should occur immediately. At the same time, rapid echocardiographic assessment of the shunt or duct should be performed; an interventional cardiologist should be summoned for consideration of therapy in the cardiac catheterization lab for angioplasty, stent placement, or thrombolytic administration; and a surgeon should be called for the possibility of shunt revision or ECMO [47–49]. A systemic heparin bolus of 100 units/kg may be given, and systemic thrombolytic therapy may be considered [50]. Predisposing factors for shunt occlusion include preoperative dehydration, elevated hematocrit, and hypotension [39,48].

The HLHS patient with a right ventricle (RV) to pulmonary artery conduit may be less vulnerable to hemodynamic instability and shunt occlusion than the patient with a B-T shunt, but the same preanesthetic preparations should be made. Patients with a pulmonary artery band often have a fixed pulmonary blood flow, and overcirculation may be impossible. However, ventricular function must be maintained. Peripheral oxygen saturations of 80–90% are appropriate [37]. It should be noted that ECMO has been used as a rescue in multiple cases of cardiac arrest or severe hemodynamic instability in infants with CHD undergoing non-cardiac surgery [28,42,43,46,49,50]. When a palliated neonate experiences cardiac arrest, ECMO activation should be considered early, i.e. after 5–10 min if spontaneous circulation has not been restored. Without the availability of ECMO, many of the patients in these case reports would have expired.

After second stage palliation

The next stage of palliation for the SV lesion is the creation of a bidirectional Glenn shunt or SCPA (Fig. 28.3) [36]. After this intervention, pulmonary blood flow is supplied by the superior vena cava. Compared with the condition in which pulmonary blood flow is supplied by a stented PDA, B-T shunt, central shunt, or RV to pulmonary artery conduit, the ventricle is partially volume unloaded, and the risk of coronary hypoperfusion is greatly reduced. This stage is often considered the optimal for non-cardiac surgery because the threat of coronary hypoperfusion is reduced, the ventricular volume overload is reduced, and the venous blood from the lower half of the body returns directly to the atrium, maintaining preload if pulmonary blood flow decreases [27,29,37,38]. In addition, the risk of catastrophic shunt/PDA stent occlusion is no longer present [39]. However, the increased resiliency of this circulation compared with that of the pre-SCPA circulation should not result in complacency on the part of the anesthesiologist. These patients still have only one functional ventricle, and they remain cyanotic with oxygen saturations usually in the 75–85% range. The echocardiogram should be reviewed preoperatively with attention to ventricular function and the presence of AV valve regurgitation. Depressed ventricular function and AV valve regurgitation are concerning and increase the risk of anesthetic complications. Cardiac catheterization data can provide information about the PVR and SCPA anatomy. Baseline oxygen saturation should be noted.

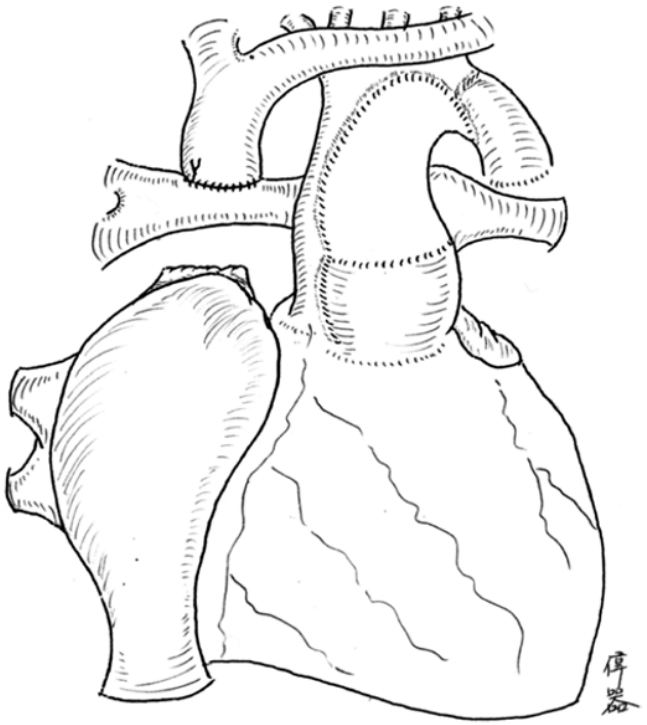

Figure 28.3 The bidirectional Glenn (superior cavopulmonary anastomosis) operation – a superior cavopulmonary connection. *Source*: Reproduced from Petit [36] with permission of John Wiley and Sons.

Hemodynamic goals when providing anesthesia for patients with a SCPA circulation involve maintaining a normal blood pressure and avoiding increases in PVR that can be associated with agitation, pain, and extreme hypoventilation. The delivery of higher oxygen concentrations is not harmful in this population, as the susceptibility to diastolic steal with coronary ischemia is not a factor. The cerebral-pulmonary–cardiac circulation is especially important in younger patients with this physiology, and a $PaCO_2$ of 40–45 mmHg allows sufficient cerebral blood flow, which then perfuses the lungs to be oxygenated. Hyperventilation is counterproductive as it decreases cerebral blood flow and therefore pulmonary blood flow, resulting in hypoxemia [27,29,37]. Ventricular function should be maintained, and these patients' tracheas are often extubated at the end of the procedure [38]. Postoperative ICU monitoring for patients with this circulation and normal cardiac function is not required.

Patients with SCPA circulation with depressed myocardial function and AV valve regurgitation should be monitored very closely. Instability should be anticipated. Inotropic and vasopressor support should be available, and if the function is extremely poor it may be prudent to initiate inotropic support prior to the induction of anesthesia. Invasive blood pressure and NIRS monitoring may be helpful. These patients are high risk; postoperative ventilation should be considered, and postoperative ICU monitoring is advised.

After third stage palliation

The third stage of SV palliation is the Fontan operation (total cavopulmonary anastomosis) (Fig. 28.4). After this procedure all systemic venous return flows directly to the pulmonary

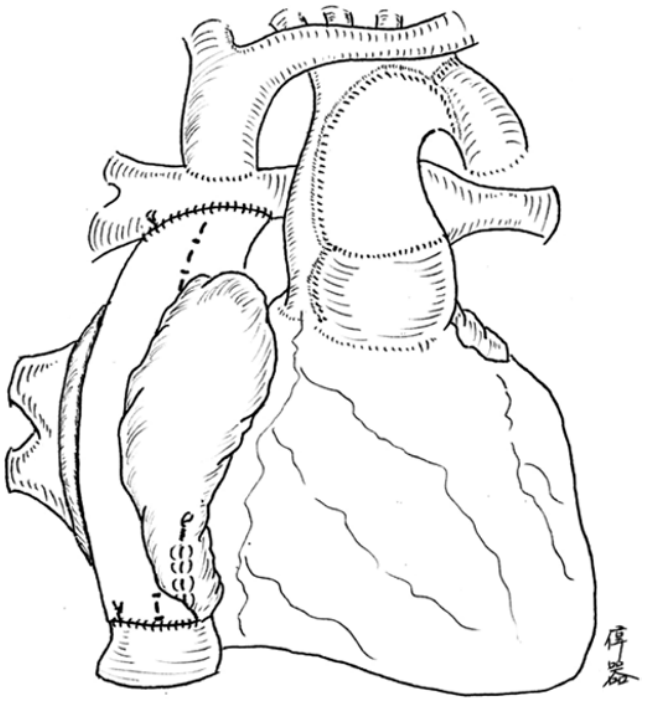

Figure 28.4 Fontan operation. *Source*: Reproduced from Petit [36] with permission of John Wiley and Sons.

arteries [36]; therefore, pulmonary blood flow is passive. An optimal Fontan circulation requires adequate preload with a central venous pressure of approximately 15 mmHg, a low PVR, a non-regurgitant AV valve, and a normal ventricular ejection fraction. These patients are at a higher risk of arrhythmia, especially those with a lateral tunnel or atriopulmonary Fontan (Fig. 28.5). Decreases in central venous pressure caused by venodilation from vasodilators or decreased sympathetic tone, acute blood loss, or dehydration are not well tolerated [29,51]. For this reason, prolonged fasting prior to induction of anesthesia should be avoided. At some centers, patients are intravascular volume loaded prior to induction [29,52], and intravenous fluid volume should be available. Others use vasopressor or low-dose inotropic support to lessen the risk of hypotension, and avoid large volume administration [29,53]. Increases in PVR are also poorly tolerated, and maintaining a normal $PaCO_2$ is recommended. Pharmacological means to decrease the PVR including inhaled prostacyclin analogs and milrinone have been described [54,55]. Depressed ventricular function may require inotropic support intraoperatively. Positive pressure ventilation worsens systemic venous return and may decrease stroke volume and cardiac output in the Fontan circulation [56]; however, the manipulation of ventilatory parameters to achieve appropriate gas exchange at the lowest mean airway pressure can minimize this effect [51]. On the other hand, increasing PVR

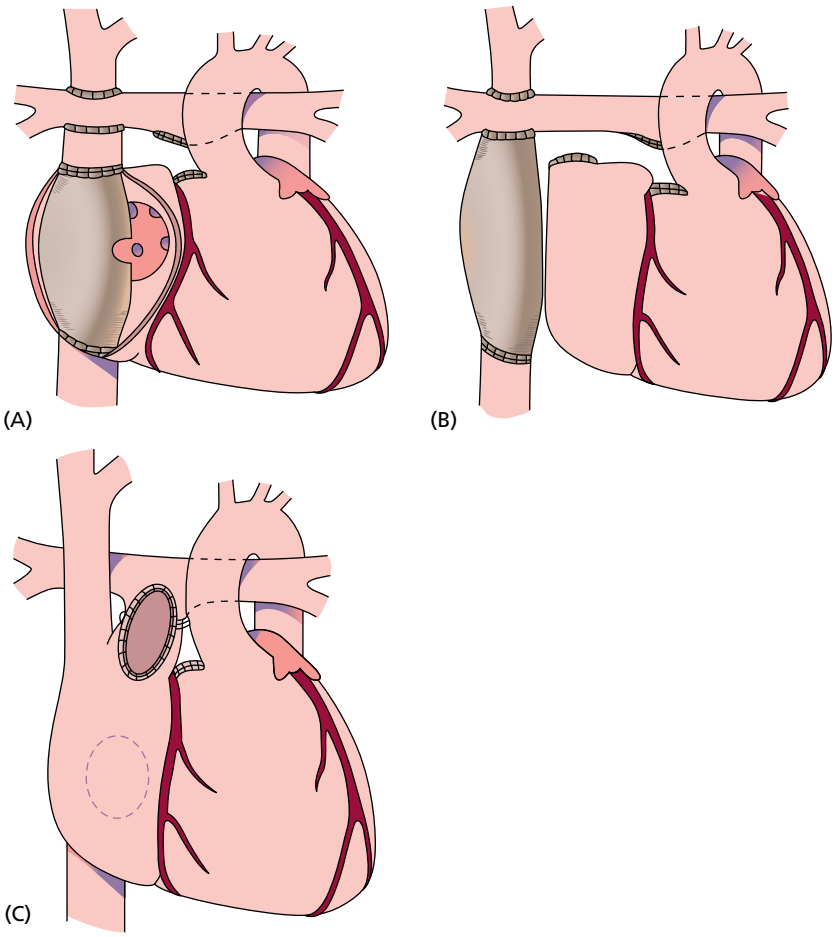

Figure 28.5 Fontan configurations for cases with (A) lateral tunnel Fontan, (B) extracardiac Fontan, and (C) atriopulmonary connection Fontan. *Source*: Reproduced from Yuki et al [29] with permission of Japanese Society of Anesthesiologists.

from ineffective ventilation can also reduce venous return to the systemic ventricle and reduce cardiac output.

In the Fontan circulation, inadequate pulmonary blood flow results in a decrease in systemic ventricular filling, reducing cardiac output. Sometimes, a fenestration may be created between the Fontan baffle and the atrium to allow systemic ventricular filling in the event of an increase in PVR. If there is no fenestration, the patient should not be cyanotic. With a fenestration, the oxygen saturation will vary based on the magnitude of the right-to-left shunt.

The Fontan circulation is the third stage of SV palliation, but it is by no means a repair. Patients with a Fontan circulation may develop depressed myocardial function, AV valve regurgitation, arrhythmias, thromboembolic events, protein-losing enteropathy, cirrhosis, lower extremity edema, plastic bronchitis, and other sequelae [57]. Many will require additional cardiac surgery including heart transplantation. When evaluating these patients prior to surgery, these conditions should be assessed.

As they age, SV patients will undergo non-cardiac procedures and may present for obstetric management. It is important to have a plan for optimizing hemodynamic status and avoiding complications intraoperatively. Intravenous fluids in adequate amounts, vasopressors, and inotropes should be immediately available. A defibrillator should be in the room with appropriately sized pads to treat arrhythmia. Patients with pacemakers and implanted defibrillators should have their devices interrogated; the patient's underlying cardiac rhythm should also be understood. These devices often should have their defibrillation function disabled, and pacing mode converted to asynchronous because of interference with their function by electrocautery. Advice and recommendations of the patient's cardiologist should be sought.

Monitoring for SV patients may include the use of an arterial catheter, a central venous catheter (which will be measuring Fontan pressure, not atrial pressure), and transesophageal echocardiography to assess ventricular filling and AV valve function. Cardiopulmonary resuscitation (CPR) is often not effective with a Fontan circulation, and ECMO is often complicated by anatomy. However, Jolley et al report improved outcome when patients are placed on ECMO before CPR is necessary [51].

They are many reports of non-cardiac surgery in patients with a Fontan circulation. In the largest series, Rabbitts et al reviewed 39 anesthetics in 31 patients with Fontan circulation who had non-cardiac surgery. A perioperative complication occurred in 31% of the operations, and one patient died postoperatively. A low preoperative ejection fraction (less than 30%) was associated with serious adverse outcomes (dialysis and death) [54]. Another predictor of periprocedural complications in adult Fontan patients is baseline cyanosis, which can be a marker for increased PVR, depressed ventricular function, or increased right-to-left shunting [58]. Laparoscopy has been successfully performed in these patients. Low insufflation pressures (8–12 mmHg) are recommended, and hypercarbia should be avoided [52,59].

There are several reports of scoliosis repair in the SV population [60–64]. Generally, invasive arterial and venous pressure monitoring are recommended, with some groups advocating transesophageal echocardiography. High venous pressure is necessary for pulmonary blood flow, but it also increases the risk of bleeding, as does abnormal baseline coagulation in these patients. Controlled hypotension to decrease blood loss is not recommended. The blood loss for scoliosis repair in the Fontan patient is larger than normal. Cell salvage and antifibrinolyic therapy should be employed [60–64]. Craniotomy for electrocorticography and seizure ablation in this population is also reported [65,66], as is craniotomy for pial synangiosis and evacuation of hematoma [53]. The intracranial vascular anatomy is also abnormal, and increased bleeding is described [53,65].

Interestingly, there are multiple reports of pheochromocytoma in the Fontan population as well. All of the patients received invasive arterial blood pressure monitoring, and most also had placement of central venous catheters. All but one was performed via open approach, and one was performed laparoscopically. An epidural catheter was placed in one patient. As this is a case in which there are multiple opportunities for hypertension and hypotension, invasive arterial blood pressure monitoring was very helpful, and vasopressors, inotropes, and vasodilators were required for most cases [55,67–69].

KEY POINTS: SINGLE VENTRICLE LESIONS

- Unpalliated neonates are at high risk for overcirculation during non-cardiac procedures, and measures to increase PVR should be employed
- Patients with a systemic to pulmonary artery shunt or PDA stent are at risk for diastolic hypotension and myocardial ischemia; they are also at risk for catastrophic stent or ductal occlusion
- Bidirectional Glenn circulation is considered the most resilient because the ventricle is unloaded and cardiac output does not rely completely on pulmonary blood flow
- Pulmonary blood flow in a patient with Fontan circulation is dependent on the transpulmonary gradient (systemic venous pressure – the left ventricular end-diastolic pressure)

Pulmonary hypertension

Pulmonary hypertension (PH) is a known risk factor for anesthetic morbidity and mortality in adults and in children [8,70,71]. In a retrospective review of 101,885 anesthetics, van der Griend et al reported an increase in anesthesia-related mortality in children with heart disease and especially those with pulmonary hypertension. In fact, 50% of the anesthesia-related deaths were in patients with PH [8]. In a retrospective review of children with PH undergoing cardiac catheterization or non-cardiac surgery, the severity of PH was also associated with increased anesthetic risk – with patients with suprasystemic pulmonary artery pressures eight times more likely to have a major complication compared with those patients with subsystemic pulmonary artery pressures [9]. Taylor et al reported an incremental increase in all complications including death with increasing severity of PH (Table 28.3) in pediatric patients undergoing procedures not involving cardiopulmonary bypass [72]. Bernier et al reported not only increased risk with severe PH, but also an association between the type of procedure and

Table 28.3 Risk of complications with degree of pulmonary hypertension

	Minor complications	Major complications	Death
Subsystemic PHT	6/188 (3.2%)	3/188 (1.6%)	1/188 (0.5%)
Systemic PHT	2/50 (4%)	2/50 (4%)	1/50 (2.0%)
Suprasystemic PHT	3/25 (12%)	4/25 (16.0%)	1/25 (4.0%)
Cochran–Armitage test for trend	0.07	0.0006	0.09

PHT, pulmonary hypertension.
Source: Reproduced from Taylor et al [72] with permission of Wolters Kluwer.

risk of a major event, with thoracic procedures being at an increased risk [73]. Symptoms at presentation may correlate with severity of disease; patients with complaints of chest pain, syncope, and dizziness were found to be at highest risk of instability and cardiac arrest [74].

PH is defined as a mean pulmonary artery pressure greater than 25 mmHg at rest, or greater than 30 mmHg during exercise. The cause of PH may be idiopathic or associated with other conditions, including CHD, disorders of the respiratory system, and many others [75,76]. A distinction should be made between precapillary PH and postcapillary PH. Postcapillary PH is due to increased pulmonary venous pressure such as that found in pulmonary vein stenosis or left heart dysfunction or obstruction [77,78]. Heart disease associated with postcapillary PH includes pulmonary vein obstruction or stenosis and conditions associated with chronic increased left atrial pressure like cardiomyopathy, coarctation of the aorta, HLHS with restrictive atrial septum, Shone complex, mitral stenosis, supravalvar mitral ring, or cor triatriatum [76]. Precapillary PH is associated with a pulmonary capillary wedge pressure (PCWP) of less than 15 mmHg (idiopathic pulmonary hypertension and intrinsic lung disease or hypoplasia), and postcapillary PH is associated with a PCWP of >15 mmHg [77]. Treatment strategies differ between the two types of PH. Before cardiac repair in patients with postcapillary etiology, therapy to decrease pulmonary resistance may result in increased pulmonary blood flow in the face of a fixed downstream obstruction, and pulmonary edema with worsening gas exchange[77,78].

Preprocedural assessment should be directed at determining the severity of the PH. Symptoms of PH may include dyspnea on exertion, reduced exercise tolerance, orthopnea, atypical chest pain, hemoptysis, cyanosis, and syncope [76,78]. Syncope is an especially concerning symptom. The echocardiographic exam should be reviewed. Findings of PH include a tricuspid regurgitation Doppler velocity of greater than 2.5 m/s or an estimated systolic pulmonary artery pressure that is greater than 50% of the systemic systolic blood pressure. It is also informative to assess at the degree of dilation and the function of the RV. A poorly contractile, massively dilated RV that causes interventricular septal bowing and compression of the left ventricle is a sign of severe pulmonary hypertension (Fig. 28.6). A decompressive shunt, such as an atrial septal defect, may also be encountered. This "pop-off" can serve to preserve cardiac output by allowing the right-to-left shunting of blood to fill the left heart during a pulmonary hypertensive crisis [72,78]. Cardiac catheterization data should also be reviewed. A PVR of >3 Wood units is indicative of PH [77]. Information regarding the etiology of the PH can also be sought; increased PCWP and/or left arterial pressure suggests postcapillary causes.

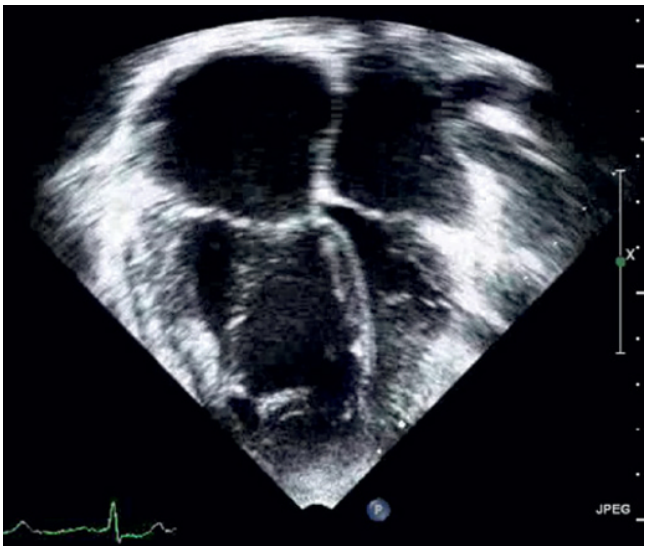

Figure 28.6 Transthoracic echocardiographic apical four-chamber view of pulmonary hypertension in systole. Note the severely dilated right ventricle, bowing of the intraventricular septum right to left, and compression of the left ventricle due to suprasystemic pulmonary artery and right ventricular pressure.

Patients may be taking medications for PH, or they may be untreated. Unfortunately, many patients who present for cardiac catheterization to evaluate newly diagnosed PH are untreated. Therapy for PH may include the endothelin antagonist bosentan, a calcium channel blocker such as diltiazem, phosphodiasterase-3 inhibitors such as milrinone, phosphodiesterase-5 inhibitors such as sildenafil, home oxygen, inhaled nitric oxide, or a prostacyclin analog (treprostinil (intravenous or subcutaneous), epoprostanol (intravenous), iloprost (inhaled), or beraprost (oral)) [72]. Some studies suggest that there is a decreased risk of adverse events when patients are receiving treatment preoperatively [73,79,80], but others suggest that this is not necessarily the case [72].

The key to avoiding an adverse event when caring for patients with PH is to minimize increases in PVR, maintain myocardial contractility, and to maintain systemic blood pressure, so that coronary perfusion is not compromised. To minimize increases in PVR, hypoxemia, hypercarbia, acidosis, and noxious stimuli without an appropriate anesthetic plane should be avoided. In addition, the prompt recognition and treatment of a pulmonary hypertensive crisis is critical. A pulmonary hypertensive crisis is characterized by an acute increase in PVR, decrease in systemic arterial blood pressure,

and RV failure (Fig. 28.7). Treatment consists of medications and maneuvers to decrease PVR. The systemic blood pressure should be supported, and cardiac contractility preserved [81]. Box 28.1 summarizes options for treatment.

When caring for patients with postcapillary pulmonary hypertension, left heart physiology should be optimized while maintaining right heart contractility and coronary perfusion [77]. In some cases such as pulmonary vein stenosis or cor triatriatum, left heart physiology cannot really be optimized, and focus should be on the right heart.

PVR can be decreased by increasing the FiO_2, hyperventilation, treating acidosis, blunting the response to noxious stimuli, and administering rescue pulmonary vasodilators such as inhaled nitric oxide or aerosolized iloprost. The possibility of hypoventilation with obstruction in an uninstrumented airway, a poorly seated supraglottic airway device, or an occluded endotracheal tube should be explored and corrected. Inhaled nitric oxide and iloprost are both effective pulmonary vasodilators [82–84]. These agents are delivered directly to the pulmonary circulation and do not cause significant systemic effects. Both drugs require specialized equipment. Inhaled nitric oxide can be delivered continuously or via a pulsing system (Fig. 28.8). Iloprost is delivered via a nebulizer, and a specialized adaptor that fits into the ventilator circuit is required (Fig. 28.9). Iloprost is not associated with rebound increases in PVR after discontinuation, as is the case with inhaled nitric oxide. However, the amount of drug that reaches the alveolus with a nebulizer in an anesthesia ventilation circuit may not be consistent [83]. There is some question about whether a combination of inhaled nitric oxide and iloprost is more potent than either agent alone, and some

Box 28.1: Treatment of pulmonary hypertensive crises

Decrease PVR	FiO_2 1.0
	Decrease $PaCO_2$
	Treat acidosis
	Avoid noxious stimuli
	Milrinone
	Inhaled nitric oxide
	Prostacyclin analog (nebulized iloprost)
Increase RV contractility	Milrinone
	Epinephrine
Support coronary perfusion pressure	Vasopressin
	Norepinephrine
	Phenylephrine

PVR, pulmonary vascular resistance; RV, right ventricle.

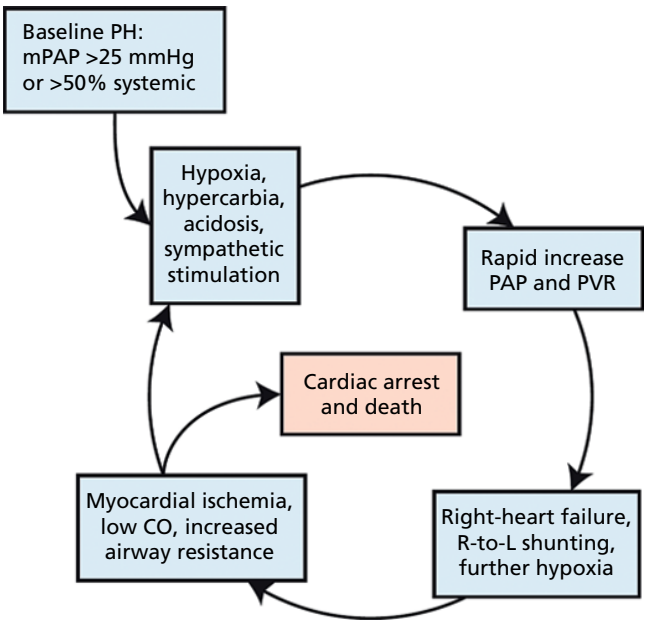

Figure 28.7 Pathophysiology of a pulmonary hypertensive crisis. A patient with baseline pulmonary hypertension (PH) experiences a stimulus that rapidly increases pulmonary artery pressure (PAP) and resistance, leading to a vicious cycle of right heart failure, right-to-left shunting and further hypoxemia, hypotension, and low cardiac output (CO). If not interrupted, this crisis can lead to cardiac arrest. mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance. *Source*: Reproduced from Gottlieb and Andropoulos [37] with permission of Wolters Kluwer.

Figure 28.8 Inhaled nitric oxide (iNO) delivery system. (A) Screen showing FiO_2, iNO in parts per million, and nitrogen dioxide concentrations; transport with 0–80 ppm iNO is available. (B) iNO injector placed proximal to the inspiratory limb of the anesthesia circuit. (C) iNO sampling/monitoring line placed in the inspiratory limb just proximal to the Y-piece.

Figure 28.9 Iloprost nebulizer system. A vibrating mesh design produces the optimized particle size for deep lung penetration. This device is compatible with volatile anesthetics and anesthetic ventilating circuits. *Source*: Photo courtesy of Aerogen, Galway, Ireland.

evidence of synergy between the two classes of drugs in animals and children [85–89].

Maintenance of SVR in patients with PH is important, and is a critical goal in the treatment of a pulmonary hypertensive crisis. In the patient without PH, right ventricular perfusion and myocardial supply compared with demand are ample, as opposed to the situation in the left ventricle. For example, the RV is normally perfused throughout the cardiac cycle, unlike the left ventricle which is perfused during diastole. When the RV is doing increased pressure work, as is the case with PH, RV perfusion becomes phasic as is seen in the left ventricle, with flow only during diastole. During a pulmonary hypertensive crisis, when RV afterload increases acutely, systemic blood pressure decreases. This can be due to decreased blood flow across the pulmonary bed with a resultant decrease in left heart filling, as well as a change in left ventricular geometry secondary to the compression of the left ventricle by the RV. This decrease in blood pressure occurs at the same time that the myocardial oxygen demand of the RV increases, and this situation often results in RV ischemia, worsened myocardial function, decreased pulmonary blood flow and left heart filling, and cardiac arrest [81]. Pharmacological means of increasing the systemic blood pressure include phenylephrine, norepinephrine, and vasopressin. There is evidence that both phenylephrine and norepinephrine increase systemic and pulmonary vascular resistance, while vasopressin increases SVR without increasing PVR [90]. A benefit of norepinephrine is the β-adrenergic receptor-mediated increase in contractility that can be helpful during acute RV dysfunction [91].

Maintaining or improving RV contractility is also important in avoiding adverse events in patients with PH and for treating pulmonary hypertensive crises. Epinephrine infusion can both increase SVR and provide inotropic support to the RV. Milrinone can also improve RV contractility, but a decrease in SVR with this drug should be anticipated. In the event of a pulmonary hypertensive crisis, epinephrine is the inotrope of choice for resuscitation [91].

Diligent case preparation when caring for this high-risk group cannot be overemphasized. Chau et al stress the importance of preoperative multidisciplinary discussion [77]. The anesthesiologist, pulmonologist, cardiologist, intensivist, and surgeon or proceduralist should be involved. Plans should be made for postoperative recovery in the ICU, if indicated, and the possibility of extracorporeal support should be discussed. Pulmonary vasodilator therapy should be continued. The patient should not be kept fasting without intravenous fluids for an extended period. Elective cases should be scheduled during normal working hours, so that subspecialty and emergency consultation and assistance are readily available. All providers should be familiar with PH, the risks involved, and the plan if a cardiac arrest or other adverse event occurs. Before starting the procedure, all necessary equipment should be immediately available, because delays in procuring equipment after the patient is anesthetized can lead to unnecessary opportunities for the patient to suffer an adverse outcome [77,79].

When providing anesthesia for patients with PH, especially those with systemic or suprasystemic pulmonary artery pressures, the anesthesiologist should anticipate instability and a pulmonary hypertensive crisis. Care should be taken to avoid hypoxemia and hypercarbia. Pulmonary vasodilators should be readily available. Because both inhaled nitric oxide and iloprost require special equipment, their use should be anticipated, and the equipment readied. Some groups advocate starting inhaled nitric oxide preinduction and continuing it intraoperatively and postoperatively [78]. Others advocate a preoperative iloprost nebulizer treatment [91]. Infusions of epinephrine, vasopressin or norepinephrine, and milrinone should be prepared. Some anesthesiologists will start infusions prior to induction [91]. Invasive arterial and central venous pressure monitoring may be helpful. Children rarely tolerate placement of invasive catheters prior to induction.

All classes of anesthetic drugs have been used in patients with PH. Anesthetic drugs should be selected to maintain myocardial contractility and to avoid decreases in SVR. For this reason, propofol or high concentrations of inhalational agent are often avoided [78,79]. A thorough understanding of the physiology associated with PH should be helpful in selecting an anesthetic plan.

KEY POINTS: PULMONARY HYPERTENSION

- Patients with systemic or suprasystemic pulmonary artery pressure are at high risk for perioperative cardiac arrest
- Treatment of pulmonary hypertensive crisis involves decreasing PVR, maintaining or improving RV contractility, and increasing SVR to maintain coronary perfusion
- Strategies to decrease PVR include high FiO_2, hyperventilation, inhaled nitric oxide, prostacyclin analogs, and phosphodiesterase inhibitors
- A distinction should be made between precapillary and postcapillary etiology of the PH as treatment differs

Cardiomyopathy

Patients with cardiomyopathy are another group with heart disease at high risk of perioperative morbidity and mortality. Cardiomyopathy accounted for 13% of the perioperative cardiac arrests in patients with heart disease in the 2011 report from the POCA Registry, and 50% of the patients with

cardiomyopathy who suffered cardiac arrest died as a result of the arrest [3]. In a study by Tabib et al, of the 12 pediatric patients who had unexpected perioperative sudden death, 75% had an undiagnosed cardiomyopathy [92]. An understanding of the different cardiomyopathy subtypes and subtype-specific perioperative management goals is important for decreasing perioperative risk and improving the rate of successful resuscitation after cardiac arrest [93].

The World Health Organization classifies cardiomyopathies into four basic categories: dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), and arrhythmogenic right ventricular dysplasia (ARVD). The European Society of Cardiology added a fifth unclassified category that included 'left ventricular noncompaction' (LVNC) [94]. Many cardiomyopathies are acquired such as acute myocarditis and those from anthracycline exposure after cancer therapy, or are associated with genetic diseases or syndromes (Table 28.4) [95].

Dilated cardiomyopathy

The most common pediatric cardiomyopathy in children is DCM, accounting for 50% of pediatric cardiomyopathy [96]. Most DCM in children is idiopathic or due to myocarditis, but it can also be associated with neuromuscular disorders, inborn errors of metabolism, or familial predisposition [97]. An important differential diagnosis in infants is anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA), which results in chronic myocardial ischemia as PVR decreases after birth, and presentation may be indistinguishable from DCM. Echocardiography can usually establish the diagnosis of ALCAPA.

DCM is associated with ventricular dilation and depressed function. Infants can present with signs of heart failure including sweating or tiring with feeds, failure to thrive, or decreased activity. Older patients may present with decreased exercise tolerance, abdominal pain, or chest pain. Unfortunately, many early signs are unnoticeable or non-specific, and patients often present with syncope, shock, or cardiac arrest.

On echocardiogram, the ejection fraction (normal >50%) or fractional shortening (normal >35%) indicates the degree of ventricular dysfunction (Fig. 28.10) [98]. The severity of dysfunction is associated with worse perioperative morbidity and mortality. In a retrospective study from Kipps et al, 83% of all complications in patients with cardiomyopathy undergoing non-cardiac surgery occurred in patients with severe myocardial dysfunction, as did the one mortality in the study [99]. This study also found an association between increased anesthetic duration and complications. Strategies to maximize good anesthetic outcomes include a plan for postoperative ICU admission, invasive arterial monitoring to facilitate prompt recognition and treatment of hemodynamic instability, and early administration of vasoactive and inotropic medications [99].

Other important preoperative information includes a history of medications that the patient is taking. Some DCM patients are receiving chronic intravenous milrinone therapy for inotropic support and afterload reduction. Common medications include diuretics, angiotensin-converting enzyme

Table 28.4 European Society of Cardiology classification of cardiomyopathies

	HCM	DCM	ARVC	RCM	Unclassified
Familial	Familial, unknown gene Sarcomeric protein mutations GSD (e.g. Pompe, *PRKAG2*, Forbes, Danon) Lysosomal storage diseases (e.g. Anderson–Fabry, Hurler) Disorders of fatty acid metabolism Carnitine deficiency Phosphorylase B kinase deficiency Mitochondrial cytopathies Syndromic HCM (e.g. Noonan syndrome, LÉQPARD syndrome) Familial amyloid	Familial, unknown gene Sarcomeric protein Z-band Cytoskeletal protein Nuclear membrane protein Intercalated disk proteins (desmosomes) Mitochondrial cytopathy	Familial unknown gene Intercalated disk protein (desmosomes) Cardiac ryanodine receptor Transforming growth factor β3 Titin Lamin A/C	Familial, unknown gene Sarcomeric protein mutations Familial amyloidosis Desminopathy Hemochromatosis Anderson–Fabry disease GSD	Left ventricular non-compaction
Non-familial	Obesity Infants of diabetic mothers Athletic training Amyloid	Myocarditis Kawasaki disease Eosinophilic Drugs Pregnancy Endocrine Nutritional Alcohol Tachycardiomyopathy	Myocarditis	Amyloid Scleroderma Endomyocardial fibrosis Hypereosinophlic syndrome Drugs Carcinoid heart disease Metastatic cancers Radiation	Takotsubo cardiomyopathy

ARVD, arrhythmogenic right ventricular dysplasia; DCM, dilated cardiomyopathy; GSD, glycogen storage disease; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy.
Source: Reproduced from Konta et al [94].

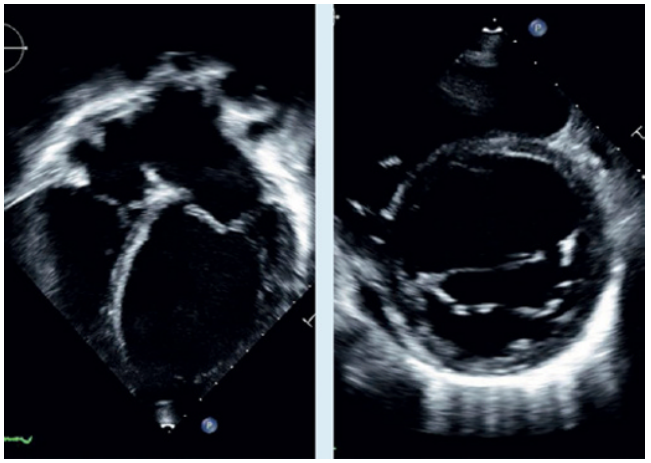

Figure 28.10 Transthoracic echocardiogram of dilated cardiomyopathy. (Left) Subcostal four-chamber view demonstrating a massively dilated left ventricle, and lack of coaptation of the mitral valve leaflets. (Right) Short axis view of dilated left ventricle. *Source*: Reproduced from Lee et al [98] with permission of Wolters Kluwer.

inhibitors, and β-blockers. A chest radiograph may reveal pulmonary edema or cardiomegaly that may affect ventilation. Other patients may have a biventricular pacemaker that has been placed for cardiac resynchronization therapy, and perioperative device management may be necessary. An increasing number of patients with DCM are now receiving mechanical support with left or biventricular support devices, all of which require anticoagulation. A preoperative discussion with the patient's cardiologist is helpful to determine if the patient's status is optimized or if there have been changes in condition. Preoperative planning for postoperative ICU disposition should also be determined. In addition, ECMO and cardiac transplant candidacy should be part of the multidisciplinary discussion, especially in patients with severe myocardial dysfunction. The benefit of the procedure should also be carefully weighed against the risks associated with the anesthetic [100].

The anesthetic management of the patient with dilated cardiomyopathy should focus on maintaining an adequate coronary perfusion pressure, maintaining adequate preload, avoiding tachycardia, maintaining cardiac contractility, and keeping SVR relatively low so that the severely depressed ventricle can eject [101]. Hemodynamic instability with induction of anesthesia should be anticipated. Because these patients are often receiving diuretic therapy and are nil per os, the hemodynamic response to vasodilation and/or a decrease in myocardial contractility related to anesthetic induction may be pronounced [100]. In fact, according to the largest review of patients with cardiomyopathy undergoing anesthetics, hypotension and/or bradycardia were reported to be the most common causes of arrest on induction of anesthesia [102]. For this reason, emergency drugs and vasoactive agents should be immediately available. For patients with severely depressed myocardial function, initiating low-dose inotropic infusions before induction (e.g. epinephrine 0.02–0.03 μg/kg/min) can be effective in preventing hypotension and low cardiac output. In addition, the placement of a preinduction or peri-induction arterial line can be helpful in this situation.

The selection of induction agent(s) is based on the severity of ventricular dysfunction and on the experience/preference of the anesthesiologist, with the goal of avoiding excessive vasodilation and myocardial depression. The use of midazolam, fentanyl, ketamine, etomidate, propofol, sevoflurane, sodium thiopental, and combinations of these drugs have all been described [99,102]. It is, however, important that the medications be carefully titrated to effect. When these drugs are administered, the patient's circulation time should be considered, and an extended time may be observed until induction occurs. High-concentration sevoflurane or large doses of propofol or sodium thiopental are not tolerated. Ketamine is often selected for its sympathomimetic properties, but it can be a direct myocardial depressant in patients in catecholamine-depleted states. Etomidate has the benefit of preserving myocardial function in DCM patients, but it is associated with adrenal suppression even after a single dose [95].

Hypotension can lead to decreased myocardial perfusion pressure, ischemia, further depressed function, decreased cardiac output, and cardiac arrest. For this reason, hypotension should be anticipated and treated early. Invasive blood pressure monitoring can lead to early recognition and treatment. Inotropic support with milrinone or low-dose epinephrine can be helpful, and vasopressor support with low-dose vasopressin or phenylephrine can counteract the vasodilation associated with the anesthetic and help maintain an adequate myocardial perfusion pressure. However, the ventricle with severe dysfunction will not tolerate excessive SVR.

Hypertrophic cardiomyopathy

According to the Pediatric Cardiomyopathy Registry, HCM comprises 42% of pediatric cardiomyopathies. Most cases are idiopathic or familial, but many are related to inborn errors of metabolism or associated with genetic syndromes. HCM is a leading cause of death in young people [95]. HCM is characterized by marked ventricular hypertrophy, which can be uniform or asymmetrical and focal. Left ventricular hypertrophy leads to a decrease in LV compliance, reduced filling and stroke volume, a propensity for subendocardial ischemia due to the thick ventricular wall, and an increase in myocardial oxygen consumption. Asymmetrical septal hypertrophy results in dynamic LVOTO, and focal hypertrophy can lead to myocardial bridges (present in 28% of patients with HCM) [103].

The hypertrophic ventricle with dynamic LVOTO is a condition with fragile physiology. Myocardial oxygen supply is limited due to the thickened myocardium and occasionally due to the presence of a myocardial bridge, which can decrease the amount of blood flow through the affected coronary artery during diastole. Myocardial oxygen demand is increased due to the hypertrophy of the ventricle. This delicate balance can be upset by normal patient activity. Tachycardia, for example, increases myocardial oxygen demand at the same time that it decreases myocardial oxygen supply by decreasing the time spent in diastole. Significant LVOTO that occurs with exercise can exacerbate the problem by decreasing the systolic and diastolic blood pressure. This can lead to ischemia and sudden cardiac death from dysrhythmia.

Patients with HCM are prescribed exercise restrictions, and they are often treated with β-antagonists, which slow the heart rate and increase the time spent in diastole, improving filling during diastole, and decreasing contractility, limiting LVOTO. Patients with arrhythmias may require automatic internal cardiac defibrillator placement, and some patients require a ventricular septal myectomy to improve symptoms [95,101].

Preoperative assessment should include an echocardiogram (Fig. 28.11). When reviewing the echocardiogram, it is important not to rely on the ejection fraction or fractional shortening alone for indices of the degree of LVOTO. These indices are often normal in patients with HCM. More important in HCM is the thickness of the left ventricle. The two-dimensional left ventricle mass index is reported in grams per meter squared, and it can be very useful to assess the degree of hypertrophy in comparison with normal values [104]. Another method to express the left ventricle thickness is the Z-score – one Z-score is one standard deviation above or below a size- or age-specific population mean for a given parameter [105]. An electrocardiogram (ECG) should be obtained and examined for signs of ischemia, and history of dysrhythmia, syncope, or aborted sudden death should be investigated.

The hemodynamic goals when anesthetizing a patient with HCM should be to maintain ventricular preload, maintain SVR (coronary perfusion pressure), avoid tachycardia, and avoid increasing LVOTO. LVOTO is increased with tachycardia, endogenous or exogenous catecholamine exposure, and hypovolemia. Tachydysrhythmias and specifically rhythms without an atrial contraction (atrial fibrillation, atrial flutter) are poorly tolerated due to poor filling of a non-compliant left ventricle.

Preoperative planning for postoperative ICU disposition should be determined. In addition, ECMO and transplant candidacy should be part of the multidisciplinary discussion, especially in patients with severe dysfunction. The benefit of the procedure should be carefully weighed against the risks associated with the anesthetic [100]. Due to the propensity for sudden death and poorly tolerated dysrhythmias, appropriately sized defibrillation pads or paddles should be available. Emergency drugs should be prepared, and infusions of esmolol and a vasoconstrictor (typically phenylephrine or vasopressin) should be ready for administration. The placement of a preinduction or peri-induction arterial catheter should be considered.

The primary goals for anesthesia induction with LVOTO are to maintain SVR and avoid tachycardia. This can be accomplished with a number of agents including midazolam, fentanyl, etomidate, ketamine, propofol, sodium thiopental, and sevoflurane, but they must be titrated in slowly and carefully. Caution should be taken when using propofol, sodium thiopental, and sevoflurane as these drugs are associated with a decrease in preload and SVR. Decreases in blood pressure should be treated quickly with a bolus of phenylephrine or vasopressin to avoid ischemia and cardiac arrest. Infusions of these vasoconstrictor can be very effective. An esmolol infusion can be initiated to improve coronary perfusion and filling and to decrease LVOTO. These vasoactive agents may also be needed throughout the anesthetic to maintain stability.

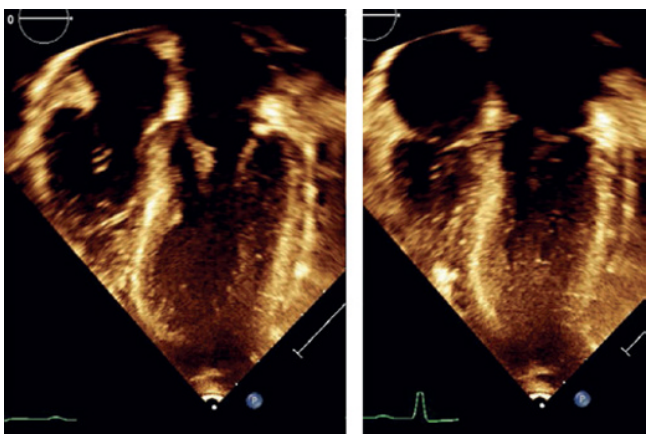

Figure 28.11 Transthoracic echocardiogram of hypertrophic cardiomyopathy. Both images are subcostal four-chamber views demonstrating a very thickened left ventricular free wall and interventricular septum, which causes left ventricular outflow tract obstruction. *Source*: Reproduced from Lee et al [98] with permission of Wolters Kluwer.

Pompe's disease, glycogen storage disease type II, is associated with HCM in early infancy. This disease was uniformly fatal until 1995, when enzyme replacement therapy (ERT) became available. With the advent of ERT, these high-risk patients often require multiple anesthetics for central line placement and for multiple muscle biopsies to follow the response to the enzyme replacement. The only cardiac arrest in the series of 13 anesthetics reported by Ing et al was shortly after an inhaled induction with sevoflurane followed by a continuous infusion of propofol for maintenance. The cardiac arrest was attributed to myocardial depression from the inhaled agent and hypotension from a propofol-induced decrease in SVR and hypovolemia [104].

It also should be noted that the sympathectomy associated with neuraxial anesthesia may also lead to ischemia and cardiac arrest in LVOTO patients. Some authorities discourage the use of spinal anesthesia in patients with hypertrophic obstructive cardiomyopathy [106]. However, if the sympathectomy associated with neuraxial anesthesia is anticipated and treated, spinal anesthesia can be performed safely [107]. Subsequent to these case reports there have been additional reports of successful epidural and spinal anesthetics. Although there are no reports in the pediatric literature, neuraxial anesthesia can be performed successfully with careful maintenance of preload and SVR.

As with any anesthetic, unexpected intraoperative events in patients with LVOTO can occur, such as anaphylaxis. Yee et al reported the case of an adult with HCM who suffered an anaphylactic reaction soon after induction. Unfortunately, the hypotension and tachycardia associated with the reaction can quickly cause a cardiac arrest in a patient with HCM. In addition, epinephrine, usually given to inhibit mast cell degranulation, cause bronchodilation, and support the blood pressure, is not a drug that is well-tolerated in HCM. The authors describe a long, unsuccessful resuscitation that ultimately resulted in emergent cannulation for bypass [108].

Postoperatively, it is also important that the patient with HCM maintains preload. Inadequate oral intake, fluid shifts, bleeding, or postoperative nausea and vomiting can lead to hypovolemia which in turn can lead to increased LVOTO, hypotension, ischemia, and cardiac arrest. Postoperative monitoring and level of care should reflect this serious potential risk.

Restrictive cardiomyopathy

Restrictive cardiomyopathy comprises 2–5% of all pediatric cardiomyopathies. This cardiomyopathy is associated with endomyocardial fibrosis, decreased myocardial compliance, and poor ventricular filling. Over time, increased left ventricular end-diastolic pressure leads to increased left atrial pressure, increased pulmonary venous pressure, and increased PVR.

Patients with RCM often present late with signs of reactive airway disease, decreased exercise tolerance, syncope, or thromboembolism, and by the time of presentation, PVR is already 10–15 Woods units/m^2 [93,98,101,109]. Echocardiographic findings associated with RCM include small non-compliant ventricles and massively dilated atria (Fig. 28.12) [98].

Hemodynamic goals when anesthetizing a patient with RCM are chosen with the aim of preserving cardiac output. Neither tachycardia nor bradycardia is well tolerated in these patients. Tachycardia leads to poor filling with a non-compliant ventricle, and bradycardia leads to a decrease in cardiac output due to a relatively fixed stroke volume. Preload and contractility should be maintained. Care should be taken to avoid further increases in PVR, and in the presence of increased PVR, afterload should be maintained (see earlier section on PH) [93,101].

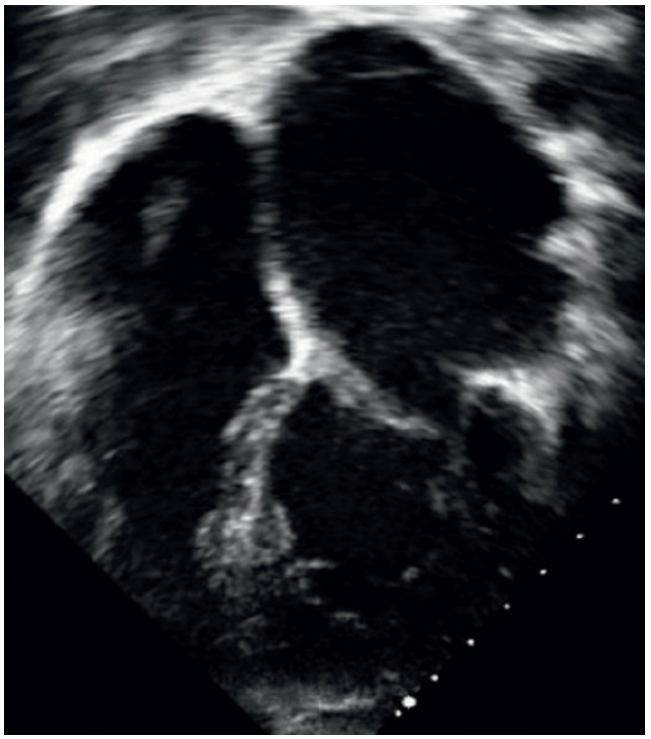

Figure 28.12 Transthoracic echocardiogram of restrictive cardiomyopathy. A subcostal four-chamber view demonstrating a massively dilated left atrium, and a normal-sized left ventricle which is not hypertrophied but is non-compliant with severe diastolic dysfunction. *Source*: Reproduced from Lee et al [98] with permission of Wolters Kluwer.

Arrhythmogenic right ventricular dysplasia/cardiomyopathy

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is an uncommon type of cardiomyopathy. It is associated with the fibrofatty infiltration of the right ventricle, arrhythmias and abnormal electrocardiographic findings, right ventricular failure, and occasionally biventricular failure [101]. This condition is associated with unexplained and unanticipated perioperative death. In a series of 50 autopsies performed on patients who suffered unexplained perioperative death, 36% were found to have ARVD/C. These patients were undergoing uncomplicated procedures. Four of these patients experienced cardiac arrest on induction of anesthesia, nine arrested during the procedure, and five arrested within 2 h of the surgery [92]. There are additional case reports of patients who suffered cardiac arrest and died perioperatively who were also found to have ARVD/C on autopsy [110–112]. For this reason, it is important to have an understanding of the disease and its course.

The clinical presentation of ARVD/C is often related to arrhythmia or ventricular failure. Common presentations include palpitations, syncope, atypical chest pain, dyspnea, right ventricular failure, arrhythmia, or sudden cardiac death. The four phases of ARVD/C include: (1) the "concealed" phase with subtle right ventricular abnormalities; (2) "overt arrhythmia" with symptomatic ventricular arrhythmias; (3) isolated right heart failure; and (4) biventricular failure that can mimic dilated cardiomyopathy [113].

Electrocardiographic findings in patients with ARVD/C include sinus rhythm with a QRS >110 ms in lead V1, an epsilon wave which is a terminal deflection within or at the end of the QRS in leads V1–V3, T-wave inversion in leads V1–V3, complete or incomplete right bundle branch block (RBBB), or in the absence of RBBB, selective prolongation of the QRS in leads V1–V3 compared with V6 (Fig. 28.13) [114].

Therapy for ARVD/C includes treatment of arrhythmia and treatment for cardiac failure. Arrhythmia can be treated with pharmacological antiarrhythmics, commonly sotalol or

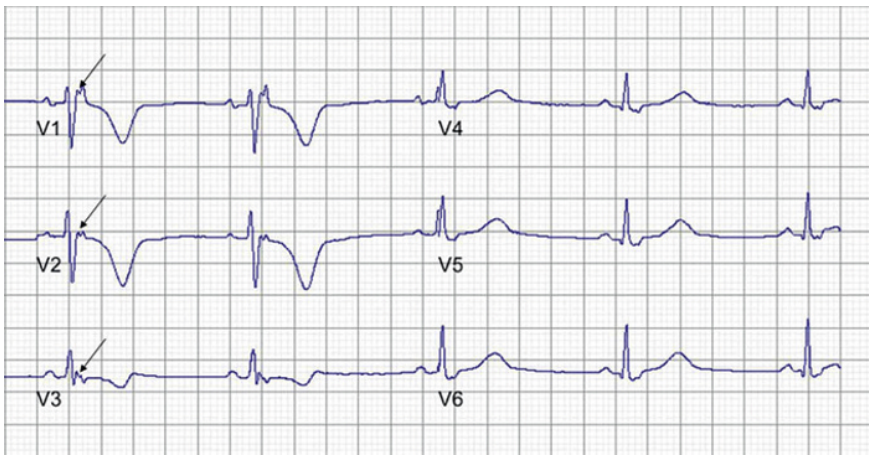

Figure 28.13 ECG in arrhythmogenic right ventricular dysplasia/cardiomyopathy. The precordial leads of an ECG are shown from a 44-year-old woman that were recorded during regular sinus rhythm, with an epsilon wave (arrow) in leads V1–V3. The ECG shows a right bundle branch block pattern. *Source*: Reproduced from Kies et al [114] with permission of Elsevier.

amiodarone. Catheter ablation can be used for patients with inducible, monomorphic ventricular tachycardia, and placement of an automatic implantable cardiac defibrillator is reserved for those at high risk for unstable ventricular tachycardia [115]. Right ventricular exclusion surgery during which a total cavopulmonary anastomosis (Fontan) is constructed and the right ventricular wall is resected has also been described [116–118]. Exercise restriction is also a component of therapy [119]. Heart transplantation is indicated for intractable arrhythmias or end-stage cardiac failure [115].

As ARVD/C may be clinically silent, special attention should be given to a history of syncope, family history of sudden cardiac death or heart failure, as well as the preoperative ECG. The presence of findings associated with ARVD/C may indicate the need for an echocardiogram.

In patients with known ARVD/C, successful anesthetics have been reported [120,121]. All antiarrhythmics should be continued in the perioperative period. In addition, appropriate defibrillator pads should be available. Strategies for improving anesthetic outcome also include the avoidance of adrenergic agents including epinephrine, noxious stimuli and sympathetic stimulation, and large doses of bupivacaine. For patients with ventricular dysfunction, transesophageal echocardiography and invasive arterial blood pressure monitoring may be helpful. Pulmonary artery catheters are relatively contraindicated due to the arrhythmogenic potential and possible perforation of the abnormal ventricular wall [101,115,122]. The avoidance of the tachycardia associated with pancuronium or excessive anticholinergic administered with reversal of neuromuscular blockade may also be considered [101]. Implanted pacemakers/defibrillators should be interrogated, and managed with the input of the patient's cardiologist.

KEY POINTS: CARDIOMYOPATHY

- The anesthesiologist should be familiar with the different types of cardiomyopathies, and know their anesthetic implications
- Anesthetic induction with dilated cardiomyopathy should focus on maintaining contractility and an adequate coronary perfusion pressure
- Goals for the induction of the patient with hypertrophic cardiomyopathy include maintaining SVR and avoiding tachycardia

Special scenarios

Anesthesia and sedation for diagnostic imaging

Patients with cardiovascular disease often require magnetic resonance imaging (MRI) and computed tomography (CT) examinations for diagnosis and planning, and many patients require anesthesia or sedation to obtain these studies. As in other anesthetizing locations, these patients are at a higher risk of adverse events [5,123]. Hypotension, cardiac arrest, tachyarrhythmias, and shunt occlusion have all been described [5,46,123,124]. However, with careful preparation and planning, some of the risks can be reduced [124,125].

The MRI and CT scanners are often located in a remote location from the operating rooms. This often leaves the anesthesiologist without additional assistance if the patient becomes unstable. This risk can be mitigated by assigning two anesthesiologists to the case for high-risk patients, if possible [124]. Other strategies include anesthetic induction and intubation in the ICU, an operating room, or a procedure room that is in close – to skilled assistance or a surgical team before traveling to a remote location. For ICU patients, a full hand-off report should take place and in some cases the ICU team may be available to transport with the anesthesia care team for high-risk patients, as the risk of adverse events is higher in hospitalized patients and those requiring general anesthesia [123]. Some institutions are building MRI suites into their heart centers so the location is no longer remote.

The MRI environment is often cold, and access to the patient is limited once they are positioned under the MRI coil and in the bore of the scanner. The physiological monitor is the primary contact with the patient, although remote cameras are now in use in many MRI suites. The anesthesiologist is often in the control room with the technologist during the scan, quite far from the patient. When two anesthesia care providers are present, one can be in the room with the patient, adjusting the anesthetic and monitoring more closely, while the other confers with the technologist and the radiologist about the scan and need for breath holding, heart rate control, and other maneuvers to improve image quality [124]. It is possible to monitor invasive arterial and central venous pressures during MRI, although one must confirm that the pressure monitoring cables for the MRI monitor is compatible with the patient transducers from the ICU.

Current disadvantages of cardiac MRI are the multiple sequences that are often necessary, and requirements for breath holding and signal averaging over a few cardiac cycles to reduce motion artifacts due to respiration, which necessitate general anesthesia for younger children [126]. Fortunately, faster acquisition techniques, ECG-gated signal acquisition, and reconstruction strategies are being developed that can decrease scanning times from 60 to 10 min and obviate the requirement for breath holding [127].

Dynamic contrast-enhanced lymphatic angiography is also being employed in patients with SV physiology to identify lymphatic abnormalities suitable for catheter intervention [126]. This study involves the injection of gadolinium into inguinal lymph nodes, with MRI image acquisition. This technique can be used to guide percutaneous thoracic duct embolization to treat chylous effusion or embolization of pulmonary lymphatic vessels to treat plastic bronchitis [128].

CT is often used for imaging the heart and extracardiac vessels, and airway. Because of the brevity of the scan (often 30 s to 2–3 min), many patients do not require anesthesia or sedation for CT imaging. Unfortunately, CT involves ionizing radiation. Newer scanners with higher gantry rotation speeds, helical scanning, and multiple dectectors decrease scan times and lower the radiation dose [129]. When anesthetic risk is high, CT without sedation may yield similar information as MRI. CT alone is not without risk, however. A serious reaction to intravenous contrast can result in cardiac arrest in a patient with fragile physiology [22]. CT for coronary angiography can require general anesthesia, heart rate control, and breath holding for image clarity in patients who have higher heart

rates (>120 bpm) and who are unable to suspend respiration. Prior discussion with the radiologist is advised, so that the requirements for successful images are met.

There are some misconceptions about diagnostic imaging and cardiac patients. First, many ordering physicians are not aware that the patient may require general anesthesia for the study, and they do not have a concept of the risk associated with anesthetizing these patients. For high-risk patients, it is worth a discussion with the ordering physician and the radiologist to determine if the risk of the anesthetic outweighs the benefit of the test, or if there is another test (e.g. CT, echocardiography) that will yield the same or similar information without requiring anesthesia. In addition, the risk for an anesthetic for imaging in high-risk patients is not less because it is "only" an MRI. For SV patients with systemic to pulmonary artery shunt or equivalent, admission to the hospital for intravenous fluids preoperatively is described to decrease the risk of instability on induction or shunt occlusion and the risk of prolonged fasting with an at-risk circulation [5,46]. Similar considerations should be given to other at-risk physiology such as LVOTO, HCM, or unrepaired tetralogy of Fallot. Postanesthetic care should be guided by the patient's physiology, not by the procedure performed [40]. At Texas Children's Hospital, outpatient SV patients are admitted for recovery in the heart center recovery unit for a planned 6–8 h of observation, instead of the radiology postanesthesia care unit. After a prolonged observed recovery period, it is determined whether the patient can be discharged home or should be admitted to the hospital for ongoing monitoring.

Anesthetic options for diagnostic imaging vary. Some older patients do well with midazolam only. Others prefer light sedation and MRI-compatible video goggles ("midazolam and a movie"). Options for general anesthesia or deep sedation include propofol infusion or propofol-ketamine infusion. General anesthesia with an inhalational agent is also a possibility, either with a supraglottic airway device or endotracheal tube. The potential need for breath holds should be discussed with the radiologist before anesthetizing the patient. Techniques for breath holding include the use of muscle relaxant, hyperventilation before the breath hold, or a bolus of propofol. Patient physiology should be considered when selecting a technique for breath holding, as hyperventilation can lead to coronary hypoperfusion via steal in shunted patients. In addition, propofol boluses in patients with other high-risk lesions can lead to hypotension, ischemia, and cardiac arrest.

Strategies to avoid sedation have both the benefit of avoiding the anesthetic risk associated with cardiac disease and avoiding the potential for anesthetic neurotoxicity [130]. "Feed, swaddle, and sleep" techniques where the patient is fasted for 4 h, fed by the caregiver, swaddled, and placed in a vacuum bag immobilizer can be used successfully in neonates and infants up until 6 months [131,132]. Of course, care should be taken when fasting vulnerable patients. Certified Child Life Specialists (CCLSs) are often able to help allay anxiety regarding the scan, and with the use of mock scanners, toy scanners, video goggles, and other modalities, many more children are able to avoid anesthesia or sedation (Table 28.5) [133–135]. These strategies involve the collaborative efforts of the radiologist, anesthesiologist, technologist, CCLS, and the family [135]. The scan should be planned by the radiologist to prioritize the sequences that answer the clinical question, in the event that the patient is unable to complete the scan [131]. They may also use new techniques in acquisition and processing and optimize MRI protocols to decrease the amount of time on the scanner [136].

KEY POINTS: ANESTHESIA AND SEDATION FOR DIAGNOSTIC IMAGING

- The MRI and CT scanners are located in remote locations in many hospitals; this necessitates careful preparation and planning when caring for high-risk patients
- Dynamic contrast-enhanced lymphatic angiography is being used to map lymphatic circulation and to plan interventions in patients with single ventricle physiology
- General anesthesia and sedation for imaging carries the same risk as for other procedures; it is not "just an MRI"
- Discussion with the radiologist regarding the requirements for successful imaging including breath holds or heart rate control should take place prior to the anesthetic

Table 28.5 Alternatives to pediatric sedation in magnetic resonance (MR) imaging preparation

Alternative	Definition	Most effective age range*
Mock scanner	Replica of MR imaging unit used for practice with a child before an MR examination	3–8 years
MR-compatible audiovisual system	MR-safe headphones and goggles allow the child to watch a movie during the scan	3–10 years
Feed–sleep manipulation	Keeping the child awake during the day, with examinations scheduled at night; fasting until just before the examination; melatonin administration	Neonates to 4 years
Play therapy	Child life specialist/play specialist conducts play sessions with the child for examination preparation	4–12 years
Incubators/immobilizers	The infant is placed in a Med-Vac vacuum bag for immobilization and sleep promotion or in an MR-compatible incubator with built-in head coil for sleep promotion	Neonates
Photo diary	Before the appointment, the family receives a photo diary to read to the child explaining the MR imaging procedure	7–12 years
Sucrose solution	An oral sucrose solution is placed on a pacifier and given to the infant for preprocedural calming	Neonates
Guided imagery	The child listens to a relaxation audiorecording with guided imagery during the examination	4–8 years

* Estimations based on previous studies.

Source: Reproduced from McGuirt [134] with permission of American Society of Radiologic Technologists.

Anesthesia for airway procedures

Airway procedures are quite common in patients with CHD due to congenital or acquired airway abnormalities. In fact, in a retrospective study of 162 neonates undergoing bronchoscopy at a tertiary care center, 30.2% of the neonates had cardiac defects. The common findings in these patients included abnormal bronchi, bronchomalacia, tracheal stenosis, complete tracheal rings, and vascular rings [137]. Direct laryngoscopy and bronchoscopy can be diagnostic, and it can also be therapeutic (to remove mucous plugs or clots, dilate the trachea, laser treatment of subglottic stenosis, or remove bronchial casts).

Patients undergoing cardiac surgery are also at risk for subglottic stenosis and vocal fold immobility. This may be due to coexisting syndromes that can be associated with subglottic narrowing such as trisomy 21 or velocardiofacial syndrome [138,139] or it may be related to hypoperfusion and mucosal injury due to the CHD or repair in association with prolonged tracheal intubation [140–143]. Recurrent laryngeal nerve injury is a well-known complication of surgery on the aortic arch and its branches. Kruse et al report a 0.7% incidence of subglottic stenosis in infants and children undergoing heart surgery with bypass; subglottic stenosis was associated with younger age, prolonged bypass time, and prolonged mechanical ventilation [144]. Balloon dilation laryngoplasty (BDL) is one treatment for subglottic stenosis that can help avoid tracheostomy placement (Fig. 28.14). Collins et al report the use of BDL on patients with subglottic stenosis and CHD. In four of five patients, the need for tracheostomy was avoided, with only one patient requiring tracheostomy and laryngotracheal resection [143]. Laser treatment of subglottic stenosis requires adhering to all necessary precautions such as utilizing the lowest possible FiO_2, eye protection for patient and providers, wet towels around the face and head of the patient, and preparations to address an airway fire. Chapter 34 reviews laser bronchoscopy and laryngoscopy in detail.

Another described use of direct laryngoscopy and rigid bronchoscopy in the population with CHD is for the evaluation and treatment of plastic bronchitis, usually in patients with Fontan physiology. Plastic bronchitis usually presents with coughing and respiratory distress. Rigid bronchoscopy and removal of the proteinaceous bronchial cast is the treatment (Fig. 28.15). In a case series of three patients with Fontan physiology and plastic bronchitis, one recovered fully after one bronchoscopy, and two required

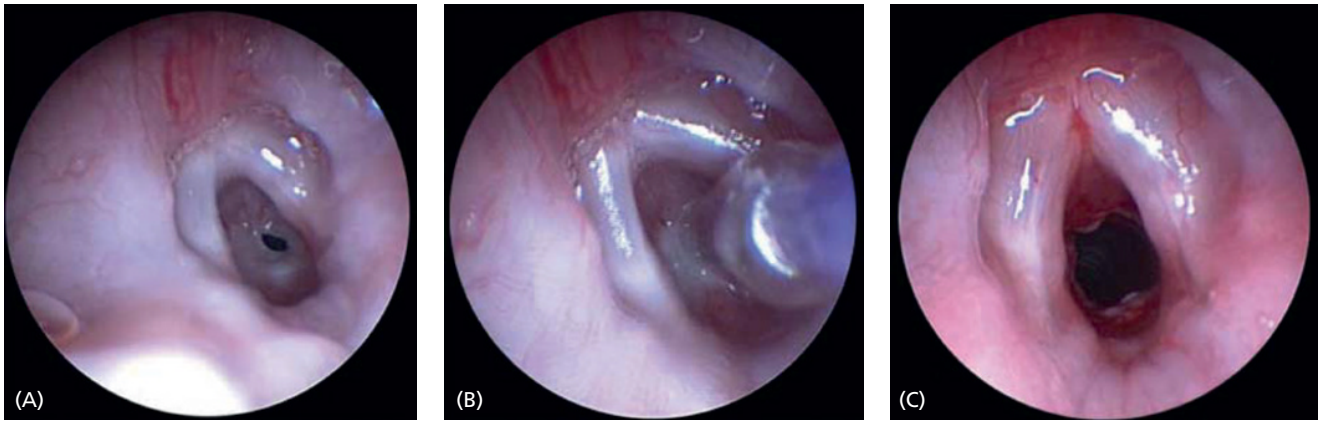

Figure 28.14 Balloon dilation of severe subglottic stenosis. (A) Sublgottic stenosis before balloon dilation. (B) During balloon dilation. (C) Immediate results after balloon dilation. *Source*: Reproduced from Collins Et al [143] with permission of JAMA Otolaryngology – Head & Neck Surgery – American Medical Association.

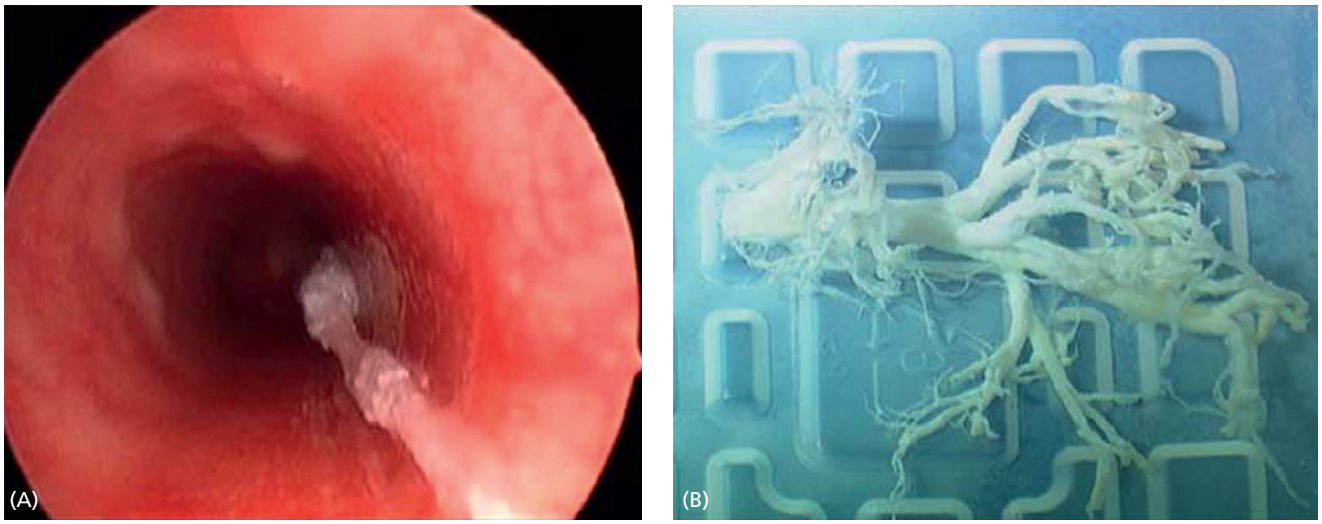

Figure 28.15 Plastic bronchitis in a patient with Fontan circulation. (A) Bronchoscopic view of removal of bronchial cast. (B) Cast after removal. *Source*: Reproduced from Preciado et al. [145] with permission of Elsevier.

multiple bronchoscopic procedures over a week with ECMO support for oxygenation [145].

Providing anesthetic care for an airway procedure in patients with CHD can be challenging due to the physiology of the cardiac lesion and the procedural requirements. Direct laryngoscopy and bronchoscopy requires a deep plane of anesthesia, as it is quite stimulating. Topical anesthesia in the form of atomized or nebulized local anesthetic is very effective; attention must be paid to not exceed the maximum tolerated doses of local anesthetic. For some indications, it is important that the patient be spontaneously ventilating, as well. At other times, the patient will need periods of apnea. Prior to anesthetizing the patient, it is important to have a discussion with the otolaryngologist about what conditions are needed for the study. It is also necessary to communicate how those conditions may or may not be possible with the patient's cardiorespiratory needs. In addition, it should be verified that all equipment needed for the procedure is in the operating room and assembled (e.g. the bronchoscope components) prior to anesthetizing the patient.

The importance of PVR has been discussed throughout this chapter for many lesions. It is especially important in unpalliated or unrepaired patients, patients with shunt or ductal stent physiology, and patients with Fontan physiology. During the anesthetic for an airway procedure, PVR changes considerably. Often prior to the laryngoscopy, the patient is preoxygenated at the same time that the anesthetic is deepened. This may increase risk for systemic and coronary hypoperfusion from increased pulmonary blood flow. Then, during the procedure, the patient may hypoventilate or become apneic with an associated increase in PVR and decrease in pulmonary blood flow. Planning for and recognition of extremes in PVR is essential in maintaining stability. Overzealous preoxygenation can result in myocardial ischemia and cardiac arrest, so it should be approached with caution and close attention paid to the systemic blood pressure and ST segment changes on ECG. Extended laryngoscopy and bronchoscopy can result in rapid desaturation and a precipitous decrease in pulmonary blood flow. The patient may not be able to tolerate long periods of apnea. Ventilation by facemask or endotracheal tube may be necessary between visualizations to allow the patient time to resaturate and ventilate. Effective communication with the otolaryngologist is essential.

Patients with Fontan physiology are also at risk for instability with airway examination due to dependence on passive pulmonary blood flow to maintain cardiac output. Increases in PVR with long periods of apnea may result in a decrease in filling of the systemic ventricle and a decrease in cardiac output. Instability may require volume resuscitation, inotropic support, limitation of apnea, and even ECMO support [145].

Laryngoscopic and bronchoscopic examinations in patients with pulmonary hypertension can lead to a pulmonary hypertensive crisis and cardiac arrest. Any increase in PVR that is associated with hypoventilation, apnea, hypoxemia, or inadequate anesthesia during laryngoscopy can lead to prompt right heart failure and cardiac arrest. Multidisciplinary discussion should take place prior to this type of procedure, and careful preparations should be made to prevent and treat pulmonary hypertensive crisis and cardiac arrest.

It is also challenging to provide a deep anesthetic in this patient population. As noted above, topical anesthesia provided by the surgeon is very effective in limiting the need for a deep plane of anesthesia. Many patients have depressed cardiac function or physiology that does not tolerate a significant decrease in SVR. There is no ideal anesthetic for these types of procedures. Caution should be taken when delivering high-concentration inhalational agent or propofol to these patients. Ketamine or remifentanil can be useful adjuncts. Anesthetic agents should be carefully titrated, and resuscitative medications should be readily available.

It is also important to note that airway manipulation by the anesthesiologist and care team may also result in the same perturbations in PVR and SVR. Limiting the duration of laryngoscopy and awareness of the PVR and SVR are critically important. Cardiac arrest during laryngoscopy has been reported [28].

KEY POINTS: ANESTHESIA FOR AIRWAY PROCEDURES

- Communication between the otolaryngologist and the anesthesiologist is imprtant for sharing information about the planned procedure and how the patient's physiology will need to be managed
- Pulmonary vascular resistance can rapidly increase during an airway examination; pausing to oxygenate and ventilate may be required
- Patients with Fontan physiology can require direct laryngoscopy and bronchoscopy for the removal of bronchial casts

Anesthesia for laparoscopic surgery

Laparoscopic surgery in children can result in shorter length of hospital stay, better pain control, and shorter time to feeding tolerance compared with open procedures [146–149]. There are several small series reporting the safe management of laparoscopic fundoplication and gastrostomy tube placement in pediatric patients with cardiac disease [44,45,150,151], and two recent cohort studies using data from the American College of Surgeons' National Surgical Quality Improvement Program – Pediatrics ' report some benefits of laparoscopic approaches including a shorter postoperative length of stay [152,153], fewer complications [152], and fewer transfusions [153] compared with the open approach in patients with CHD. However, in patients with major or severe CHD, the laparoscopic approach was comparable to the open approach in terms of morbidity and mortality [153]. There is also evidence that the severity of the CHD correlates with morbidity and mortality after laparoscopic procedures [154]. Concerns remain regarding the effects of insufflation and pneumoperitoneum on patients with reduced cardiorespiratory reserve [154,155].

Laparoscopic surgery requires the creation of a pneumoperitoneum by insufflating carbon dioxide into the abdomen. In healthy children, insufflation to 6 and 12 mmHg results in increases in SVR and mean arterial pressure. Insufflation to 12 mmHg is also associated with a decrease in

cardiac index of 13% and a decrease in left ventricular systolic function on echocardiography. This suggests that patients with impaired cardiovascular reserve may not tolerate the change in intra-abdominal pressure. In addition, the release of the pneumoperitoneum at the end of the procedure may result in a decrease in SVR and mean arterial pressure [156]. An increase in intra-abdominal pressure during laparascopy can affect ventilation, causing atelectasis, reducing functional residual capacity, and increasing intrathoracic pressure and mean airway pressure. Absorption of CO_2 into the blood can also result in hypercarbia and an increase in PVR. Carbon dioxide embolism may also occur limiting pulmonary blood flow or resulting in paradoxical embolism [52].

Due to concerns about reflux, aspiration, and failure to thrive, patients who are between the first and second stages of SV palliation are often scheduled for laparoscopic fundoplication and gastrostomy tube placement. Insufflation-related decreases in SVR, mean arterial pressure, cardiac index, and systolic function that healthy children tolerate quite easily may result in hemodynamic instability and cardiac arrest. Increases in CO_2 absorption can lead to increases in PVR. High PVR coupled with decreased systemic pressure can result in reduced flow through a systemic-to-pulmonary shunt, shunt thrombosis, and cardiac arrest [44,157,158].

Although these serious sequelae can occur, the successful management of such patients is possible. First, insufflation pressures should be limited to 8–12 mmHg. Invasive arterial pressure monitoring is helpful for rapid recognition and treatment of hemodynamic instability with volume or vasoactive infusion to improve blood pressure or cardiac function. Arterial blood gases should be analyzed frequently, and ventilation should be adjusted based on the $PaCO_2$ [44,45]. End-tidal CO_2 is not a reliable reflection of $PaCO_2$ in SV patients undergoing laparoscopic surgery [157]. Extubation usually takes place within 24 h after the procedure, and most patients should be monitored postoperatively in an ICU [44,45]. A standardized perioperative management strategy is helpful for providing a framework for better outcomes.

Laparoscopic surgery in patients with Fontan physiology may also be a challenge. The combination of the effects of positive pressure ventilation and insufflation of the abdomen may affect the transpulmonary gradient that promotes pulmonary blood flow in the patient with Fontan physiology. The transpulmonary gradient is the difference between the central venous pressure and the left ventricular end-diastolic pressure (LVEDP). Decreases in central venous pressure that can be seen with tracheal intubation, positive pressure ventilation, and venodilation with anesthetic induction and airway management, and increases in LVEDP that can be seen with insufflation (increased systemic arterial pressure, decreased cardiac index, and decrease contractility), may significantly decrease the amount of pulmonary blood flow and systemic ventricular filling in the patient with Fontan physiology. In addition, CO_2 absorption may increase the PVR, further limiting pulmonary blood flow and systemic ventricular filling. Carbon dioxide embolus may also be poorly tolerated, and paradoxical embolus through a fenestration remains a concern [52,59].

Although challenging, laparoscopic procedures in patients with Fontan physiology have been described. Preservation of a reasonable transpulmonary gradient by augmenting preload, minimizing high ventilator pressures, preserving myocardial contractility, and keeping insufflation pressures below 12 mmHg is advised. Invasive arterial blood pressure monitoring is helpful for recognition and treatment of hemodynamic compromise [52,59]. Arterial blood gas monitoring ($PaCO_2$) may be used to guide the management of ventilation and PVR. Intraoperative transesophageal echocardiography can also help guide management. Resumption of spontaneous ventilation and extubation at the end of the procedure preserves the transpulmonary gradient, pulmonary blood flow, and cardiac output. Postoperative disposition in the ICU may be indicated.

Patients with other cardiac lesions may have derangements in physiology with laparoscopic procedures. Patients who require a higher mean arterial blood pressure for coronary perfusion include those with LVOTO, coronary abnormalities, and HCM. These patients may tolerate insufflation quite well as it increases SVR and mean arterial pressure. However, the decrease in these indices with the release in the pneumoperitoneum may result in sudden coronary insufficiency and cardiac arrest [23]. These changes should be anticipated, release of the pneumonperitoneum should be slow and gradual, and concurrent treatment of the SVR should be considered.

KEY POINTS: LAPAROSCOPIC SURGERY

- Laparoscopic procedures can be successfully performed in patients with CHD; an understanding of the patient anatomy and physiology is important
- Insufflation pressures should be limited to 8–12 mmHg in patients with CHD
- The hemodynamic effects of insufflation include an increase in systemic vascular resistance, a decrease in cardiac output, and a decrease in contractility; the release of the pneumoperitoneum has the opposite effects

Antibiotic prophylaxis for infective endocarditis

Patients with CHD are at risk for infective endocarditis. Approximately 35–60% of children with IE have CHD [159]. Rushani et al reported that the children with CHD who were found to be at higher risk of infective endocarditis include cyanotic CHD lesions, left-sided lesions, and endocardial cushion defects, and that the relative risk of developing infective endocarditis is elevated during the 6 months (the length of time it takes prosthetic material to endothelialize) after cardiac surgery and in children <3 years of age [160].

The American Heart Association (AHA) guidelines for the prevention of infective endocarditis were updated in 2007 to restrict the groups of patients for whom antibiotic

prophylaxis was indicated before invasive procedures. The revision in the guidelines were due the fact that: (1) infective endocarditis is more likely to result from random bacteremia, not bacteremia related to a medical procedure; (2) prophylaxis probably prevents an exceedingly small number of cases of infective endocarditis; (3) the risk of antibiotic-associated adverse events exceeds the benefit of prophylaxis; and (4) maintenance of good oral health is more effective at reducing the incidence of bacteremia from daily activities than prophylaxis for dental procedures is for reducing infective endocarditis. The high-risk groups who should receive antibiotic prophylaxis for infective endocarditis are displayed in Box 28.2. Antibiotic regimens for dental procedures are displayed in Table 28.6. For patients undergoing respiratory tract procedures that involve the incision of the respiratory tract mucosa, prophylaxis should be given. For patients undergoing genitourinary or gastrointestinal procedures, infective endocarditis prophylaxis is not recommended. However, if the patient already has a genitourinary or gastrointestinal tract infection, it is reasonable to include an agent that is active against enterococci. Patients with the conditions in Box 28.2 with infected skin, skin structures, or musculoskeletal tissue might also receive antibiotic coverage against staphylococci and β-hemolytic streptococci [161].

Box 28.2: Cardiac conditions associated with the highest risk of adverse outcome from endocarditis for which prophylaxis with dental procedures is reasonable

- Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
- Previous infective endocarditis
- Congenital heart disease (CHD):*
  Unrepaired cyanotic CHD, including palliative shunts and conduits
  Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure†
  Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
- Cardiac transplantation recipients who develop cardiac valvulopathy

*Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.
†Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure.
Source: Reproduced from Wilson et al [161] with permission of Wolters Kluwer.

KEY POINTS: ANTIBIOTIC PROPHYLAXIS FOR INFECTIVE ENDOCARDITIS

- Good oral hygiene is required for the prevention of infective endocarditis
- The risk of developing infective endocarditis is elevated during the 6 months after cardiac surgery; it takes 6 months for prosthetic material to endothelialize
- The 2007 AHA guidelines restricted the groups of patients for whom antibiotic prophylaxis is required before dental procedures

Table 28.6 Antibiotic regimens for dental procedures

Situation	Agent	Regimen: single dose 30–60 min before procedure	
		Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin	2 g IM or IV	50 mg/kg IM or IV
	OR		
	Cefazolin or ceftriaxone		
		1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin – oral	Cephalexin*†	2 g	50 mg/kg
	OR		
	Clindamycin		
	OR		
	Azithromycin or clarithromycin		
		600 mg	20 mg/kg
		500 mg	15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone†	1 g IM or IV	50 mg/kg IM or IV
	OR		
	Clindamycin		
		600 mg IM or IV	20 mg/kg IM or IV

* Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.
† Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.
Source: Reproduced from Wilson et al [161] with permission of Wolters Kluwer.

Perioperative planning

Multidisciplinary discussion

The care of the patient with cardiac disease undergoing a noncardiac procedure is a collaborative effort involving the cardiologist, cardiac surgeon, anesthesiologist, intensivist, pulmonologist (if applicable), and the proceduralist (surgeon, radiologist, gastroenterologist, etc.). This group should confer about perioperative planning including preprocedural and postprocedural disposition, determination of ECMO candidacy, and arrangement for ECMO availability. In addition, concerns about the risks, benefits, and timing of the procedure should take place.

Preoperative concerns

Many of these fragile patients do not tolerate a long fasting time due to concerns about hypovolemia and instability on induction of anesthesia. It has been discussed previously in this chapter that patients who are between the first and second stages of SV palliation (pre-SCPA) are at risk for instability, shunt thrombosis, and death [5,46]. Patients with LVOTO are also at a higher risk of instability and cardiac arrest on induction of anesthesia, and care should be taken to prevent hypovolemia. It is recommended that these patients are encouraged to drink clear fluids until 2 h prior to the anesthetic, and hospital admission prior to the procedure for management of the fasting period and intravenous fluids should be a serious consideration for high-risk patients. Procedures should also be scheduled early in the day to minimize fasting time. Angiotensin-converting enzyme inhibitors and diuretics should be held prior to the procedure. Antiarrhythmic medications and β-blockers should be continued.

Postoperative disposition

Before the procedure, the postoperative disposition of the patient should be planned. For high-risk physiology, an ICU bed should be requested. For other patients, a regular ward bed should suffice. High-risk patients rarely undergo outpatient procedures. If discharge home is considered, patients should be observed for at least 6–8 h after the procedure. Only if the patient is fully recovered from the effects of anesthesia, with intravascular volume status optimized, and hemodynamic parameters, respiration, and oxygen saturation at baseline without supplemental oxygen, should discharge home be allowed.

Anesthesiologist selection

These patients should be cared for by anesthesiologists who have a thorough understanding of the anatomy and physiology of CHD and who feel comfortable managing them. This may include pediatric anesthesiologists, pediatric cardiac anesthesiologists, and pediatric anesthesiologists with consultation with a pediatric cardiac anesthesiologist. Some pediatric programs have guidelines that specify which patients are assigned a pediatric cardiac anesthesiologist, such as preoperative and pre-SCPA SV patients. Institutional requirements vary widely.

Location and time of day

In general, high-risk cardiac patients should not be anesthetized in office settings or in ambulatory surgical centers where there is no access to invasive monitoring, subspecialty pediatric care, intensive care, and ECMO support. For some high-risk patients, procedures in remote locations like the gastroenterology suite may be moved to an operating room where more equipment, resources, and personnel are available. These patients should ideally be scheduled during regular daytime working hours, and as early in the day as possible.

Consent

Preoperative discussion with the parent or guardian should include the anesthetic plan, the risks associated with the procedure, and the implications of the cardiac disease. Discussion of interventions if the patient is unstable or has a cardiac arrest may be appropriate, e.g. ECMO support. The family should be given ample time to ask questions, and it is possible that multiple disciplines should be involved.

Preparedness and chance

A keen understanding of the anatomy, physiology, and "pitfalls" of each cardiac lesion is necessary. Having a plan for the management of predicted intraoperative issues, like hypotension in a shunted SV undergoing MRI or cardiac arrest during induction in a patient with Williams syndrome, is very important. The entire operating room team should be briefed on the patient's disease and potential intraoperative events prior to proceeding to the procedure room. It can also be helpful to review cognitive aids for the treatment of common dysrhythmias and events prior to induction in a patient with a history of them.

Unexpected events occur in patients with cardiac disease. Anaphylaxis can occur. Hemodynamic and physiological changes due to the operative procedure can result in cardiac arrest. Paradoxical air or CO_2 embolus can lead to coronary ischemia. A patient can experience sudden catastrophic blood loss. Tools such as cognitive aids, point-of-care ultrasound, and transesophageal echocardiography can aid in diagnosis and treatment.

Unfortunately, undiagnosed patients with cardiac disease can present for anesthetic care. It is important to take a history and listen carefully for symptoms of decreased exercise tolerance or heart failure, to review the vital signs, and to auscultate the heart and lungs. Causes of intraoperative instability should include undiagnosed cardiac disease, and an understanding of how to treat high-risk lesions can be helpful.

KEY POINTS: PERIOPERATIVE PLANNING

- Multidisciplinary planning is useful for discussing the risks and benefits for a given procedure
- ECMO candidacy should be determined before proceeding to the operating room
- Fasting times should be minimized and/or intravenous fluids should be given to avoid hypovolemia in patients with fragile physiology

CASE STUDY

In the weekly heart center multidisciplinary planning conference, a 2-month-old girl weighing 3.6 kg with hypoplastic left heart syndrome (HLHS) who is status post Norwood stage I palliation with a right modified BT shunt, is presented for an open gastrostomy due to difficulty with oral feeds and failure to thrive. In attendance are representatives from cardiology, cardiac surgery, critical care, anesthesiology, and general surgery. All agreed that although the patient had not had her superior cavopulmonary anastomosis operation, she was not growing well and met indications for gastrostomy tube placement.

The infant was born at full term and had a prenatal diagnosis of HLHS. She underwent the Norwood stage I palliation at 7 days of age after an uneventful preoperative course during which ductal patency was maintained with prostaglandin E1. The stage I palliation went well. A right ventricle to pulmonary artery conduit (Sano shunt) was planned, but coronary anatomy precluded its placement, and a right modified Blalock–Taussig shunt was placed instead. The baby had been extubated and was being cared for in the ICU. She had a heart rate of 138 bpm, a non-invasive blood pressure of 66/30 mmHg on the left arm, SpO_2 of 89%, and temperature of 37.1°C. She was NPO and receiving 5% dextrose in 0.25 normal saline at a 14.4 mL/h. Her medications included aspirin, ranitidine, and enalapril. Physical examination revealed that the lungs were clear to ausculation and a shunt murmur was present. Echocardiogram findings included minimal atrioventricular valve regurgitation and mildly depressed right ventricular function. A 22 G peripheral IV was present on the right forearm, and there was a neonatal PICC line in the right saphenous vein. After discussing the anesthesia plan and obtaining consent from the family, the patient was transported to the operating room.

Routine monitors were applied. Her heart rate was 144 bpm with normal sinus rhythm. The non-invasive blood pressure measured on the left arm was 74/40 mmHg, and the pulse oximeter reading was 93% on room air. Anesthesia was induced with midazolam 0.4 mg, fentanyl 10 µg, and low-concentration sevoflurane in a mixture of air/oxygen (FiO_2 0.5). After loss of consciousness, neuromuscular blockade was achieved with 0.4 mg of vecuronium. The trachea was intubated orally with a 3.5 cuffed endotracheal tube. After intubation, the heart rate was 130 bpm, the blood pressure was 60/25 mmHg, and the SpO_2 was 97%. The FiO_2 was decreased to 0.21, and ventilation was adjusted to an $ETCO_2$ of 45 mmHg. Sevoflurane was reduced to 0.6% inspired concentration. A left radial arterial line was placed with ultrasound guidance. Arterial blood gas results were pH 7.32/$PaCO_2$ 49 mmHg/PaO_2 46 mmHg/lactate 0.9 mmoL/base excess –5.2 with a hematocrit of 32%.

As the patient was being prepped for surgery, the heart rate increased to 155 bpm, the arterial blood pressure decreased to 44/21 mmHg, and the SpO_2 was 90% (FiO_2 of 0.21). ECG ST segments in multiple leads were unchanged from baseline. Infusions of epinephrine 0.02 µg/kg/min, vasopressin 0.02 units/kg/h, and calcium chloride 10 mg/kg/h were started via the neonatal PICC line. A packed red blood cell transfusion of 10 mL/kg was given. With these interventions, blood pressure increased to 62/30 mmHg. For the remainder of the procedure, anesthesia was maintained with 1.4% sevoflurane in air, and the patient received a total of 10 µg/kg of fentanyl (including induction). Local anesthetic infiltration of the would by the surgeon, and intravenous acetaminophen 15 mg/kg were administered for analgesia. The patient was transported back to the ICU in a stable condition where her trachea was extubated on postoperative day 1.

This case illustrates a number of points presented in this chapter. First, patients with high-risk anatomy must be identified preoperatively. In this case, a multidisciplinary group discussed the risks and benefits associated with the procedure and decided to proceed. With a preoperative oxygen saturation of 89% it could be inferred that the patient had slightly generous pulmonary blood flow. Indeed, after induction and intubation, the patient's systemic blood pressure was low, especially the diastolic pressure, placing the patient at risk for myocardial ischemia. Interventions were taken to restore a normal blood pressure including increasing PVR by decreasing the FiO_2 and reducing minute ventilation to achieve a $PaCO_2$ of approximately 45 mmHg, transfusing red blood cells to increase the hematocrit to 40–45% and using medications (epinephrine, vasopressin, calcium) to augment blood pressure. At the end of the case, the patient was transferred with her trachea intubated to the ICU, avoiding immediate postoperative hemodynamic and respiratory instability.

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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122 Alexoudis AK, Spyridonidou AG, Vogiatzaki TD, Iatrou CA. Anaesthetic implications of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Anaesthesia 2009; 64: 73–8. This paper provides a practical review of ARVD and its anesthetic implications. As ARVD is a noted cause of unexpected perioperative mortality, an understanding of the disease is warranted.

154 Chu DI, Tan JM, Mattei P, et al. Mortality and morbidity after laparoscopic surgery in children with and without congenital heart disease. J Pediatr 2017; 185: 88–93. This large cohort study using NSQIP-P data demonstrated significantly higher morbidity and mortality in children with major or severe CHD undergoing laparoscopic procedures compared with children without CHD. Of note, children with minor CHD also experienced significantly higher postoperative complications than those without CHD.

CHAPTER 29
Anesthesia for Spinal Surgery in Children

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Introduction

Procedures involving the vertebral bodies and spinal column represent one of the most common of the major orthopedic surgeries in the pediatric-aged patient. Spinal deformities requiring orthopedic surgical intervention may be the result of congenital, acquired, or traumatic conditions. They may be related to primary defects of the vertebral column (hemivertebrae), neuromuscular conditions (muscular dystrophy, cerebral palsy), or neoplastic, infectious, or therapy-related problems (surgical resection of oncological processes or radiation). Regardless of the cause, during surgical procedures to correct spinal deformities, there are several potential factors that may result in morbidity or even mortality, including associated co-morbid disease processes, patient positioning, blood loss, and neurological damage from surgical distraction of the spinal cord or instrumentation. The most recent data from the Pediatric Perioperative Cardiac Arrest (POCA) Registry in the pediatric-aged patient demonstrate that cardiovascular causes of cardiac arrest are most common (41%), with hypovolemia from blood loss and hyperkalemia from transfusion being the most common causes of cardiovascular deterioration leading to cardiac arrest [1]. These issues occurred most commonly during either craniofacial reconstruction or spinal surgery [1]. Beyond the patient with idiopathic scoliosis, the perioperative risk is further compounded by the fact that many patients presenting for spinal surgery have a higher American Society of Anethesiologists (ASA) physical classification (III versus I or II) with associated neuromuscular disorders, including muscular dystrophy or spinal muscular atrophy and pre-existing central nervous system (CNS) involvement, including cerebral palsy, seizure disorders, and meningomyelocele. Furthermore, the chronic care required by such patients may result in problems related to vascular access. To limit perioperative morbidity and mortality, these patients should be approached in a standardized fashion, which includes a preoperative evaluation for the identification of co-morbid features, design of the intraoperative anesthetic plan with attention to monitoring of neurological function with motor and somatosensory-evoked potentials, patient positioning, maintenance of normothermia, techniques to limit the need for homologous transfusion, and control of coagulation function during large volume transfusions. The postoperative regimen should include maintenance of hemodynamic and respiratory function as well as the provision of postoperative analgesia.

Surgical procedures on the pediatric spine may involve one or several vertebral levels with an incision at any level of the vertebral column (cervical, thoracic, lumbar, sacral). Further variations include the surgical approach, which may be anterior, posterior, or in the case of thoracic and lumbar spine procedures, a combined anterior–posterior (AP) approach. A majority of the procedures performed in the pediatric-aged patient involve long segment surgery on the thoracic and lumbar spine related to either neuromuscular or idiopathic scoliosis. The following chapter reviews the developmental and gross anatomy of the spine; details the more common surgical procedures; outlines preoperative assessment; discusses intraoperative anesthetic care, including methods to limit the need for homologous blood transfusion, and spinal cord monitoring; and provides options for postoperative care, including pain management.

Developmental and gross anatomy of the spine

Overview

The spine can be divided into four regions corresponding to four natural spinal curves: cervical, thoracic, lumbar, and sacral. These naturally occurring spinal curves are either kyphotic or lordotic. The "normal" spine has thoracic and sacral kyphosis with corresponding cervical and lumbar lordosis. The lordotic curvature of the cervical neck and of the

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

lumbar spine develops as a response to weight bearing. As an infant gains strength in the posterior neck muscles, the cervical spine develops a lordotic curve to support the head. At approximately 12 months of age, the lumbar spine develops a lordotic curve as a result of upright walking. Cervical and lumbar lordoses are considered secondary curves due to their development dependent on weight bearing. Their purpose is to keep the spine balanced and to reduce the workload on the posterior spinal musculature. Thoracic and sacral kyphosis are considered to be primary curves. Normal cervical lordosis ranges typically from 20° to 40° while lumbar lordosis ranges between 30° and 50°. Acceptable thoracic kyphosis curvature is 20–50°. Medically, there is a broad range of acceptable sacral curvatures since the sacral segments (S1–5) are fused in a kyphotic angle.

Abnormal curvatures of the spine include both scoliosis and excessive kyphosis [2,3]. Scoliosis is a complex three-dimensional deformity that involves changes in the coronal, sagittal, and axial alignment of the spine [2,3]. The structural changes include wedging of the vertebral body; rotation of the vertebral body to the convex side of the curve; and deformities of the posterior elements. These structural changes are greatest at the apex of the curve. The pedicle is shortened and thickened, the lamina is heavier, and the spinous process is deviated toward the concave aspect of the curve. The vertebral body becomes wedge shaped and thicker on the concave aspect of the curve as a result of the compressive forces during spinal growth. On the convex side, the vertebral body becomes thinner since it is expanded. The transverse processes approach the sagittal plane on the convex side and are closer to the concave side in the frontal plane. Rib prominence is often noticed on the convex side of the curve. This is due to the rotation of the thoracic vertebra. These spinal structural and rib alterations result in an asymmetrical thoracic cavity and may compromise respiratory function, leading to restrictive lung disease.

There are several potential etiologies for scoliosis [2,3]. Congenital scoliosis describes a failure of formation or failure of segmentation of the vertebrae. Neuromuscular scoliosis may be caused by cerebral palsy, primary muscular involvement (muscular dystrophy), myelomeningocele, poliomyelitis, and other disease affecting the muscle or nervous systems. Idiopathic scoliosis is by far the most common of all scoliosis and is classified according to age of development. Syndromes associated with development of a scoliotic spine include Marfan syndrome, neurofibromatosis, and bone dysphasia.

Abnormal kyphosis is a spinal deformity that is usually classified as either postural kyphosis, congenital kyphosis, or Scheuermann kyphosis. Postural kyphosis, otherwise known as round-back deformity, is a flexible spinal deformity that generally responds to non-operative treatments. Less common, yet more serious, is congenital kyphosis. Surgery is usually recommended with a congenital kyphosis diagnosis given its rapid rate of progression at 5–7° per year and the potential for neurological compromise related to spinal cord compression. Congenital kyphosis, similar to congenital scoliosis, is known to be caused by either a failure of part or all of the vertebral body to form or a failure of segmentation of part or all of the vertebral body.

Scheuermann kyphosis may affect the thoracic, thoracolumbar, and/or lumbar spine. Although several possible etiologies, including hormonal, nutritional, traumatic, vascular, and genetic causes, have been suggested, no definitive etiology for thoracic and thoracolumbar Scheuermann disease has been defined. Trauma is the usual causative factor of lumbar Scheuermann kyphosis. All three Scheuermann kyphosis variations clinically result in rigidity of the affected area. Using a standard radiograph, the diagnostic criteria includes ≥5° of wedging in at least three adjacent vertebrae in a lateral radiograph. Additionally, the vertebral endplates are irregular and the disk plates are narrowed. Schmorl nodes, the result of a herniated disk protruding through the weakened endplate, are often visible on x-ray. Depending on the symptoms and the degree of the curve, treatment includes both non-operative and operative modalities. A curve that is ≥75–80° generally warrants surgical intervention.

Spinal nerves and cord

There are 31 pairs of spinal nerves: eight cervical; 12 thoracic, five lumbar, five sacral, and one coccygeal. The first cervical root exits between the skull and C1 while the 8th cervical nerve root exits between C7 and T1. Thereafter, all nerve roots exit at the same level as their corresponding vertebrae. However, the nerve roots branch from the spinal cord higher than their actual exit point through the intervertebral foramen as the growth of the vertebral column exceeds that of the spinal cord [4]. Therefore, the spinal nerve travels in a caudad direction adjacent to the spinal cord prior to exiting through the vertebral foramen.

The neural tube is crucial in embryonic development of the CNS, including the spinal cord and the spinal nerves [5]. The neural tube becomes the CNS and the neural crest forms the majority of the peripheral nervous system. As the neural tube closes, the neural crest cells migrate between the neural tube and the somite. These neural crest cells form the peripheral nervous system, Schwann cells, and melanocytes. The neural tube becomes the spinal cord, the brain, and the peripheral afferent nerves and preganglionic fibers of the autonomic nervous system.

While the neural tube closes, the dorsal region separates into two halves, the alar and basal laminae, referred to as the roof and floor plates. The alar plate becomes the sensory pathways, or dorsal columns, whereas the basal plates develop into the motor pathways. The motor pathways or the ventral horn neurons develop axons that form the ventral roots. The axons of the ganglion cells form central processes, which become the dorsal roots and peripheral processes that end in sensory organelles. Motor neurons develop capabilities before sensory nerves, and autonomic nerve function is established last.

Upon gross dissection, one can identify that the motor fibers are located on the anterior side of the spinal cord with the sensory fibers on the posterior side. A group of motor fibers are referred to as ventral roots (anterior roots) while a collection of sensory fibers comprise the dorsal root (posterior root). The sensory nerves have an accumulation of cell bodies outside of the spinal cord known as the dorsal root ganglia, which contain the nuclei of the sensory (afferent) nerves. Directly lateral to the ganglia, the anterior and posterior (ventral and dorsal) nerve roots join to form a common spinal nerve surrounded by a dural sheath. This point is where the peripheral

nerve begins. Immediately after formation the nerve divides into a small dorsal (posterior) ramus and a much larger ventral (anterior) primary ramus. The posterior primary rami innervate a column of muscles on either side of the vertebral canal and a narrow strip of overlying skin. All of the other muscle and skin is supplied by the anterior primary rami, which form the cervical, brachial, lumbar, and sacral plexuses and the intercostal nerves.

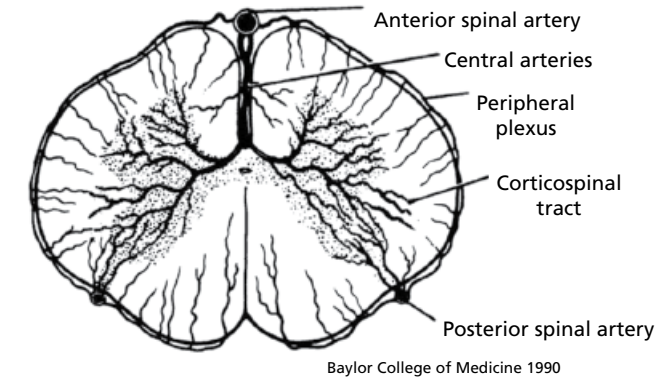
Additional gross dissection will provide a view of the multiple layers of the spinal cord. Protection of the spinal cord is provided by three layers of meninges including the dura mater, arachnoid, and pia mater. The dura mater, constructed of connective tissue, is the most external layer, gray in color, and is typically easily identified within the spinal canal. A thin subdural space separates the dura mater from the next layer, the arachnoid. This middle layer provides much of the vascular supply. Between the arachnoid layer and the deepest layer, the pia mater, lies the subarachnoid space which houses the cerebrospinal fluid (CSF). The CSF protects the spinal nerves by providing fluid which acts as a shock absorber. The pia mater is closely adherent to the spinal cord and the individual nerve roots. Similar to the arachnoid layer, the pia layer is highly vascularized, providing additional blood supply to the nerves.

The spinal cord extends from the foramen magnum to L1–4 depending on the age of the patient. With growth and development, the caudal end of the cord moves from its initial position of L3–4 in infancy to its adult level of L1. The end of the spinal cord terminates as the conus medularis and, below this, the thick flexible dural sac contains the spinal nerves collectively known as the cauda equina. Within the cauda equina, is the filum terminale, which extends from the conus medularis to the coccyx. The filum terminale acts as an anchor to keep the lower spinal cord in its normal shape and position.

Vascular components

Circulation to the spinal cord is provided by multiple arteries and arteriolar branches (Fig. 29.1) [6–9]. The anterior arterial trunk and the two posterior lateral trunks are important suppliers of blood to the cervical, thoracic, and lumbar cord. All of these arteries arise from the vertebral arteries. Radicular arteries of the spinal cord assist these longitudinal arterial pathways. There are up to 17 radicular arteries anteriorly, and as many as 25 posteriorly. The thoracic and lumbar radicular arteries are supplied by the aorta whereas the vertebral arteries supply the majority of the radicular arteries in the cervical spine. The blood supply of the thoracic spine is more tenuous than the cervical or lumbar spine, especially at the T4–9 watershed area, which is more prone to ischemic injury. The artery of Adamkiewicz provides significant circulation to the lumbar section of the spinal cord. It is usually on the left side, located at the level of T9–11. It is the largest of the radicular arteries that supply the spinal cord by anastomosing with the anterior (longitudinal) spinal artery. Injury to the artery of Adamkiewicz from trauma or during surgical procedures can result in devastating ischemia of the lower spinal cord and paraplegia.

A pair of segmental arteries, arising from the aorta, are present at every vertebral level providing blood flow to the extraspinal and intraspinal structures. The segmental arteries



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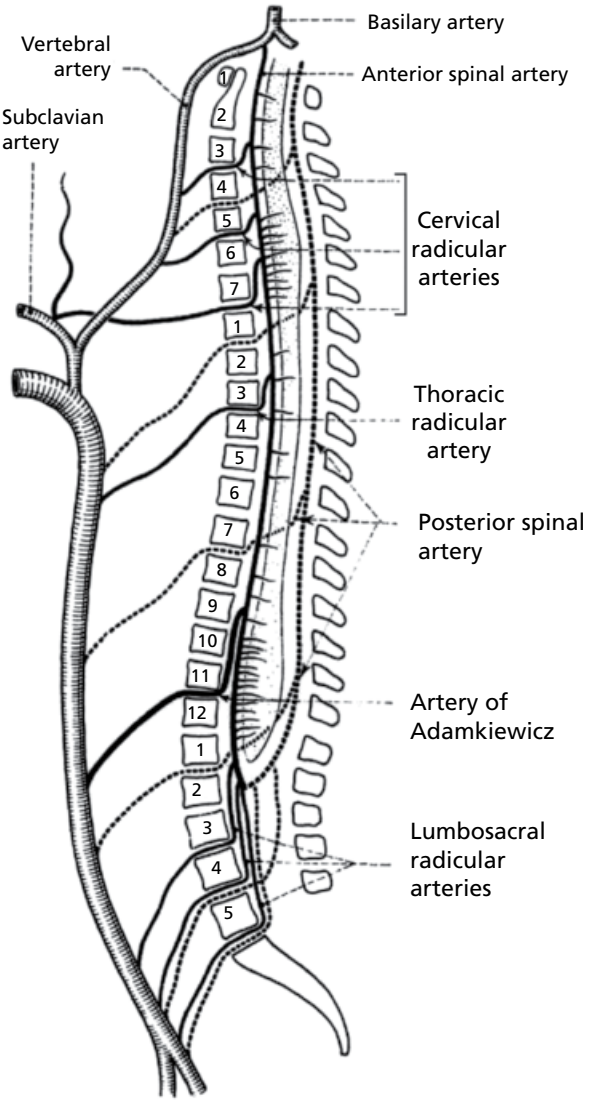


(B)

Figure 29.1 Blood supply to the spinal cord. (A) Axial view. (B) Sagittal view. See text for details. *Source*: (A) Reproduced from Mawad et al [9] with permission of American Society of Neuroradiology. Courtesy of Baylor College of Medicine 1990. (B) Reproduced from Connolly et al [8] with permission of Elsevier.

divide into many branches at the intervertebral foramen. A second network of segmental arteries lies within the spinal canal in the loose connective tissue of the extradural space. This second anastomotic network provides an alternative

pathway of arterial blood flow ensuring adequate spinal cord circulation after ligation of the segmental arteries during surgery.

Bony components

The surrounding, outer layer of the vertebrae consists of cortical bone, which is dense, solid bone tissue made of compact Haversian systems. Within the vertebra lies cancellous bone, a porous, loosely connected bone. Cancellous or trabecular bone is weaker and more susceptible to disease and loss of bone density than cortical bone. Together, these two types of bone (trabecular and cortical) form the vertebral body, which has the shape of a thin ring with an hour-glass shape. The outer cortical bone extends above and below the superior and inferior ends of the vertebrae to form rims. The pedicles, consisting of dense cortical bone surrounding a medullary canal, are two short, rounded processes that extend posteriorly from the lateral margin of the dorsal surface of the vertebral body. The anterior third of the pedicle and the vertebral body together are referred to as an anterior arch (Fig. 29.2) [10].

The posterior arch, which directly attaches laterally to the anterior arch, includes the laminae, the processes (spinous process, transverse process, superior particular process), and the posterior two-thirds of the pedicles. The laminae are two flat plates of bone extending medially from the pedicles to form the posterior wall of the vertebral foramen. The part of the lamina located between the superior and inferior articular processes is called the pars interarticularis. Spondylolysis is a term used to refer to a defect in the pars, most commonly at the L5 level.

The three spinal processes are projections of bony tissue that are the insertion site for tendons and ligaments. Specifically, two inferior and two superior articular processes extend from the junction of the pedicles and laminae. These inferior articular processes meet with the superior articular processes to form facet joints. The facet joints are surrounded by a capsular membrane containing synovial fluid that, along with the intervertebral disk, provides mobility of the spine. Additionally, two transverse processes (one on each side of the pedicles), extend laterally and provide an attachment point for ligaments and tendons. A single spinous process arises posteriorly from the junction of the two laminae, again providing an attachment point for ligaments and tendons and serving as a lever for motion of the vertebrae.

Additional bony components include the endplate and apophyseal ring. Endplates are located superiorly and inferiorly within the rim of each vertebral body. Each endplate consists of a cartilaginous external layer and a bony internal layer and provides vascular nutrition to the avascular intervertebral disk. These endplates also serve as a growth ring, predominately in height, for the vertebral body. The endplates are closed by 17–18 years of age. The apophyge ring of cortical bone surrounds the vertebral body below portions of the endplate. Surgically, it is important to leave as much of the bony endplate intact as possible, thus preventing subsidence of the device into the soft cancellous bone. The endplate is well vascularized, offering an excellent site for a fusion graft. The apophyseal ring is an ideal site for interbody fusion devices.

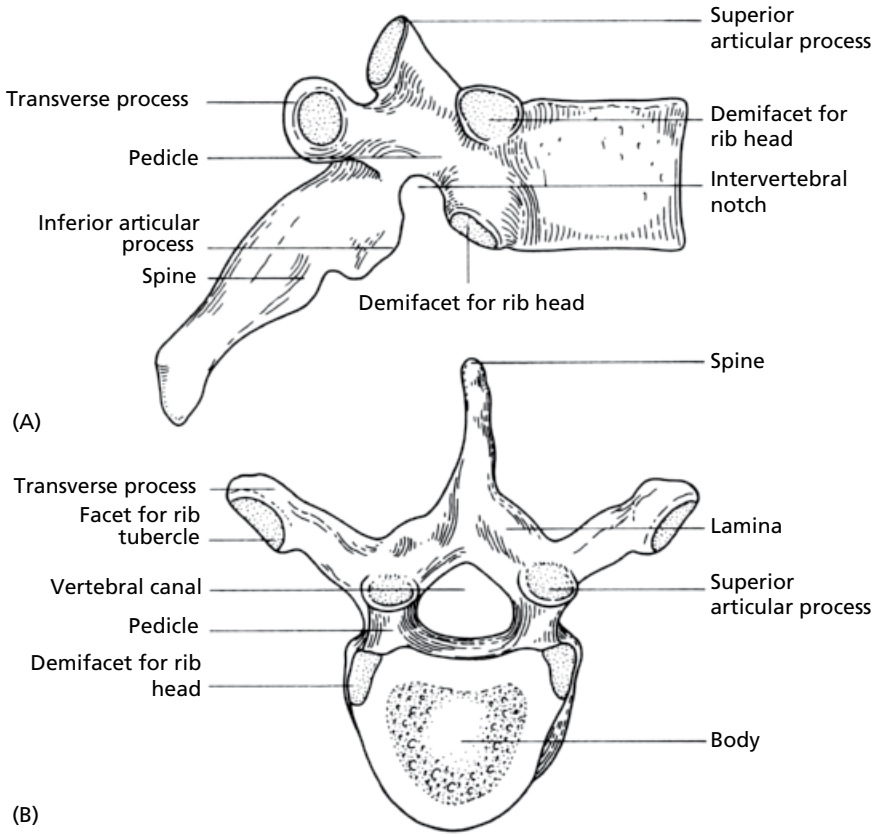


Figure 29.2 A "typical" thoracic vertebra. (A) Lateral aspect. (B) Superior aspect. *Source*: Reproduced from Ellis and Mahadevan [132] with permission of John Wiley and Sons.

KEY POINTS: DEVELOPMENTAL AND GROSS ANATOMY OF THE SPINE

- Lumbar lordosis of the spine develops at about 12 months of age due to upright walking, cervical lordosis starts developing by about 4 years and is complete by adolescence
- The three types of scoliosis are congenital, neuromuscular, and idiopathic
- Motor fibers are on the anterior side of the spinal cord, sensory fibers are posterior
- The blood supply of the thoracic spine is more tenuous than the cervical or lumbar spine, especially at the T4–9 watershed area
- The artery of Adamkiewicz at T9–11 provides significant circulation to the lumbar section of the spinal cord

Surgical procedures on the pediatric spine

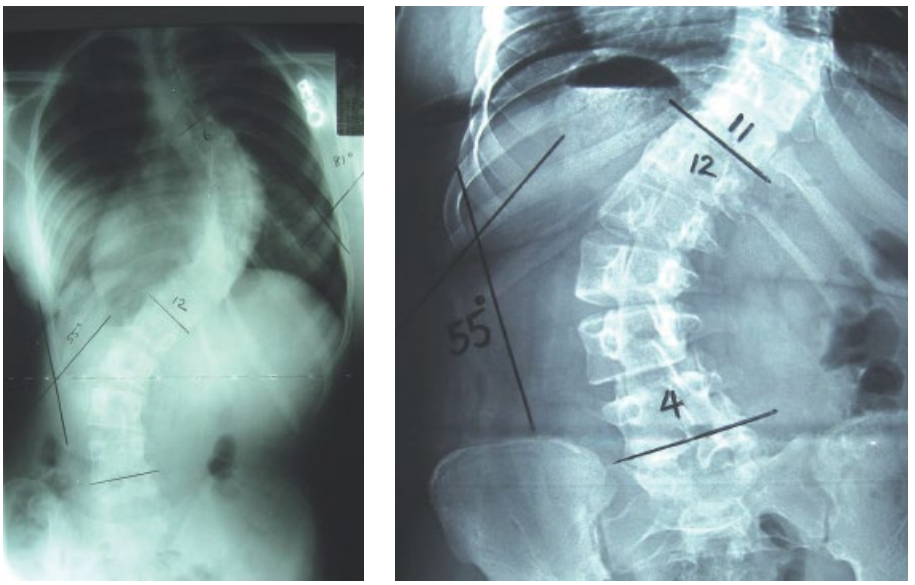
Scoliosis is a lateral and rotational deformity of the vertebral column. Its etiology is most commonly idiopathic (60–70%), neuromuscular, or related to congenital bony deformities (Table 29.1) [11–14]. Adolescent idiopathic scoliosis has an incidence of 1–3% in children aged 10–16 years. Most of these patients can be managed with conservative therapy, e.g. observation or bracing. Congenital scoliosis is diagnosed at birth and results from vertebral or costal maldevelopment, and occurs in approximately one of every 1000 live births. Neuromuscular scoliosis results from a number of disorders, with muscular dystrophy and cerebral palsy among the most common etiologies [14].

Other less common etiologies for scoliosis include post-traumatic injuries and therapy-related ones (previous surgical procedure or radiation for oncological diseases). Idiopathic scoliosis is more common in females with a female:male ratio of 3–4:1. The timing or need for surgery is based on the Cobb angle. The Cobb angle is calculated by identification of the most affected vertebra in the curve also known as the apical vertebra (Fig. 29.3). The apical vertebra is the vertebral body that has the greatest rotation and displacement from its ideal alignment. The top and bottom vertebrae of the curved or scoliotic segment are identified. These vertebrae have the most tilt, but the least amount of rotation and displacement. They are located above and below the apical vertebra, respectively. On the radiograph, a line is drawn along the edge of these two vertebrae and extended out. On the top vertebrae, the line starts on the top, is drawn along the top edge, and slopes downward according to the angle of the vertebra. On the bottom vertebra, the line is drawn along the bottom edge in an upward direction. Perpendicular lines are then drawn from both lines so that they meet each other at the level of the apical vertebra. The Cobb angle is the angle formed by these two intersecting perpendicular lines. Treatment modalities are based on the Cobb angle. If the Cobb angle is ≤15°, follow-up visits are scheduled to monitor the progression of the scoliosis. Bracing is generally indicated for a Cobb angle of 20–40°, while surgical intervention is indicated when the Cobb angle

Table 29.1 Scoliosis classification and associated conditions

Scoliosis classification	Associated conditions
Idiopathic	Infantile (0–3 years) Juvenile (4–10 years) Adolescent (>10 years)
Congenital	Bony deformity Neural tube defects
Neuromuscular	Cerebral palsy Poliomyelitis Muscular dystrophy Spinal muscular atrophy Neurofibromatosis

Source: Reproduced from Glover and Carling [14] with permission of Elsevier.



(A) (B)

Figure 29.3 Radiographs showing the determination of the Cobb angle.

is greater than 40° in the lumbar spine or greater than 50° in the thoracic spine. Although some correction of the curve may be feasible, the primary goal of surgical treatment is to stop progression of the curve. Without intervention, progression of the scoliosis will invariably lead to physical deformity with a negative self-image, physical pain, functional limitations, and cardiopulmonary dysfunction. The latter includes the development of progressive restrictive lung disease and respiratory insufficiency which may result in severe morbidity (chronic hypoxemia and hypercarbia) and eventual death from cor pulmonale.

Decision regarding the surgical approach and surgical therapy include the age of the patient, the underlying cause of the spinal deformity, and the severity of the curve. A patient with neuromuscular scoliosis may be surgically treated with a posterior procedure or may require an anterior spinal release followed by posterior fusion if the deformity is more severe to gain better correction. Although idiopathic scoliosis has been most commonly treated by a posterior approach (Fig. 29.4), in some centers an anterior approach with instrumentation is being used for idiopathic scoliosis (Fig. 29.5) [15,16]. The underlying diagnosis, curve magnitude, and the patient's age are all important factors when determining the type of procedure.

One issue that affects the timing of surgery is that the fused segments will no longer grow. As such, complete surgical correction with fusion is undertaken only when spinal growth is nearly complete, generally at ≥12–14 years of age. When surgical treatment is necessary for the juvenile idiopathic scoliosis patient, non-segmental posterior spinal instrumentation without fusion is used (i.e. growing rods) (Fig. 29.6A) [17]. This approach serves to allow correction of the scoliosis without decortication of bone and fusion of numerous vertebral segments. Therefore, normal growth will continue. During the growing rod procedure, specific vertebral levels are decorticated and fused in an attempt to allow for correction of the curvature with normal growth of the remaining spine. In general, the convex sides are decorticated and fused so that the concave sides straighten out with the ensuring growth of the vertebral bodies. Patients undergoing growing rod procedures will require repeated operative intervention at 4–6-month intervals to adjust the growing rods (Fig. 29.6B) [17]. To obviate the need for repeated procedures for adjustment and lengthening of the growing rods, which is performed under general anesthesia, new instrumentation with magnetic rods, otherwise known as magnet-driven growth rods (Fig. 29.7A, B) [17]. These devices allow lengthening of the rod with the child awake without a skin incision and the need for general anesthesia (Fig. 29.7C) [17–19]. Following periodic adjustments of the growing rods, the definitive posterior spinal fusion procedure with instrumentation is performed once growth of the vertebral column has ceased. This approach is used most commonly in patients with bony congenital anomalies or muscular dystrophies that result in the early onset (birth to 10 years of age) of scoliosis.

Another recent approach for scoliosis surgery in growing children is the vertical expandable prosthetic titanium rib (VEPTR) (Fig. 29.8) [17]. This system was originally designed to treat thoracic insufficiency syndrome caused by congenital spine and chest wall deformities, such as missing ribs in vertebral, anal, cardiac, tracheoesophageal renal and limb (VACTERL) syndrome, or Jeune syndrome. The VEPTR is positioned around the ribs, and can be expanded during subsequent less invasive surgical procedures. The VEPTR can also correct associated scoliosis as the device is expanded. A second VEPTR device may be attached to the spine, or pelvis, depending on the deformity.

Anterior surgery for scoliosis

Although idiopathic scoliosis has generally been treated via a posterior approach with posterior spinal fusion, anterior approaches have been developed more recently [15,16]. Advocates of the anterior approach believe that successful correction of the curve can be achieved while limiting the extent of the fusion, thereby maintaining flexibility and mobility of the spine. The approach addresses the higher curve and depends on the natural regression of the lower curve which is generally compensatory for the higher pathological curve. This approach is usually used for patients with idiopathic, non-neuromuscular scoliosis. The anterior approach can be performed through an open standard incision (thoracotomy)

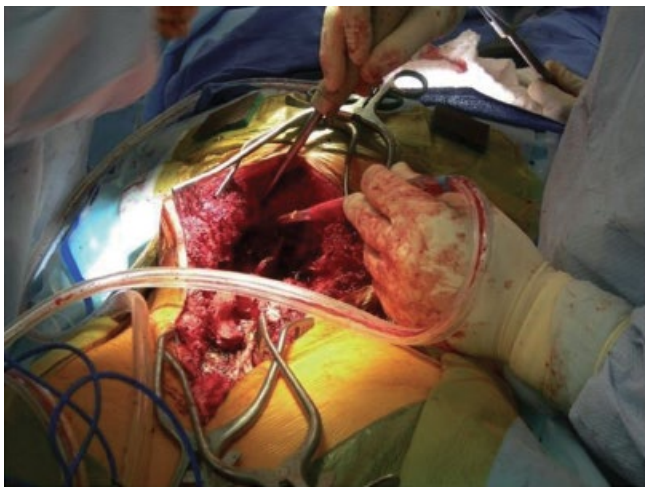


Figure 29.4 Standard long vertical posterior incision for instrumentation and correction of scoliosis.

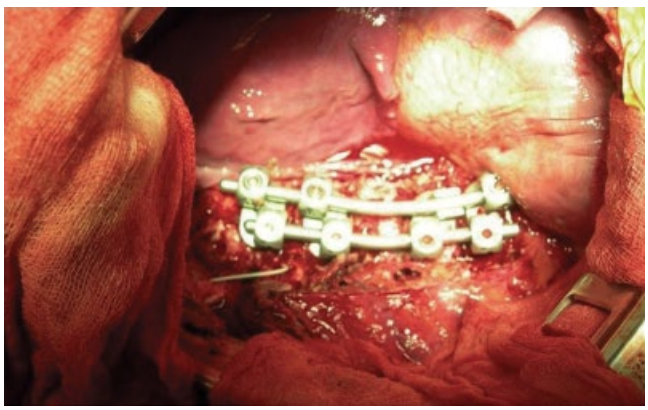
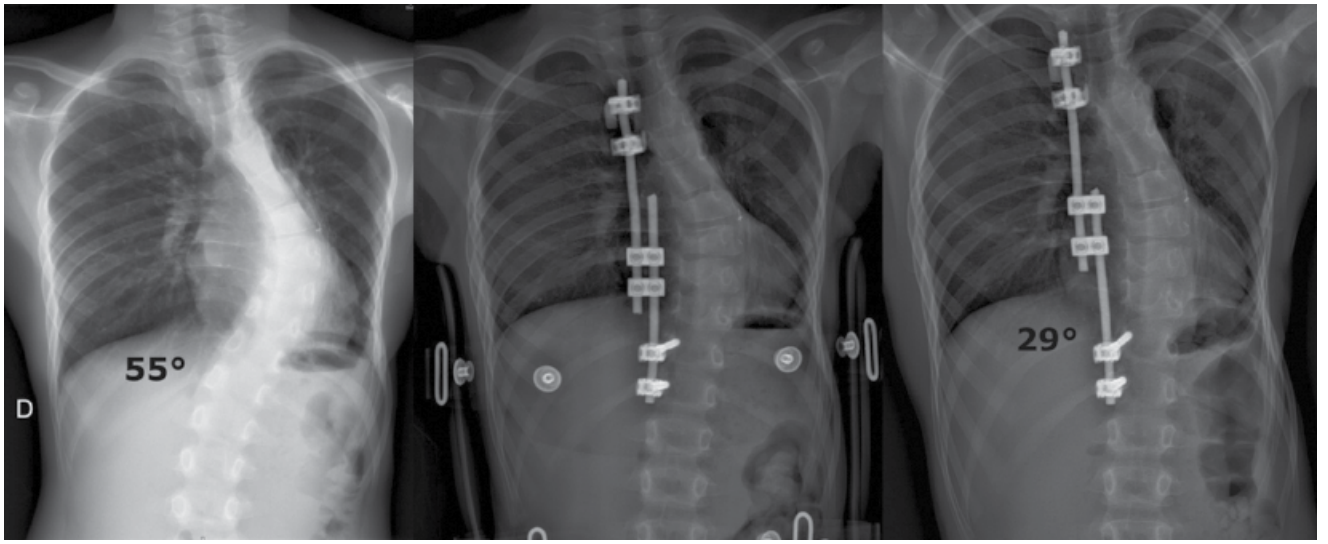


Figure 29.5 Anterior approach for surgical exposure and instrumentation in the treatment of scoliosis. With the use of one-lung ventilation, the surgeon's access to the anterolateral aspect of the thoracic and lumbar vertebral bodies can be facilitated.



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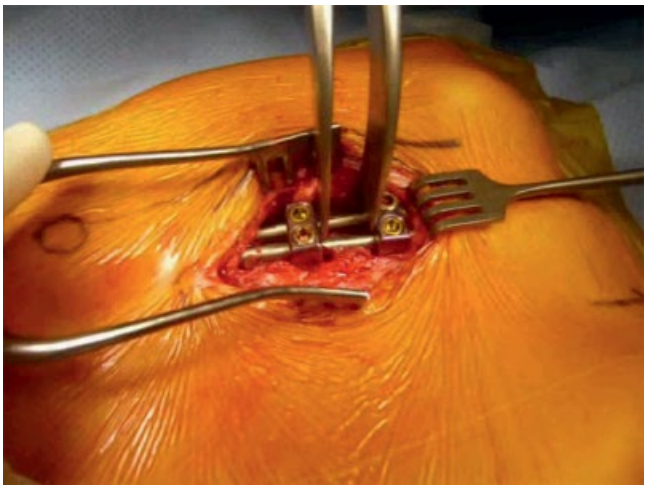


(B)

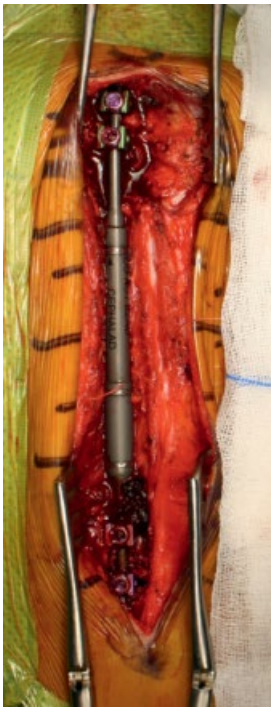
Figure 29.6 (A) Juvenile scoliosis after resection of a tumor in the chest wall; since the brace did not stop the progression and deformed the thorax, it was replaced with growing rods. (B) Surgical lengthening of the growing rod. *Source*: Reproduced from Cunin [17] with permission of Elsevier.

or more recently via a mini-thoracotomy using minimally invasive thoracoscopic techniques.

For the anterior approach, the patient is placed in the lateral decubitus position with the operating table flexed. The upper arm is moved forward and rotated away from the posterior portion of the spine. An axillary roll is placed to minimize pressure on the brachial plexus and the vasculature structures. Depending on the level of scoliosis (thoracic versus lumbar), entry into the thoracic cavity may be required. When the thoracic cavity is entered, the use of one-lung ventilation (OLV) may greatly facilitate the surgeon's access to the anterior spine for open procedures and is generally routinely used and necessary during minimally invasive approaches. Following skin incision, access to the spine is achieved through the bed of the convex 5th rib for visualization of T5–12, or via the bed of the 10th rib for access to the thoracolumbar spine. The initial incision extends anteriorly to the lateral border of the rectus sheath with its length determined by the number of levels required to be exposed. The rib to be excised corresponds to the most superior vertebral body requiring exposure. For example, with a T6–12 anterior fusion, the 5th rib is excised. The costal cartilage is split anteriorly which can later serve as a landmark for closure. Once the spine is exposed, retractors are positioned to protect the lung tissue and peritoneum. The surgeon can now access the vertebral disk or vertebral body with the caveat that segmental vertebral vessels (artery and vein) are present at each level. When necessary, these vessels can be ligated as vascular compromise of the spinal cord after ligation is uncommon, even if several segmental vessels are ligated.

Video-assisted thoracoscopic surgery

Video-assisted thoracoscopic surgery (VATS) techniques have also been incorporated into the surgical treatment of scoliosis. As with other types of VATS procedures, specialized surgical equipment is necessary including the scope, light sources, cameras, flexible portals, monitors, and specific instrumentation. For the successful completion of such procedures, OLV is generally mandatory to allow for adequate visualization of the spine (see section "Intraoperative anesthetic care"). Contraindications to this approach include the inability to



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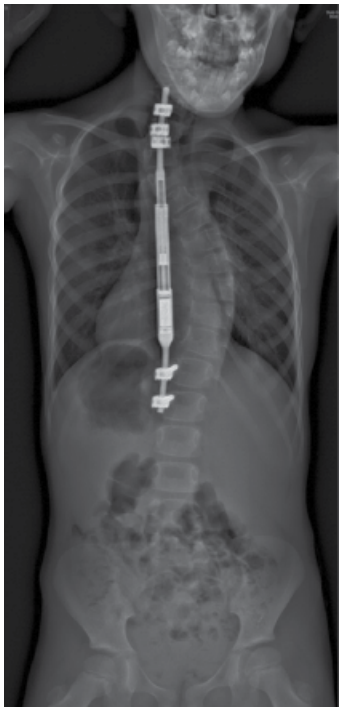
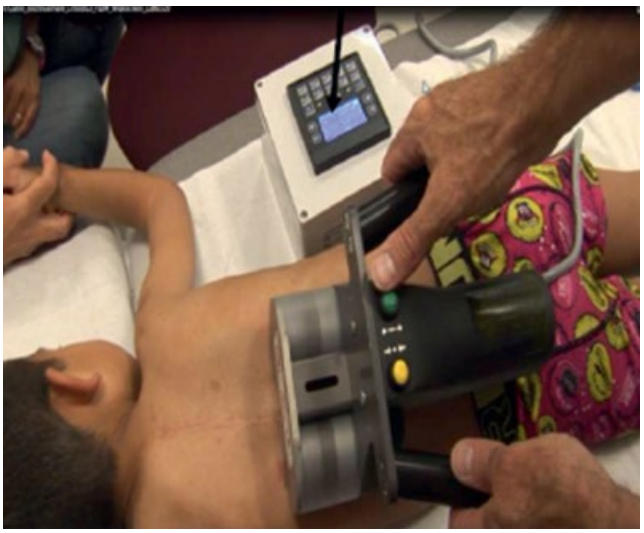


(B)

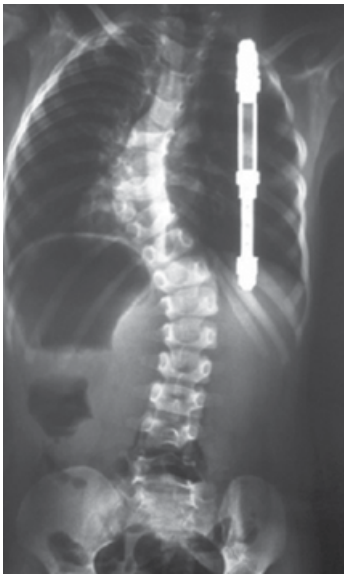


(C)

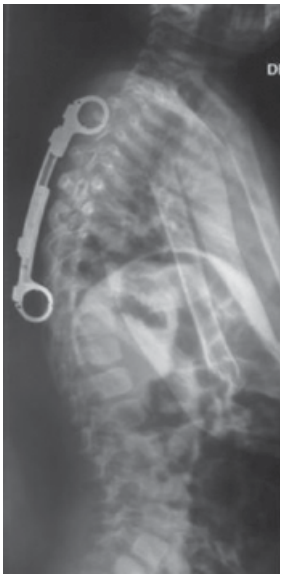
Figure 29.7 (A) Implantation of a Magec® magnetic growing rod. (B) Radiograph of Magec rod for scoliosis secondary to neurofibromatosis. (C) Lengthening of a Magec rod in the office without general anesthesia; the amount of lengthening is controlled externally. *Source*: Reproduced from Cunin [17] with permission of Elsevier.

tolerate OLV, severe respiratory insufficiency, high airway pressures with positive pressure ventilation, and previous thoracotomy which may result in adhesions, thereby limiting surgical access and the ability to obtain lung deflation during OLV. Positioning and preparation are generally the same as for the open, anterior approach. The surgical landmarks for trocar and instrument placement include the scapular border, 12th rib, and iliac crest.

The first portal is placed at or near the T6–7 interspace in the posterior axillary line. After surgical incision, dissection continues with electrocautery through the intercostal muscle to enter the thoracic cavity. Once adequate lung deflation is



(A)



(B)

Figure 29.8 (A) Posterior–anterior and (B) lateral view of a vertical expandable prosthetic titanium rib (VEPTR) system. See text for details. *Source*: Reproduced from Cunin [17] with permission of Elsevier.

ensured, flexible ports are inserted in the intercostal spaces with a trocar. A blunt-tipped needle is placed adjacent to the thoracic spine and a roentgenogram is obtained to confirm the disk spaces intraoperatively. The parietal pleura is completely resected without ligation of the segmental thoracic vessels. The disks and endplates are then removed. After the necessary discectomies are completed, rib grafts are harvested through the portal sites. Prior to closure, a chest tube is placed through the most posterior inferior portal. The pleura may be closed or left open. The chest tube is connected to water seal and the anesthesiologist tests for an air leak in the reinflated lung. Potential perioperative issues include bleeding, damage to the lung tissue, dural tears, lymphatic injury, and sympathetic dysfunction on the operative side. If hemostasis cannot be obtained or visualization is not optimal, conversion to an open anterior approach may be required. Postoperatively, pulmonary problems may occur within the deflated lung leading to recurrent atelectasis.

Posterior surgery for scoliosis

Over the past 20 years, the surgical approach to scoliosis has changed with advancements in segmental posterior spinal instrumentation. As such, correction of both sagittal and coronal plane spinal deformities has improved compared with older systems such as the Harrington rods. The posterior surgical approach with instrumentation uses the spinous processes, the pedicles, the facets, and the laminae to control the alignment of the vertebral bodies with laminar hooks, pedicle hooks, pedicle screws, facet screws, and wires.

For the classic posterior approach, the patient is placed prone on an appropriate spinal frame with the abdomen hanging freely to avoid compression of the intra-abdominal portion of the inferior vena cava. This prevents increased intra-abdominal pressure thereby decreasing venous pressure with decompression of the epidural veins to limit venous bleeding. It also prevents an increase in intra-abdomianl

pressure that may interfere with diaphragmatic movement. Traditionally a Hall frame or more recently a Jackson table is used to support the patient in this position (Fig. 29.9). The patient's face should be well padded without pressure on the eyes (see later for an expanded discussion of postoperative visual compromise) (Fig. 29.10). The patient's back is completely draped with exposure to the entire spine and the iliac crest for harvesting of the bone graft. A midline incision over the spinous processes is made, followed by splitting the apophysis and subperiosteal dissection to expose the spine laterally to the transverse processes. Placement of a blunt needle is followed by confirmation of the appropriate vertebral body using either fluoroscopy or plain radiography. After a facetectomy and wide posterior release at each level, the instrumentation is placed. The surgeon inserts pedicle hooks, pedicle screws, laminar hooks, and sublaminar wires at the vertebral levels requiring surgical correction of the scoliosis. The first rod is placed on the concave side of the curve and rotated to correct the spinal deformity. This represents a key moment during the instrumentation procedure as alterations in spinal cord perfusion may occur during correction of the curvature with distraction of the spinal cord and its associated perfusion. Changes during neuromonitoring may occur at any point during the surgical procedure, but are most common during this portion of the surgery. Once correction is maintained with the first rod, the second rod is placed. Cross-links are added, allowing an increase in torsional stiffness of the rod's construct. Decortication of the posterior elements prepares the spine for fusion. The placement of the bone graft completes the procedure and is followed by a layered closure of the muscles, fascia, and skin.

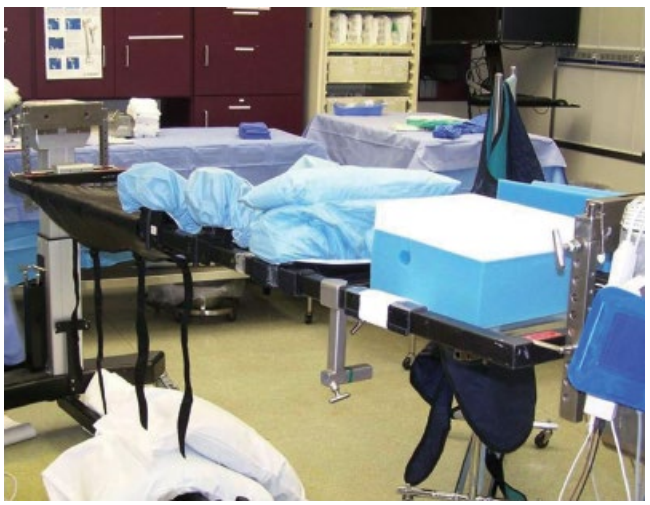


Figure 29.9 Jackson table for positioning of patients in the prone position for posterior spinal fusion.

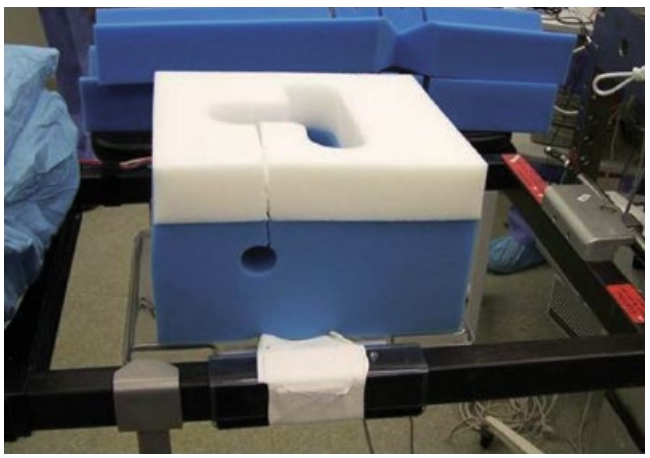


Figure 29.10 Specialized cushion or pillow used for positioning on the Jackson table. When applied appropriately, the pillow should eliminate pressure points on the face or eyes. The endotracheal tube can be brought out the side hole of the pillow or through the bottom of the pillow.

KEY POINTS: SURGICAL PROCEDURES ON THE PEDIATRIC SPINE

- Surgical intervention is indicated when the Cobb angle is greater than 40° in the lumbar spine or 50° in the thoracic spine
- Special techniques for the growing spine are used before skeletal maturity, i.e. growing rods, magnetic adjustment rods, and vertical expandable titanium ribs
- An anterior approach to the spine may correct the curve while limiting the extent of the fusion, thereby maintaining flexibility and mobility
- Open thoracotomy or video-assisted thoracoscopic approaches can be used for anterior spine fusion
- Posterior spine fusion is the most common approach, and advances in instrumentation have led to improved outcomes

Preoperative and intraoperative care

Preoperative evaluation

The initial step in the perioperative care of pediatric patients presenting for spinal surgery is the preoperative evaluation to identify co-morbid features that may impact their perioperative care and to maximize the patient's preoperative state in the hopes of preventing perioperative complications. Of primary importance when evaluating children and adolescents for spine surgery is the impact of the disease process on airway management and cervical spine stability. Cervical spine stability is the spine's ability to resist displacement under normal physiological loads. Patients presenting for cervical spine surgery, especially the trauma patient, should be assumed to have an unstable cervical spine or the potential for subluxation during flexion or extension of the neck, which can result in spinal cord compromise [20,21]. Cervical spine issues and any resultant instability may be related to a traumatic event or a congenital syndrome with cervical spine involvement such as trisomy 21, achondroplasia, or other more uncommon craniofacial syndromes, such as Pfeiffer, Aperts, or Crouzon syndrome [22–25]. Subluxation and upper cervical intervertebral fusions have been reported in 30% of patients with Pfeiffer syndrome, and odontoid hypoplasia with the risk of C1–2 subluxation has been reported in patients with Crouzon syndrome and the mucopolysaccharidoses [23,24]. Ligamentous laxity and the potential for cervical subluxation is also present in patients with trisomy 21 [25].

Patients with achondroplasia may have associated stenosis of the foramen magnum, which may also impact airway management strategies and intraoperative positioning. Foramen magnum stenosis results from hypertrophy of the bony margins of the foramen magnum and can lead to narrowing of the cervical spinal canal with compression of the cervical spinal cord or medulla. In children with achondroplasia, who manifest neurological or respiratory symptoms related to foramen magnum stenosis, the diameter of the foramen magnum has been shown to be more than 3 standard deviations from the mean for age-matched controls of normal stature.

Even in the absence of associated syndromes, cervical spine involvement from scoliosis or kyphosis may limit normal cervical spine movement thereby leading to difficulties with tracheal intubation or positioning for the subsequent surgical procedure. Given these issues, as time permits, an evaluation of the cervical spine may be indicated as part of the preoperative work-up in such patients. Preoperative evaluation for cervical spine abnormalities includes a physical examination with questioning regarding the presence of neck pain and an evaluation of neck movement (flexion, extension, and lateral rotation). This is supplemented with radiograph examination (flexion/extension films) or computed tomography scanning when historical or clinical findings are noted. If potential issues are identified during the evaluation process, various approaches to tracheal intubation are available, which can be performed in either the anesthetized, sedated, or awake state [20,21].

Patients with craniofacial syndromes may also have midface anatomical issues that impact on airway management, including ease of bag-valve-mask ventilation and tracheal intubation [22,23]. Common features of many of the craniofacial syndromes include micrognathia, microstomia, midface (maxillary) hypoplasia, and lip/palatal abnormalities. Glossal hypertrophy may be present in neuromuscular conditions or in association with trisomy 21. Although beyond the scope of this chapter, identification of potential difficulties with direct laryngoscopy and tracheal intubation should prompt alternative approaches to the airway including indirect videolaryngoscopy or fiberoptic techniques. Additionally, there should be ready access to the equipment required for management of a difficult airway including various sizes of laryngeal mask airways or a similar type of supraglottic device. Chapter 16 presents a thorough discussion of management of the difficult pediatric airway.

Another situation faced by the anesthesiologist that impacts perioperative airway management is the patient with an *in situ* tracheostomy requiring airway management and prone positioning for spinal surgery. Although there have been some suggestions regarding strategies to manage a tracheostomy in the perioperative period, including use of an existing tracheostomy, exchange to a cuffed tracheostomy, placement of an endotracheal tube through the tracheostomy stoma, or use of standard orotracheal intubation, there are no definitive consensus guidelines available [26]. Although the presence of a tracheostomy initially may facilitate airway management, positioning and other intraoperative issues may affect airway patency. Most importantly, if a standard tracheostomy tube is used, given its rigidity, traction from the anesthesia circuit may cause posterior displacement of its lumen with occlusion against the tracheal wall, especially in patients with scoliosis or kyphosis, which may affect airway anatomy and integrity [27,28]. Such problems can generally be avoided by exchanging the tracheostomy tube for an appropriately sized armored tracheal tube. Use of the armored tube may avoid positional changes related to traction on the tube due to the weight of the anesthesia circuit. After exchange for the tracheostomy tube, the armored tracheal tube can be secured in place using a suture to the neck or the anterior chest wall. Given that the tracheostomy site enters the trachea closer to the carina than standard tracheal intubation techniques, careful placement and auscultation of bilateral breath sounds is necessary to avoid endobronchial intubation. Appropriate positioning of the tracheal tube should be confirmed in the neutral position and with the neck flexed.

Following the evaluation of the airway and cervical spine, the preoperative examination follows a sequential organ system approach. Co-morbidities of the central and peripheral nervous and muscular systems may be a frequent feature in the pediatric patient presenting for spine surgery. These may include cerebral palsy, seizure disorders, static encephalopathy, or associated neuromuscular conditions. The preoperative assessment and documentation of neurological and neuromuscular function will help in the identification of perioperative injuries related to the surgical procedure or positioning and aid in differentiating these from pre-existing conditions. During the preoperative evaluation, therapeutic serum anticonvulsant concentrations should be documented and the parents instructed to give the usual anticonvulsant medications on the morning of surgery regardless of other nil per os instructions [29]. If morning doses are missed, these can be given in the preoperative holding area prior to anesthetic care. Although many of the newer medications have long half-lives, ongoing perioperative dosing is recommended to maintain therapeutic plasma concentrations. Intraoperatively, conversion to intravenous administration is available for several anticonvulsant medications so that therapeutic levels are maintained perioperatively. Postoperatively, dosing can be switched back to the oral route when the patient's status permits or alternative routes of delivery (intravenous or rectal) may be used. Chronic anticonvulsant therapy leads to the induction of hepatic enzymes thereby altering the pharmacokinetics and pharmacodynamics of several medications, including neuromuscular blocking agents (NMBAs). Increasing the intraoperative doses of NMBAs and certain intravenous anesthetic induction agents may be necessary with concomitant anticonvulsant therapy [30–32]. A second factor affecting dosing of NMBAs is the fact that many anticonvulsant agents have weak neuromuscular blocking properties, leading to the upregulation of acetylcholine receptors. Therefore, increased dosing requirements may be seen even for agents such as *cis*-atracurium which are not dependent on hepatic metabolism for their elimination.

Developmental delay, visual impairment, and hearing disturbances may present a major challenge in the communication with and assessment of the patient during the perioperative period. Some degree of intellectual impairment is noted in 30–50% of patients with Duchenne muscular dystrophy and in a greater percentage of patients with cerebral palsy and other syndromic conditions. Many of these patients will have heightened perioperative anxiety and fear which may be mitigated by premedication or parental presence

during the induction phase. In addition to limiting preoperative cooperation and understanding, these issues may be particularly problematic during the postoperative period when pain assessment may be difficult (see later).

Depending on the degree of scoliosis and the presence of co-morbid disease processes, there may be some degree of preoperative compromise of respiratory function from restrictive lung disease. Progressive scoliosis results in a restrictive defect with a decrease in the vital capacity, total lung capacity, and forced expiratory volume with no change in residual volume. The decrease is greater in patients with congenital or infantile scoliosis when compared with adolescent scoliosis [33,34]. The severity of respiratory impairment is related to the angle of the scoliosis, the number of vertebral levels involved, the cephalad level of the scoliosis, and the loss of the normal thoracic kyphosis. Respiratory compromise is worse in younger patients and those with infantile or congenital scoliosis. Muirhead and Conner noted that there was a moderate or severe ventilation defect (40–59% predicted for age) in 14 of 41 children with either infantile or congenital scoliosis compared with only four of the 51 adolescents with idiopathic scoliosis [33]. However, unlike the adult population, the impact of moderate degrees of respiratory compromise is generally limited. In the previous study, there was no requirement for postoperative respiratory support in patients with a preoperative vital capacity ≥40% predicted for age. The effect of the surgical procedure on postoperative respiratory function is dependent on the surgical approach and the type of surgery. Surgical procedures involving the thorax (anterior spinal fusion) lead to a reduction in lung function at 3 months with a return to preoperative values by 2 years, while the standard posterior approach leads to improved respiratory function at both 3 months and 2 years [34,35].

Of even greater concern for the preoperative evaluation of patients with neuromuscular disorders is the ability to determine the degree of respiratory compromise that contraindicates scoliosis surgery. Given its greater impact on respiratory function, this need is greater if an anterior approach is chosen when compared to a standard posterior approach. In the adult population, it has been suggested that prolonged postoperative mechanical ventilation is likely to be required in patients with a reduction of the forced vital capacity (FVC) or the forced expiratory volume in 1 second (FEV_1) to less than 40% predicted. However, as there are generally fewer co-morbid features in children, such as associated cardiac disease, when compared with adults, it is likely that the same criteria used to predict postoperative respiratory function in adults should not necessarily be applied to pediatric-aged patients. The lack of predictive power of preoperative pulmonary function testing in children has been previously demonstrated in a cohort of pediatric oncology patients requiring repeated thoracotomy for excision of metastatic disease [36]. After 32 thoracotomies in 19 pediatric oncology patients, there was a consistent decrease in pulmonary function test (PFT) values with a decrease in the FVC (% predicted for age) from 68 ± 3.6% to 60 ± 2.4% ($p < 0.01$) and the FEV_1 from 69 ± 4.2% to 60 ± 3.8% ($p < 0.01$); there was no permanent morbidity noted even in patients with decreased preoperative respiratory function. Five of the patients had severe preoperative decreases in pulmonary function (≤40% predicted for age). Although the incidence of morbidity defined as postoperative ventilation, supplemental oxygen for more than 12 h, or persistent air leak was three of five in this group versus three of 20 in patients with mild or moderate lung disease (PFT 60–80% predicted for age), there was no postoperative mortality and no need for prolonged mechanical ventilation. Similar data were also reported in a cohort of 45 adolescents with Duchenne muscular dystrophy and compromised respiratory function [37]. Twenty patients had a preoperative FVC ≤30% predicted for age. Despite the low FVC, there was no statistically significant difference in several postoperative variables including the duration of postoperative tracheal intubation, duration of bi-level positive airway pressure (BiPAP) support, total time with ventilator assistance, and inpatient stay. However, there were significant cardiorespiratory complications noted in both groups demonstrating that this is a high-risk population with the potential for perioperative complications. Five patients (25%) with an FVC ≤30% had complications, including adult respiratory distress syndrome (ARDS), respiratory tract infections, and the need for a tracheostomy, while four (16%) with a preoperative FVC ≥30% also had complications. The one death in the cohort was in a patient with an FVC of 18% who initially had an uncomplicated postoperative course, but went on to develop ARDS.

Although the majority of patients presenting for spinal surgery without co-morbid conditions (idiopathic scoliosis) will not require postoperative mechanical ventilation, factors such as co-morbid conditions, intraoperative blood loss, and surgical duration may mandate the option of providing a short period of postoperative mechanical ventilation to ensure patient safety. In addition to respiratory function, airway issues may necessitate postoperative mechanical ventilation. Prolonged procedures in the prone position may result in airway or lingual edema thereby necessitating postoperative tracheal intubation. Almenrader and Patel reviewed their 18-month experience in a cohort of 42 patients with non-idiopathic scoliosis [38]. In their series, 23.8% of patients required postoperative mechanical ventilation. Consistent with the data of Harper et al [37], they noted that patients with Duchenne muscular dystrophy and those with a preoperative FVC ≤30% were more likely to require postoperative respiratory support (40% in their series). The authors suggested the use of non-invasive ventilator techniques to ease the transition from mechanical to spontaneous ventilation. The use of non-invasive ventilation including BiPAP can greatly facilitate the ability to rapidly provide tracheal extubation during the immediate postoperative period [39]. This pathway was the result of a cooperative effort between healthcare providers from pediatric anesthesiology, pediatric intensive care unit (ICU) medicine, pediatric pulmonology, and respiratory care.

In addition to respiratory issues in patients undergoing scoliosis surgery, perioperative morbidity and mortality may also be related to secondary cardiac involvement. Myocardial dysfunction in this group of patients may be related to the primary disease process such as muscular dystrophy or less commonly due to chronic hypoxemia from restrictive lung disease and associated cor pulmonale. The latter is uncommon as scoliosis is frequently addressed prior to the development of chronic cardiovascular effects. More

commonly, various neuromuscular conditions such as the muscular dystrophies or myotonic dystrophies may lead to myocardial involvement with alterations in the contractile function or conduction abnormalities. Of these conditions, Duchenne muscular dystrophy is the most common disorder, with an incidence of one in 3300 male births [40]. Although skeletal muscle involvement with weakness predominates as the major clinical feature of this disorder, as these patients enter the second and the third decades of life, progressive myocardial involvement leads to impaired myocardial contractility, conduction disturbances, and arrhythmias. The potential impact of this disorder on perioperative morbidity and even mortality cannot be ignored as the literature has demonstrated a significantly increased risk during anesthetic care in these patients [41]. Sethna et al reported intraoperative cardiac arrest and death in two of 25 patients requiring anesthetic care during various surgical procedures [41]. Given the potential for associated myocardial involvement, preoperative evaluation should include transthoracic echocardiography and a 12-lead electrocardiogram (ECG). It has also been suggested that the combination of a preoperative chest x-ray and ECG can be used to screen for the presence of myocardial dysfunction 42]. Although Clendenin et al noted that an abnormality on the chest x-ray (increased cardiac silhouette) and abnormal findings on the ECG was predictive in 81% of their 255 patients, echocardiography remains the gold standard [42].

A second group that tends to be increasing in the spinal surgery population are those with associated congenital heart disease. In this group of patients, especially those with residual lesions or single ventricle physiology, preoperative assessment is of paramount importance to guide intraoperative care. When myocardial dysfunction is identified, additional intraoperative monitoring (transesophageal echocardiography) with consultation from pediatric cardiology may be required. Furthermore, close observation during positioning is suggested as the condition of these patients may deteriorate rapidly with the institution of positive pressure ventilation or when turned prone due to changes in venous return or increased intrathoracic pressure. Furthermore, once cardiovascular deterioration occurs, successful resuscitation may be more problematic than in patients without co-morbid cardiac involvement.

The period of preoperative evaluation and preparation of the patient is also an essential time to institute measures to limit allogeneic blood product needs. Simple measures include identification and treatment of anemia prior to elective spinal surgery. In the adult population, age greater than 50 years, preoperative hemoglobin less than 12 g/dL, fusion of more than two levels, and transpedicular osteotomy have been identified as independent risk factors for the need for perioperative transfusion [43]. Routine screening for preoperative anemia and its treatment, many times with nothing more than supplemental iron, may prevent the need for perioperative transfusion. Such interventions are particularly important in patients with poor nutritional status or in adolescent females following menarche. Although treatment with oral iron is generally effective, a more rapid response within 2–3 weeks can be obtained with intravenous iron therapy [44]. The latter is more costly and associated with a higher incidence of adverse effects. As such, the risk:benefit ratio must be closely evaluated.

More aggressive and more expensive preoperative blood avoidance techniques may include the administration of erythropoietin to augment preoperative autologous donation or the success of intraoperative isovolemic hemodilution (see section "Intraoperative anesthetic care"). Issues with erythropoietin include, most importantly, its cost and the lack of reimbursement from most insurance companies when it is used in this clinical setting. Furthermore, there are varying reports of its efficacy in the literature with some studies showing no benefit, variations in dosing regimens, the need for weekly visits with laboratory measurement of hemoglobin and subcutaneous injections, as well as the potential to increase the incidence of postoperative deep vein thrombotic events. In a retrospective analysis of 178 pediatric patients undergoing spinal surgery, homologous transfusions were administered to 30.6% of patients who did not receive erythropoietin versus only 17.5% of those who did ($p < 0.05$) [45]. In a subgroup analysis of the patients with idiopathic scoliosis, the need for homologous transfusion was 3.9% in those receiving erythropoietin versus 23.5% of those who did not ($p = 0.006$). However, subsequent work from the same investigators demonstrated no benefit of preoperative erythropoietin in limiting the need for allogeneic transfusion in a cohort of 61 patients with neuromuscular scoliosis [46]. Other investigators have suggested the efficacy of erythropoietin when used in combination with an autologous blood donation strategy [47]. Although such techniques are feasible in the pediatric population, given the need for repeated phlebotomy and laboratory analysis with the inherent time, cost, and needle-stick pain, there has been a significant decrease in interest in the use of preoperative autologous blood donation. Furthermore, as a clerical error remains the most common cause identified for death related to blood transfusion, the inherent safety of autologous transfusion may not be clinically different from allogeneic transfusion, especially in the pediatric population. The prothrombotic potential of erythropoietin deserves consideration when deciding on its role in perioperative blood avoidance. In the adult, population, Stowell et al reported a higher incidence of deep vein thrombosis of 4.7% versus 2.1% in a cohort of 680 adults [48].

Patients presenting for major orthopedic surgery may have co-morbid conditions or nutritional conditions that affect coagulation function. The chronic administration of anticonvulsant agents, including phenytoin and carbamazepime, may adversely affect coagulation function. Nutritional issues and poor intake of vitamin K may result in a low levels of vitamin K-dependent coagulation factors resulting in preoperative coagulation dysfunction. Preoperative screening of coagulation function and simple measures such as the administration of vitamin K (oral or intramuscular) may alleviate such problems. Patients with chronic orthopedic problems and pain frequently use non-steroidal anti-inflammatory drugs (NSAIDs). Although acetylsalicylic acid irreversibly inhibits cyclo-oxygenase and platelet function for the life of the platelet, NSAIDs result in reversible inhibition of platelet function that is dependent on the plasma concentration and hence the half-life of the NSAID. Discontinuation of most NSAIDs for 2–5 days prior to surgery will allow for the return of normal platelet function.

KEY POINTS: PREOPERATIVE EVALUATION

- Thorough evaluation, particularly of airway and cervical spine stability in neuromuscular and congenital spine patients, is essential
- All preoperative medications for pulmonary, neurological, and cardiac disease are generally continued through the day of surgery. Most NSAIDs should be discontinued 2–5 days preoperatively
- Neuromuscular spine patients often have respiratory compromise; but even those with FEV_1 <40% predicted may have an uncomplicated postoperative course
- Cardiac involvement for neuromuscular spine patients may include cardiomyopathy in Duchenne muscular dystrophy, or congenital heart disease including single-ventricle patients
- Erythropoietin therapy or autologous blood collection may lessen the need for intraoperative blood transfusion, but with the complexity of these procedures and increasing safety of allogeneic transfusion, they are infrequently used

Premedication, anesthetic induction, and positioning

Various agents or combinations may be required preoperatively in patients undergoing spinal surgery. Premedication regimens may include:

- High-flow nebulization of albuterol and an anticholinergic agent such as ipratroprium in patients with airway reactivity.
- Topical or aerosolized administration of lidocaine if a fiberoptic intubation is planned due to a difficult airway scenario.
- Gastrointestinal prophylaxis in patients at risk for gastroesophageal reflux and aspiration may include agents to increase gastric pH, such as H_2 antagonists, proton pump inhibitors, or oral non-particulate antacids and motility agents such as metoclopramide to decrease to gastric volume.
- Dexamethasone for patients with airway reactivity and to decrease postoperative nausea and vomiting.
- An anticholinergic agent such as glycopyrrolate or atropine to dry secretions, blunt cholinergic-mediated airway reactivity, and to prevent bradycardia during laryngoscopy.
- Hydrocortisone if patients are chronically receiving corticosteroids. Such therapy is frequently used in patients with Duchenne muscular dystrophy given data suggesting their ability to slow progression of the disease [49].
- An anxiolytic agent, such as oral midazolam, in patients without intravenous access or intravenous midazolam in those with pre-existing IV access.

Following premedication, the patient is transported to the operating room and routine ASA monitors are placed. From the start of anesthetic care, attention should be directed at the maintenance of normothermia. Hypothermia is particularly common and may occur rapidly in patients with cerebral palsy and failure to thrive who may have limited body fat. Patients with static encephalopathy and related conditions may have abnormal central control of temperature thereby placing them at further risk of hypothermia. In addition to other physiological effects, perioperative hypothermia has been shown to be a key factor in increasing intraoperative blood loss during major surgical procedures [50,51]. The maintenance of normothermia includes preoperative warming of the patient using forced-air devices, keeping the operating room warmed until the patient is positioned and covered, warming intravenous fluids, blood, and blood products, and the intraoperative use of forced-air warming devices. Some type of invasive continuous monitoring of core temperature should be used. This can be either nasopharyngeal, esophageal, or bladder. The availability of Foley catheters with a built-in temperature probe provides an easy and accurate means of intraoperative temperature monitoring.

The technique and medications used for the induction of anesthesia should be guided by the patient's co-morbid conditions, the assessment of the ease of tracheal intubation, as well as the patient's preference and/or demographics (age and cognitive function). For anterior or posterior spinal surgery, a reinforced endotracheal tube (ETT) may be used to prevent inadvertent airway occlusion during surgical dissection and/or extreme neck flexion (Fig. 29.11). During prolonged cases with significant neck flexion, there may be a risk for non-reinforced ETTs to warm, bend, and obstruct if they are held in a flexed position over a protracted period of time. The time-honored practice of using uncuffed ETTs in patients less than 6–8 years of age has recently changed with a transition to the use of cuffed ETTs in patients of all ages [52]. Once the ETT is secured in place, a gauze roll is placed in the mouth to prevent biting during motor evoked potential stimulation (see later).

When considering agents for anesthetic induction, several options are available for the induction and maintenance of anesthesia in patients with stable cardiovascular function. In the absence of intravenous access, anesthetic induction can be carried out by the inhalation of an incremental concentration of sevoflurane in oxygen or oxygen and nitrous oxide. Alternatively, a peripheral intravenous cannula can be painlessly placed following 2–3 min of breathing 50–70% nitrous oxide. In patients with previously established intravenous access, several of the commonly used intravenous induction agents are suitable. If there is a plan for tracheal extubation in the operating room or

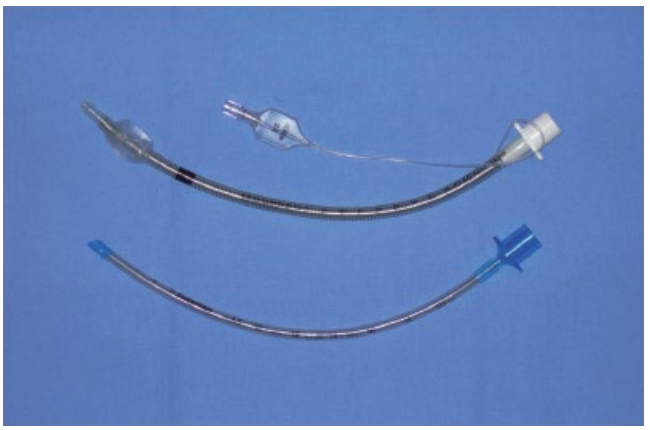


Figure 29.11 Wire reinforced endotracheal tube to prevent kinking during prone positioning with head flexion or for placement through a tracheostomy stoma.

immediately postoperatively, propofol may provide a more rapid awakening and a better recovery profile during the immediate postoperative period than induction with barbiturates such as thiopental. The latter are rarely if ever used for intravenous induction in the United States. Although its effect on adrenal function has led to the suggestion that its use should be re-evaluated, etomidate may still be an appropriate choice for anesthetic induction in patients with diminished myocardial function [53,54].

Once adequate bag-mask ventilation has been demonstrated, inhalation or an intravenous induction technique can be followed by the administration of a non-depolarizing neuromuscular blocking agent (NMBA). Succinylcholine is contraindicated in patients with various neurological and myopathic conditions given the potential for rhabdomyolysis, hyperkalemia, and cardiac arrest. Similar problems with succinylcholine may occur in patients within 48–72 h following a spinal cord injury. In the absence of concerns of a difficult airway, tracheal intubation can be facilitated with an intermediate-acting (vecuronium, rocuronium, *cis*-atracurium, atracurium) or short-acting (mivacurium) non-depolarizing NMBA [55]. The dosing of these agents should be titrated using train-of-four monitoring, especially in patients with Duchenne muscular dystrophy and other myopathies, as even a single dose for tracheal intubation of an intermediate-acting NMBA may result in a prolonged duration of neuromuscular blockade. When motor-evoked potentials (MEPs) are being used to monitor spinal cord function, a single, small dose of a non-depolarizing NMBA (rocuronium 0.3–0.4 mg/kg) can be used to facilitate tracheal intubation as its effects will generally dissipate prior to the need to initiate MEP monitoring after the patient is turned prone. In rare circumstances, the new reversal agent, sugammadex, can be used when the duration of effect of either vecuronium or rocuronium interferes with the need for MEP monitoring [56,57].

After the airway is secured, adequate intravenous access and invasive cardiovascular monitoring are obtained as indicated. Several factors may be responsible for hemodynamic changes during spinal surgery in pediatric patients, including co-morbid conditions, positioning on the operating room table, and blood loss. In general, for major spinal surgical procedures, two large-bore peripheral intravenous cannulae are placed for the rapid administration of fluids, blood, and blood products. Additional invasive hemodynamic monitoring with an arterial cannula and central venous access may be obtained depending on the patient's condition and the surgical expertise. In experienced hands, blood loss is generally minimal in patients with idiopathic scoliosis (400–600 mL) thereby eliminating the need for central venous access. Additionally, the accuracy of central venous pressure monitoring in the prone position has been questioned, thereby limiting its clinical utility [58]. In our clinical practice, central venous access is not routinely obtained during spinal surgery. Its use is limited to those patients who may have difficulties with peripheral vascular access postoperatively, when the use of specific vasoactive agents is anticipated or when central venous saturation monitoring is planned. Ultrasound imaging has been shown to be helpful if obtaining peripheral venous and arterial access is problematic, especially in patients with a history of previous difficulties with vascular access [59].

Once appropriate vascular access and monitoring has been established, the patient is then positioned on the operating room table. Patient positioning will be dependent on the specific type of surgery, with either prone positioning for posterior spinal fusion or lateral positioning if an anterior approach is chosen. If the cervical spine and upper thoracic vertebrae are included in the surgical field, neutral positioning of the head is required. Alternatively, for posterior spinal fusion that does not involve the lower cervical or high thoracic area or isolated lumbar surgery, the patient can be positioned prone and the head turned to the side, thereby limiting the potential for pressure points on the eyes and face. Regardless of the positioning, careful padding of pressure points is needed since these procedures may last up to 10–12 h. Positioning should minimize the venous pressure at the surgical site to reduce bleeding. This is done by using specialized operating room tables, placing rolls under the chest and pelvis to keep the abdomen free, and by reverse Trendelenburg positioning. Mild reverse Trendelenburg positioning also helps limit the development of dependent edema in the face, tongue, and upper airway and limits the increase in intraocular pressure (IOP) which may occur with prone positioning. A specialized frame (Wilson frame) or operating room table (Jackson table) is generally used to position the patient, and to decrease venous pressure and surgical bleeding (see Fig. 29.9). The Jackson table with longitudinal bolsters has been shown to have the least effect on reducing cardiovascular performance [60]. Keeping the abdomen free also facilitates mechanical ventilation by preventing limitation of diaphragmatic movement.

A major concern during surgical procedures in the prone position is the occurrence of postoperative visual impairment or blindness [61]. Increased IOP with prone positioning has been postulated to be one of the contributing factors for this rare, but devastating, complication of blindness following prone surgical procedures [62–64]. In a cohort of 20 adults undergoing surgery in the prone position, IOP was 19 ± 1 mmHg in the awake state, which decreased to 13 ± 1 mmHg in the supine position after the induction of anesthesia, but then increased to 40 ± 2 mmHg after 320 ± 107 min in the prone position. Although various etiologies may be responsible for postoperative visual loss (POVL), no unifying theory (ischemic, thrombotic, oncotic, and embolic) has been accepted or can explain all of the events. Given the devastating consequences and potential medicolegal implications of this phenomenon, the Postoperative Visual Loss Registry was established in 1999 in an attempt to determine factors associated with POVL [65]. In the registry, the authors reviewed 93 voluntarily reported cases of POVL following spinal surgery and noted that when considering the 83 cases of ischemic optic neuropathy, blood loss greater than 1000 mL and surgical duration ≥ 6 h were present in 96% of the cases. Owing to the concerns over POVL, controlled hypotension to limit intraoperative blood loss is not routinely employed in the adult population.

For anterior procedures, the patient can be positioned in the lateral position and a thoracotomy performed to gain access to the vertebral column. Alternatively, there is increasing experience with the use of thoracoscopic approaches for such procedures. Regardless of the approach (open thoracotomy or thoracoscopy), OLV can greatly enhance the surgeon's view of the surgical field.

KEY POINTS: PREMEDICATION, ANESTHETIC INDUCTION, AND POSITIONING

- Premedication considerations include midazolam for anxiolysis, continuing respiratory and neurological medications, stress dose corticosteroids as indicated, anticholinergic drugs to dry secretions as indicated, and long-acting analgesics such as methadone or clonidine
- The difficult airway should be anticipated and all necessary preparations made in advance with equipment and additional personnel available during induction
- A reinforced tracheal tube may be needed to ensure a patent airway in the prone position or extreme neck flexion
- Arterial cannulation is usually performed, central venous cannulation is used as indicated, and secure large-bore peripheral intravenous access is essential

One-lung ventilation for anterior approaches

Options for OLV include a tracheal double-lumen tube (DLT), a bronchial blocker, or selective mainstem intubation [66–68]. The smallest, commercially available DLT in most countries is 26 Fr, thereby allowing its use in patients who are 8–10 years of age. Advantages of a tracheal DLT include rapid placement, easy separation of the lungs, complete deflation of the operative lung, improved pulmonary toilet with access for suctioning of both lungs, the ability to rapidly switch to two-lung ventilation if needed, and the feasibility of administering continuous positive airway pressure (CPAP) or oxygen insufflation to the operative lung should this become necessary to improve oxygenation. In patients whose size precludes the use of a DLT, the bronchus on the operative side can be occluded with a balloon-tipped catheter that is placed using fiberoptic bronchoscopic guidance. Several different devices can be used as bronchial blockers including a Fogarty embolectomy catheter, atrio-septostomy catheter, pulmonary artery catheter, the Arndt endobronchial blocker (Cook Critical Care, Birmingham, IN, USA), and the Univent tracheal tube (Fuji Systems, Tokyo, Japan). Devices with a central channel provide the advantage of allowing some degree of suctioning through the channel, not to clear the lung of secretions as the channel is too small for that purpose, but rather to deflate the operative lung and improve surgical visualization or for the insufflation of oxygen and the application of CPAP. Without the central channel, air or gas cannot exit from the lung once the balloon is inflated; therefore the lung may not deflate totally and may obscure surgical visualization. The final option for lung separation is selective endobronchial intubation. The major disadvantage of selective mainstem intubation is that it is not possible to quickly change from OLV to two-lung ventilation as this requires repositioning the ETT from the mainstem bronchus into the trachea and vice versa. Additionally, with movement of the ETT, inadvertent extubation may occur, which may be particularly problematic for the patient in the lateral decubitus position. Placement into the right mainstem bronchus can generally be accomplished blindly while left-sided placement requires guidance with a fiberoptic bronchoscope because of the different anatomical orientation of the left and right mainstem bronchi. See Chapter 26 for additional discussion of one-lung ventilation.

Techniques to limit homologous transfusion

There is a growing body of evidence demonstrating the potential adverse effects of the administration of allogeneic blood and blood products [69–73]. These adverse effects include the transmission of infectious diseases, immunosuppression, transfusion-related acute lung injury, hemolytic and non-hemolytic transfusion reactions, transfusion-associated circulatory overload, and graft-versus-host disease. Of specific concern during the performance of major orthopedic surgical procedures is accumulating data demonstrating the association and potential causative role of allogeneic blood product use in postoperative infectious complications [70,71]. The primary focus on techniques to limit perioperative transfusion remains the appropriate preoperative preparation of the patient as well as attention to basic intraoperative tenets of pediatric anesthesiology, such as patient positioning and maintenance of normothermia. The general perioperative considerations that have a major impact on the perioperative need for allogeneic blood products include optimization of preoperative hemoglobin and coagulation function with avoidance of NSAIDs preoperatively as well as attention to intraoperative anesthetic technique including choice of fluid for intraoperative resuscitation and fluid therapy, proper patient positioning, and maintenance of normothermia [74,75]. The use of preoperative erythropoietin may be costly and not reimbursed by most insurance companies when it is used as a means of increasing the hematocrit to limit perioperative transfusion therapy. Furthermore, as weekly visits are needed for hemoglobin checks and injections, it is time-consuming and therefore generally reserved for specific circumstances where avoidance of allogeneic transfusions is mandated, such as the Jehovah witness patient [76]. On the other hand, an extremely simple and cost-effective measure is the identification of preoperative anemia, which may be prevalent in girls who have started their menstrual cycle. In many circumstances, treatment of anemia can be accomplished with nothing more than oral iron therapy.

While the exact clinical impact is questionable, laboratory tests demonstrate that the choice of intraoperative fluid administration affects coagulation function, including platelet function. During acute normovolemic hemodilution, intraoperative phlebotomy is performed and the removed blood is replaced with crystalloids or colloids. The removal of 10–15 mL/kg of whole blood followed by the administration of crystalloid results in the dilution of proteins with anticoagulation functions, such as antithrombin III. This results in increased coagulation [77]. Replacement of blood with albumin- or gelatin-based solutions have no effect or may actually improve coagulation function, while either medium or high molecular weight hydroxyethyl starches, because of their effects on von Willebrand factor, adversely affect coagulation function, in particular platelet function [78].

Limitation of perioperative blood and administration of blood products can also be achieved by acceptance of the tenet that there is no universal trigger for the administration

of blood products [79,80]. In the absence of co-morbid diseases that compromise end-organ oxygenation or limit the compensatory mechanisms for anemia, hemoglobin levels down to 7 g/dL are generally well tolerated. In a recent prospective trial in the adult ICU population, a restrictive strategy for the administration of blood (blood administered only for a hemoglobin less than 7 g/dL), no difference in outcome was noticed when compared to a liberal transfusion protocol (blood administered for a hemoglobin less than 10 g/dL) [80]. In the less critically ill patients and in those less than 55 years of age, there was a statistically significant improvement in 30-day mortality in the restrictive transfusion group.

Outside of the preoperative phase, there are several additional techniques or medications that may have a role in limiting perioperative allogeneic blood transfusions during spinal surgery:

- Autologous transfusion therapy including:
  a. Preoperative donation with the use of erythropoietin.
  b. Intraoperative collection using acute normovolemic hemodilution.
- Intraoperative and postoperative blood salvage.
- Pharmacological manipulation of the coagulation cascade with:
  a. Antifibrinolytic agents (ε-aminocaproic acid or tranexamic acid).
  b. Procoagulant agents including desmopressin (DDAVP) and recombinant factor VIIa (rFVIIa).
- Controlled hypotension.

The goal of performing pediatric spine surgery without the use of allogeneic blood products is best accomplished by combining several of these techniques [81]. Use of these techniques depends on the co-morbidities of the patient, the type of surgery, and the likelihood of the need for allogeneic transfusions. During spinal surgery, factors that increase the likelihood of needing allogeneic transfusions include the number of vertebral bodies fused and the presence of neuromuscular scoliosis [82,83]. Depending on the expertise of the surgeon, it may be that surgery for idiopathic scoliosis can be performed with few if any of these techniques, while several or all may be required for neuromuscular scoliosis.

Preoperative donation

Although preoperative donation of autologous blood was first suggested by Fantus in 1937 when he founded the first blood bank in the United States, the technique did not gain clinical popularity until the 1980s. Advantages that have been cited of preoperative donation include a reduction of exposure to allogeneic blood, the availability of blood for patients with rare phenotypes, reduction of blood shortages, and avoidance of transfusion-induced immunosuppression [84]. In individual cases, patients who refuse transfusions based on religious beliefs may accept autologous donation, although most will refuse it once the blood is separated from the body.

There are no contraindications to the autologous donation based on the patient's weight or age. Patients who weigh more than 50 kg, can generally donate a standard unit of blood, whereas patients weighing less donate proportionately smaller volumes based on their weight and the presenting hemoglobin or hematocrit. Prior to donation, the hematocrit should be more than 33%. All patients enrolled in an autologous donation program should be on replacement iron therapy to augment erythropoiesis [85]. Cost and scheduling concerns aside, the efficacy of red blood cell production can be augmented by the administration of erythropoietin. Specific contraindications to autologous blood donation are similar to those for the donation of blood for allogeneic use. In general, patients with end-organ disease or limitations of the compensatory mechanisms that maintain tissue oxygen delivery during anemia are not candidates.

Donations are generally made no more often than once a week with the last unit donated at least 5–7 days prior to surgery to allow plasma proteins to restore intravascular volume and to allow ample time for adequate erythropoiesis so that the patient is not anemic upon arrival in the operating room. Although this technique has been endorsed as the easiest means of avoiding allogeneic transfusions, its use has decreased significantly over the past 5–10 years. Concerns regarding the use of autologous blood include the lack of universal screening of these units for infectious diseases with the potential to have an infected unit of blood sitting in the blood bank. Additionally, as the primary event responsible for death following allogeneic blood administration is a clerical error and transfusion of the wrong blood product, autologous units can have the same incidence of this error as allogeneic units. Many of the units of autologous blood are never used. Therefore, they are wasted when there is no standardized policy and procedure for their routine screening and subsequent move into the allogeneic pool. Additional limitations include the cost involved, time constraints, as patients must return to the hospital several times before their operative procedure, and difficulties with vascular access in infants and children. In most centers, this practice has fallen out of favor and is no longer used.

Acute normovolemic hemodilution

Perhaps a more cost-effective and safer means of obtaining autologous blood is acute normovolemic hemodilution [86]. The technique involves the intraoperative removal of blood, generally after the induction of anesthesia and prior to the start of the surgical procedure. Blood is removed from a large-bore intravenous cannula, arterial cannula, or central line, and the volume withdrawn is replaced with colloid or crystalloid in a ratio of 1:3 to maintain normovolemia. The blood is collected in standard CPD-A (citrate phosphate dextrose with adenosine) blood bank bags until they are full (approximately 450–500 mL) or weighed to ensure that the appropriate amount of blood is removed. The amount of blood that can be safely removed is determined by the formula:

$$\text{Estimated blood volume} \times \left(\text{initial hematocrit} - \text{target hematocrit}\right) / \text{mean hematocrit}$$

The mean hematocrit is the average between the initial and the target hematocrit. The removed blood can kept at room temperature for up to 4 h to maintain the function of platelets and clotting factors, thereby providing a significant advantage over allogeneic blood and even predonated autologous blood. Intraoperatively, as needed, the blood is infused in the opposite order to that in which it was withdrawn so that the units with the highest hematocrit are saved until the end of the procedure when there is the least amount of bleeding. Compensatory physiological mechanisms to maintain tissue

oxygen delivery despite a decrease in hematocrit include a decrease in blood viscosity that results in increased venous return, peripheral vasodilation, increased cardiac output, and rightward shift of the oxyhemoglobin dissociation curve. Additionally, as oxygen delivery declines, oxygen extraction at the tissue level can increase to maintain adequate oxygen delivery to tissues [87].

Intraoperative blood salvage

Intraoperative blood salvage involves the collection of blood lost into the surgical field. The collected blood is anticoagulated, filtered for clots and debris, washed (with some devices), and then reinfused. There are three different techniques of intraoperative salvage. Semicontinuous flow devices were the first to be introduced and, although they are the most complex and labor intensive to use, are still the type used most commonly for intraoperative blood collection and reinfusion. The commercially available equipment consists of an aspiration and anticoagulation assembly, a reservoir (various sizes are available depending on the size of the patient), a centrifuge bowl, a waste bag, and tubing. A double-line aspiration set includes an anticoagulation line that permits either heparin or citrate to combine with the aspirated blood at a controlled rate. The anticoagulated blood is collected into a disposable reservoir containing a filter. The filtered blood is then pumped into a bowl, centrifuged, washed with saline, and pumped into a reinfusion bag. Most of the white blood cells, platelets, clotting factors, free plasma hemoglobin, and anticoagulant are removed in the washing process and eliminated in the waste bag. The process takes approximately 5–10 min resulting in a blood cell suspension with a hematocrit of 50–60%. Pediatric-specific devices are available that allow the processing of smaller volumes of blood.

The second type of intraoperative salvage uses a rigid canister with a sterile, disposable liner. Blood is aspirated from the wound and anticoagulant added in a manner similar to that of semicontinuous flow devices. The blood is collected in a rigid plastic reservoir containing a disposable liner. The blood can either be washed prior to infusion or reinfused without washing. Functioning platelets and coagulation factors are present if the blood is left unwashed; however, there is an increased risk for adverse effects due to cellular debris, free hemoglobin, and fragmented blood components. This type is rarely used in the perioperative setting.

The third type of collection is a single-use, self-contained rigid plastic reservoir that collects the shed blood. The anticoagulant (citrate) is placed in the container prior to use. This apparatus is most commonly used for postoperative blood collection and reinfusion. The surgical drains are connected to the canister, and every 4 h the canister is replaced and the blood reinfused. Coagulation factors and platelets are present in this blood as well. Adverse effects may occur as a result of cell fragmentation and the release of free hemoglobin.

Suggested indications for perioperative blood salvage include anticipated blood loss exceeding 20% of the patient's blood volume or a procedure during which more than 10% of patients require transfusion. Contraindications include situations in which there may be contamination of the collected blood with infectious or non-infectious agents (amniotic fluid, hemostatic agents such as topical thrombin, or protamine). Potential complications include air and fat embolism, hemolysis, pulmonary dysfunction, renal dysfunction, coagulopathy, hypocalcemia, and sepsis [88]. Coagulopathy may occur related to the initiation of disseminated intravascular coagulation due to improper technique and the infusion of blood cell fragments or the infusion of residual anticoagulant after washing [89]. Hemolysis may occur if the suction level is too high or if the aspiration method causes excessive mixing of air with blood. Free hemoglobin may be released during salvage and washing because of erythrocyte damage. Free hemoglobin levels exceeding 100–150 mg/dL may lead to hemoglobinuria and acute renal failure, as the binding capacity of haptoglobin is saturated and free hemoglobin is filtered in the renal tubules. Metabolic consequences of cell salvage may also be seen including a metabolic acidosis and alterations in electrolytes, such as magnesium, calcium, and potassium. Despite the list of potential complications and cost for the initial purchase of the machine and disposable items, the incidence of significant adverse effects is low and it represents an effective means of limiting the need for allogeneic transfusion [90].

Pharmacological manipulation of the coagulation cascade

Various agents have been used as prophylactic measures, even in patients with normal baseline coagulation function, to decrease intraoperative blood loss. Although these agents have been studied in well-designed prospective trials, the outcomes of the studies are, at times, conflicting. Another issue to consider with the administration of any agent that alters coagulation function is the potential to invoke a prothrombotic state with venous or arterial thrombotic complications.

1-Deamino-8-D-arginine vasopressin (DDAVP) is a synthetic analog of vasopressin initially used in the treatment of diabetes insipidus. Its hemostatic effects result from the release of factor VIII and von Willebrand factor (vWF) from endothelial cells. Factor VIII, a glycoprotein, accelerates the activation of factor X by factor IX, while vWF increases platelet adherence to vascular subendothelium, augments the formation of molecular bridges between platelets to increase aggregation, protects factor VIII in the plasma from proteolytic enzymes, and stimulates the synthesis of factor VIII. Although anecdotal reports have demonstrated its efficacy in augmenting coagulation function in various acquired and inherited forms of platelet dysfunction, prospective trials have failed to show an effect on blood loss during spinal surgery in pediatric patients [91]. Although routine use is not recommended and of limited utility, it may have a role in patients with specific defects of coagulation function or number.

ε-Aminocaproic acid (EACA) and tranexamic acid (TXA) are γ-amino carboxylic acid analogs of lysine that inhibit fibrinolysis by preventing the conversion of plasminogen to plasmin. They represent the agents that are used most commonly to manipulate the coagulation cascade to limit allogeneic transfusions during spinal surgery. In the plasma, plasminogen is activated by tissue plasminogen activator to form plasmin which cleaves fibrin, thereby preventing the formation of the fibrin mesh. This fibrinolytic system is a basic defense mechanism that prevents the excessive deposition of fibrin following the activation of the coagulation cascade. Plasmin can also hydrolyze activated factors V and VIII. EACA and TXA bind

to the lysine group that binds plasminogen and plasmin to fibrinogen, thus displacing these molecules from the fibrinogen surface and inhibiting fibrinolysis.

One of the issues with the use of agents such as EACA and TXA is that various dosing regimens have been reported in the literature and there remains significant variation in current clinical practice [92]. In general, both medications are administered as a loading dose followed by an infusion during the intraoperative period, with some studies continuing the infusion for a brief period of time into the postoperative course. Ninety percent of EACA is excreted in the urine within 4–6 h of administration. Although TXA is generally considered to be pharmacologically 7–10 times as potent as EACA, some studies have reported similar dosing regimens. Adverse effects of EACA or TXA may be related to the effect on coagulation function and the route of excretion. Since these agents are cleared by the kidneys, thrombosis of the kidneys, ureters, or lower urinary tract may occur if urological bleeding is present. Both EACA and TXA may be associated with hypotension during rapid intravenous administration. Seizures have been reported with TXA administration, most commonly during cardiac surgery; however, its use has not been restricted in patients with seizure disorders or those receiving anticonvulsant medications [93]. Given the limited adverse effect profile and general efficacy in the pediatric-aged patient, these agents are commonly used as a means of limiting intraoperative blood loss during spinal surgery [94,95]. In prospective, randomized trials, both EACA and TXA have been shown to decrease intraoperative blood loss during posterior spinal fusion in children and adolescents with either idiopathic or neuromuscular scoliosis [95–97]. As noted, dosing regimens vary greatly among the clinical trials with many centers, including our own, using a loading dose of 50 mg/kg followed by an infusion of 5 mg/kg/h [98].

Controlled hypotension

Controlled hypotension (deliberate or induced hypotension) may be defined as a deliberate reduction of systolic blood pressure to 80–90 mmHg, a reduction of mean arterial pressure (MAP) to 50–65 mmHg or a 30% reduction of baseline MAP. The latter is relevant for the pediatric-aged patient whose baseline MAP may be within the 50–65 mmHg range to start with. Although the primary premise for the use of controlled hypotension is to limit intraoperative blood loss, an additional benefit may be improved visualization of the surgical field and thereby shorter surgical times.

Advances in drug therapy have provided the clinician with several pharmacological options for controlled hypotension in pediatric-aged patients [99]. The agents available for controlled hypotension can be divided into those used by themselves (primary agents) and adjunctive or secondary agents which are used to limit the dose requirements and therefore the adverse effects of primary agents. Primary agents include regional anesthetic techniques (spinal and epidural anesthesia), the inhalational anesthetic agents (halothane, isoflurane, sevoflurane), the nitrovasodilators (sodium nitroprusside, nitroglycerin), prostaglandin E1, and adenosine. The calcium channel blockers and β-adrenergic antagonists have been used as both primary agents as well as adjuncts to other agents. Pharmacological agents used as adjuncts or secondary agents include the angiotensin-converting enzyme inhibitors and α-adrenergic agonists such as clonidine. When neurological monitoring is used (see next secton), the potential impact of the agent used for controlled hypotension must be considered.

Sodium nitroprusside (SNP) is one of the most commonly used agents for controlled hypotension [100]. It is a direct-acting, non-selective peripheral vasodilator that primarily dilates resistance vessels leading to venous pooling and decreased systemic vascular resistance. It has a rapid onset of action (approximately 30 s), a peak hypotensive effect within 2 min with a return of blood pressure to baseline values within 3 min of its discontinuation. SNP releases nitric oxide (formerly endothelial-derived relaxant factor), which activates guanylate cyclase leading to an increase in the intracellular concentration of cyclic guanosine monophosphate (cGMP). cGMP decreases the availability of intracellular calcium through one of two mechanisms: decreased release from the sarcoplasmic reticulum into smooth muscle or increased uptake by the sarcoplasmic reticulum. The net result is decreased free cytosolic calcium and vascular smooth muscle relaxation. Adverse effects include rebound hypertension, coronary steal, increased intracranial pressure, increased intrapulmonary shunt with ablation of hypoxic pulmonary vasoconstriction, platelet dysfunction, and cyanide/thiocyanate toxicity. Direct peripheral vasodilation also results in baroreceptor-mediated sympathetic responses with tachycardia and increased myocardial contractility. The renin–angiotensin system and sympathetic nervous system are also activated. The result is increased cardiac output which may offset the initial decrease in MAP. Plasma catecholamine and renin activity may remain elevated after discontinuation of SNP, resulting in rebound hypertension. The considerable expense of this drug in many areas has limited its use, with alternative drugs such as nicardipine in more common use.

Nicardipine is a calcium channel blocker of the dihyropyridine class that dilates the systemic, cerebral, and coronary vasculature with limited effects on myocardial contractility and stroke volume. Unlike SNP, nicardipine does have some intrinsic negative chronotropic effects which may limit the rebound tachycardia. Like other direct-acting vasodilators, nicardipine and the other calcium channel antagonists may increase intracranial pressure. Studies comparing SNP with nicardipine have demonstrated several potential advantages of nicardipine including fewer episodes of excessive hypotension, less rebound tachycardia, less activation of the rennin–angiotensin and sympathetic nervous systems, and, in some studies, decreased blood loss [101]. One disadvantage of nicardipine is that its effect is somewhat prolonged (20–30 min) following discontinuation of the infusion. More recently, a new dihydropyridine, clevidipine, has been added to the list of agents that may be used for intraoperative blood pressure control [102]. Although its hemodynamic effects are similar to those of nicardipine, it is metabolized by plasma and tissue esterases thereby resulting in a half-life of 2–3 min.

Although controlled hypotension is effective at reducing blood loss, care must be taken not to decrease blood pressure excessively due to the risk of spinal cord ischemia. Spinal cord monitoring must be carefully assessed for effects of hypotension, and the blood pressure increased if evoked potentials are decreased in the face of hypotension.

KEY POINTS: TECHNIQUES TO LIMIT HOMOLOGOUS TRANSFUSION

- Intraoperative techniques include acute normovolemic hemodilution, intraoperative and postoperative blood salvage, antifibrinolytic agents such as TXA and EACA, and procoagulants like DDAVP and recombinant factor VIIa
- Deliberate hypotension can be induced with anesthetic agents, sodium nitroprusside, nicardipine, or clevidipine. Care must be taken to not lower blood pressure excessively to avoid the risk of spinal cord ischemia

Spinal cord monitoring

Without electrophysiological monitoring, the incidence of neurological deficits following surgical procedures on the vertebral column may be as high as 3.7–6.9%. This can be decreased to less than 1% with appropriate monitoring [103]. In their guidelines on intraoperative monitoring, the American Academy of Neurology concluded that the evidence favors the use of monitoring as a safe and efficacious tool in clinical situations where there is a significant nervous system risk, provided its limitations are appreciated [103]. A recent meta-analysis of multimodality spinal cord monitoring for idiopathic scoliosis surgery included seven studies and 2052 patients [104]. Both somatosensory-evoked potentials (SSEPs) and transcranial MEPs were utilized and the incidence of neurological deficit was 0.93%. All 19 patients with neurological deficit had a neuromonitoring change in SSEP and/or transcranial MEP. No patient without neuromonitoring change had a deficit. The overall sensitivity for predicting neurological deficit when both modalities were utilized was 83%, specificity was 94%, positive predictive value 12%, and negative predictive value 99.8%. One of the major limitations is that animal studies have demonstrated a window of opportunity of less than 10 min from the time when a change in monitoring parameters is noted until permanent damage occurs. Additionally, when various techniques are used, such as SSEPs or MEPs, the anesthetic technique must be modified to facilitate processing of the signals.

In general, there are four techniques of intraoperative monitoring: (i) the ankle clonus test; (ii) the wake-up test; (iii) SSEPs; and (iv) MEPs. The ankle clonus test was the first to be used intraoperatively to assess spinal cord integrity [105]. During the normal awake state, descending inhibitory fibers prevent clonus in response to an ankle stretch. The reflex is also inhibited during deep levels of anesthesia. However, during emergence from anesthesia, inhibition of the central descending pathways allows ankle clonus to be elicited following dorsiflexion of the foot/ankle. If there has been damage to the spinal cord, flaccid paralysis will be present and no spinal reflexes can be elicited. To elicit ankle clonus, neuromuscular blockade must be reversed or absent and the patient is allowed to emerge from general anesthesia, as is done with a wake-up test. In most circumstances, the ankle clonus test can be elicited prior to the patient regaining consciousness and therefore at a deeper level of anesthesia than a true wake-up test [105]. The test is both extremely sensitive and specific; however, it does not provide a continuous monitor of spinal cord function and is present only at a specific depth of anesthesia.

The wake-up test was originally reported in the 1970s as a means of monitoring spinal cord integrity. The potential need for the technique should generally be included during the preoperative discussion with the patient. Details may include what the test entails, its purpose, timing during the procedure, and the fact that there may be some intraoperative recall during the period of time when the test is performed. Given the increased sophistication of neurophysiological monitoring techniques, the wake-up test is no longer routine, but is reserved for times when changes in MEPs or SSEPs are noted and do not respond to interventions. When a wake-up test is performed, neuromuscular blockade is reversed as needed and the depth of anesthesia decreased. The speed with which a patient will respond to verbal stimuli can be increased by the use of short-acting anesthetic agents (desflurane and remifentanil). When these agents are used, responsiveness and a successful wake-up test can generally be accomplished in less than 10 min after the surgeon's request. The use of reversal agents for opioids and benzodiazepines, although available, in clinical practice is not generally recommended as they may have prolonged effects that will interfere with the resumption of anesthesia after the wake-up test. However, if longer acting, high-potency opioids are used (sufentanil), the administration of naloxone may be necessary. The depth of anesthesia and the patient's awakening can also be judged by the use of neurophysiological or depth of anesthesia monitors. As the depth of anesthesia is decreased, one anesthesia provider stands at the head of the bed with one hand on the patient's head to limit the risk of sudden inadvertent movements that may dislodge the tracheal tube. The other hand is used to feel the patient's response to a verbal command to squeeze one's hand. When the patient reaches a light plane of anesthesia, a voluntary movement in the motor groups above the level of surgery (e.g. squeezing one's hand) is requested initially to ensure that the patient is awake enough to follow commands. This is then followed by a request to move the lower extremities to ensure that motor function is still intact. Once a positive response is achieved in the lower extremities, the depth of anesthesia is deepened by the bolus administration of propofol. The wake-up test entails certain risks including having an awake patient in the prone position on the operating room table. Inadvertent or sudden movements may result in patient injury, dislodgment of venous or arterial cannula, and hypertension with exacerbation of bleeding. Additionally, like the ankle clonus test, it provides only a single assessment of spinal cord integrity. In most centers, the wake-up test is used only when there are questionable findings on electrophysiological monitoring.

Electrophysiological monitors include both SSEPs and MEPs. SSEPs are monitored by stimulation of a distal nerve, generally in the leg (posterior tibial), and measuring the response at the cervical level and the central nervous system via standard electroencephalography electrodes. The pathways involved include the peripheral nerve, the dorsomedial columns (fasciculus gracilis and fasciculus cuneatus) of the spinal cord, and the cerebral cortex. SSEPs do not monitor anterior cord (motor) function. Given the close proximity of the tracts (motor and sensory) in the spinal cord, damage to the motor tracts generally results in damage to the sensory tracts making SSEPs a fairly reliable measure of motor function. However, given that the dorsomedial tracts and the

anterior aspect of the spinal cord do not share the same arterial supply, isolated damage to the motor tract with intact SSEPs has been reported.

Since SSEPs can be affected by anesthetic agents, baseline recordings are performed after an appropriate level of anesthesia has been achieved [106]. During the subsequent anesthetic care, effective monitoring is facilitated by maintaining a similar depth of anesthesia. While various agents have differing effects on the ability to obtain MEPs and SSEPs, it is most important to not maintain too deep a plane of anesthesia as this will invariably decrease the ability to obtain effective neurophysiological monitors. Given these concerns, we have found depth of anesthesia monitors very useful during neurophysiological monitoring, and suggest maintaining the bispectral index (BIS™, Medtronic Corp., Minneapolis, MN, USA) at 55–60 [107].

The variables measured for SSEPs include both the height of the response (amplitude) and the time it takes the response to travel from the periphery to the central nervous system (latency). Significant changes include a reduction in the amplitude of ≥50% or an increase in the latency of ≥10%. The potent inhalational anesthetic agents and nitrous oxide cause a decrease in the amplitude and an increase in the latency of SSEPs. However, acceptable monitoring can be achieved with 0.5 MAC (minimum alveolar concentration) of isoflurane, sevoflurane, or desflurane. Although practices vary from center to center, nitrous oxide is generally avoided. Intravenous anesthetic agents have been shown to have less of an effect on SSEPs, making a total intravenous anesthetic technique using propofol or midazolam combined with an opioid an effective technique. In general, either propofol or 0.5 MAC of an inhalational anesthetic agents can be combined with a continuous infusion of a potent synthetic opioid, either sufentanil or remifentanil. Neuromuscular blocking agents have no effect on SSEPs, but will obviously eliminate the ability to obtain MEPs [107]. When a volatile agent such as desflurane is chosen, a 0.5 MAC amount can be titrated using the BIS and incremental doses of a benzodiazepine (midazolam) administered as needed to ensure amnesia while allowing for a low enough desflurane concentration to allow for neurophysiological monitoring.

Due to the concern that there can be isolated motor damage with intact SSEPs, most centers monitor MEPs along with SSEPs. As with SSEPs, MEPs are affected by the type of anesthetic agent used. Various techniques have been recommended and there remains variation from center to center, but the anesthetic technique is generally the same as for SSEP monitoring. Dexmedetomidine has also been used during spinal surgery, given its ability to decrease requirements for inhalational anesthetic agents and propofol as well as its ability to decrease postoperative opioid requirements [108,109]. Provided that the depth of anesthesia is maintained, no change in MEPs or SSEPs have been reported with the use of dexmedetomidine as part of the intraoperative anesthetic care [109,110]. With MEP monitoring, the level of neuromuscular blockade must be kept stable with maintenance of one or two twitches of the train-of-four. Alternatively, as is our preference, neuromuscular blockade with a short-acting agent is used only for tracheal intubation and no neuromuscular blocking agents are used during the procedure. Regardless of the anesthetic technique used for these cases, a protocolized approach should be in place should there be loss of SSEPs or MEPs (Box 29.1). Two examples of abrupt loss of MEP signal, and the interventions employed, are presented in Fig. 29.12 [111]. A summary of anesthetic agents' effects on neuromonitoring parameters is presented in Table 29.2 [112].

Box 29.1: Treatment protocol for loss of neurophysiological monitors

- Consider any recent surgical correction and attempt to reverse it, including removal of distraction devices, wires, hardware, or pedicle screws
- The anesthesiologist should prepare for a wake-up test to confirm the MEP and SSEP findings if the following steps are not effective
- Discontinue controlled hypotension
- Increase MAP to ≥90 mmHg by:
  a. reducing the depth of anesthesia
  b. increasing intravascular volume by the administration of crystalloid or colloid
  c. administering a vasoactive agent (phenylephrine)
- Increase the hematocrit to a hemoglobin ≥8–10 g/dL
- Adjust mechanical ventilation parameters:
  a. increase oxygen concentration to 100%
  b. ensure normocarbia
- If the MEP or SSEP changes are not reversed, a wake-up test should be performed
- If there is a neurological deficit confirmed by the wake-up test:
  a. a spinal cord injury protocol should be instituted with consideration for the administration of methylprednisolone (30 mg/kg as a loading dose over 60 min followed by an infusion at 5.4 mg/kg every hour for the next 23 h)
  b. surgical consideration for removal of spinal hardware and instrumentation
  c. emergent radiological imaging (computed tomography or magnetic resonance) as clinical care allows

KEY POINTS: SPINAL CORD MONITORING

- There are four techniques of spinal cord monitoring: the ankle clonus test, the wake-up test, somatosensory-evoked potentials (SSEPs), and motor evoked potentials (MEPs)
- Monitoring of SSEPs and MEPs are standard care and together have high sensitivity and specificity for spinal cord ischemia detection
- The wake-up test is reserved for cases where neuromonitoring is persistently abnormal
- Volatile anesthetics and nitrous oxide have significant effects on SSEPs and MEPs and are avoided or used only in low concentrations
- An acute change in SSEPs or MEPs mandates timely response, including raising blood pressure and hemoglobin, ensuring normocarbia, decreasing depth of anesthesia, reversing surgical manipulaton like hardware placement or spine distraction, and use of the wake-up test if signals are not restored quickly

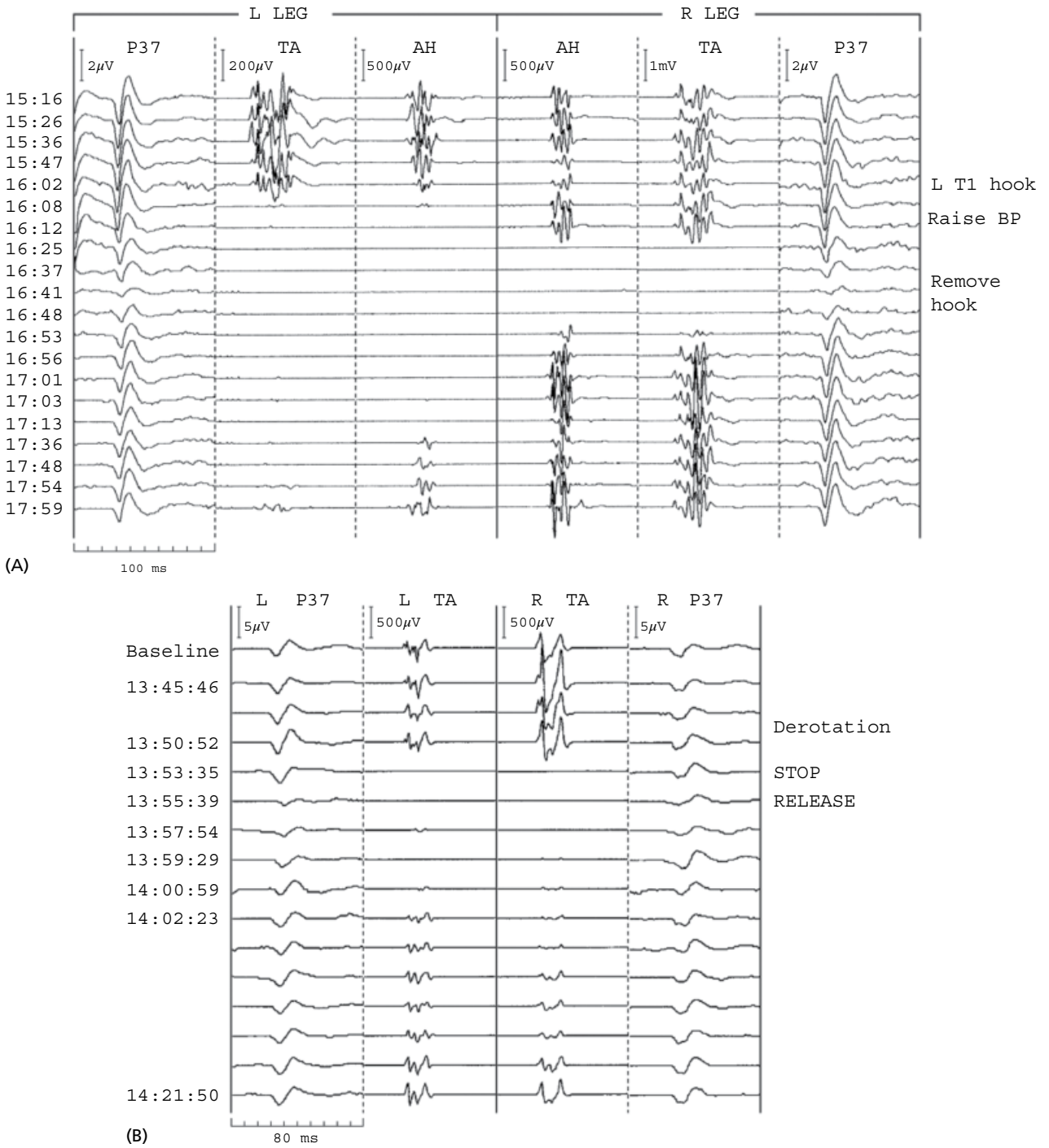


Figure 29.12 Two examples of intervention for MEP disappearance during scoliosis surgery. (A) Raising blood pressure (BP) had no beneficial effect on abrupt left leg MEP loss after sublaminar hook insertion. Instead, deterioration progressed to right leg MEP loss and bilateral SEP reduction. The hook was finally removed and evoked potential restoration followed, but left leg MEP absence was protracted (>40 min) and there was left leg paresis lasting a few days. Immediate hook removal might have been a more effective initial intervention. (B) Immediate instrumentation release without raising BP was quickly followed by restoration of abrupt bilateral leg MEP loss and subsequent SEP deterioration during derotation. There was no deficit. AH, abductor hallucis; P37, tibial nerve cortical SEP; TA, tibialis anterior. *Source*: Reproduced from Macdonald et al [111] with permission of Elsevier.

Intraoperative anesthetic care

Intraoperative anesthesia is generally best coordinated with the physicians and technicians providing intraoperative neurophysiological monitoring, as significant variations in preference vary from center to center. The techniques generally combine either a propofol infusion or a low dose inhalational anesthetic agent (0.5 MAC) with a potent synthetic opioid infusion (remifentanil or sufentanil). Some centers avoid inhalational anesthetics altogether, mandating a total intravenous anesthesia approach. As mentioned previously, dexmedetomidine may be added to the intraoperative regimen to limit the requirements for either propofol or the inhalational anesthetic agent. We have also found that these agents can be effectively titrated to achieve an acceptable level of blood

Table 29.2 Properties pertinent to neuromonitoring of commonly used anesthetic agents in major spine surgery

Drug name	Drug class	Effect on SSEPs	Effect on MEPs	Length of emergence	Approximate CST½ (min) at 2/4/6 h and B:GC for volatile agents	Clinical advantages relating to intraoperative neuromonitoring	Disadvantages
Propofol	GABA agonist	↓	↓	+++	15/20/30	Titratable, smooth emergence	Accumulation, slow wake-up
Etomidate	GABA agonist	↑↑	–	++	5/10/20	Titratable, hemodynamically stable	Adrenal suppression, PONV, myoclonus seizures
Midazolam	Benzodiazepine	↓	–	+++	40/60/65	Amnestic	Prolonged emergence
Ketamine	NMDA antagonist	↑	–/↓	+++	15/30/40	Analgesic, amnestic, sympathomimetic, hemodynamically stable	Hallucinations
Fentanyl	Opioid synthetic	–/↓	↓	+++	40/160/240	Analgesic	Accumulation, respiratory depression
Remifentanil	Opioid synthetic	–/↓	–/↓	+	7/7/7	Potent analgesic	Hyperalgesic effect after discontinuation
Sufentanil	Opioid synthetic	–/↓	↓	++	15/20/30	Potent analgesic	Respiratory depression
Dexmedetomidine	α_2-agonist	–/↓	–/↓	+++		Sedato-hypnotic with preserved respiratory drive, awake intubation	Bradycardia and heart block
Isoflurane	Inhalational	↓↓	↓↓↓	+++	1.4	Low cost	Reduced $CMRO_2$ of CNS
Sevoflurane	Inhalational	↓↓	↓↓	++	0.65	Mask induction	Emergence delirium
N_2O	Inhalational	↓↓	↓↓	+	0.47	Rapid elimination, analgesic effect	Synergistic effect on signal depression, PONV
Desflurane	Inhalational	↓↓	↓↓	+	0.42	Rapidly titratable, fast elimination	Emergence delirium, branchospasm
Rocuronium	NDMR	–	↓↓↓	N/A	N/A	Relatively short half-life and quick elimination after IOA with low doses	Interindividual variability of elimination, risk of residual NMB
Succinylcholine	Depolarizing muscle relaxant	–	↓↓↓	N/A	N/A	Rapid elimination after IOA	Contraindicated in MH and muscular dystrophies, pseudo-cholinesterase deficiency leads to long half-life

B:GC, b!ood:gas partition coefficient (the higher the value, the more agent is dissolved in blood and the longer it takes for the volatile anesthetic to be eliminated); $CMRO_2$, cerebral metabolic rate for oxygen; CNS, central nervous system; CST½, context sensitive half-time (elimination half-life as a function of duration of infusion); GABA, γ-aminobutyric acid; IOA, induction of anesthesia; MEPs, motor-evoked potentials; MH, malignant hyperthermia; NDMR, non-depolarizing muscle relaxant; NMB, neuromuscular blockade; PONV, postoperative nausea and vomiting; SSEPs, somatosensory evoked potentials.
Source: Reproduced from Rabai et al [112] with permission of Elsevier.

pressure control to provide controlled hypotension with a limited need for supplemental antihypertensive agents. In most cases when remifentanil and dexmedetomidine infusions are used, controlled hypotension can be maintained with only an occasional need for intermittent doses of labetolol.

Although remifentanil is a frequent component of intraoperative care for spinal surgery, one issue that has been identified with its use is the development of acute opioid tolerance [113]. This may result in an increased opioid requirement during the postoperative period. Crawford et al investigated the effects of remifentanil on postoperative opioid requirements in a cohort of 30 adolescents undergoing posterior spinal fusion for the treatment of idiopathic scoliosis [114]. Cumulative morphine use during the first 24 postoperative hours was 30% greater in the group receiving remifentanil. Despite such observations, the mechanisms responsible for the postoperative hyperalgesia remain undefined. Although it has been attributed to effects of remifentanil at the N-methyl-D-aspartate receptor, the hyperalgesia is not blocked by the administration of ketamine [115]. Given the potential for hyperalgesia following the intraoperative use of remifentanil, several centers have incorporated a single intraoperative bolus dose of methadone at the start of the anesthetic regimen [116–118].

Another potential adjunct for the intraoperative anesthetic care of patients during spinal surgery is the inclusion of a magnesium infusion [119,120]. A magnesium infusion has been shown to decrease intraoperative anesthetic requirements for propofol, the need for inhalational anesthetic agents and neuromuscular blocking agents, effectively control hypotension, and even decrease postoperative opioid requirements. In a prospective trial of 61 children with cerebral palsy undergoing spinal fusion, patients were randomized to receive magnesium (50 mg/kg followed by an infusion of 15 mg/kg/h) or a saline placebo [121]. Postoperative analgesic requirements and pain scores were lower at 24 and 48 h in the group that had received magnesium. Our clinical practice suggests that care must be exercised with the administration of the bolus dose of magnesium, as we have anecdotally noticed significant changes in MEPs following the bolus dose.

Additional intraoperative considerations include alterations in care, which may affect postoperative surgical site infections (SSIs) and the treatment of acute intraoperative events. Although various factors are involved in the genesis of a SSI, recent data have focused on the potential beneficial impact of the intraoperative F_iO_2. As oxygen is required for neutrophil killing of bacteria, it has been postulated that increasing the inspired FiO_2 may decrease the incidence of SSIs. In a case–control study, Maragakis et al compared the intraoperative course of 104 adult patients with SSIs to a randomly selected control group [122]. Risk factors for SSI included an intraoperative FiO_2 of less than 0.5 (adjusted odds ratio 12, 95% confidence interval 4.5–33, $p < 0.001$).

Given the complexity of the surgical procedure, various unique intraoperative complications may occur. As there is extensive removal of cortical bone and placement of screws, intraoperative hemodynamic instability may occur related to emboli (air, bone marrow, or fat), blood loss, or even anaphylactoid reactions to thrombotic or other pharmacological agents [123,124]. Early recognition of such events is mandatory, as cessation of surgical manipulation and flooding the surgical field with saline may limit the impact of air embolism on hemodynamic status. In more extreme cases, resuscitation in the prone position may be necessary. Although flipping the patient may be an option, even rapid closure of the surgical wound and flipping can result in the loss of precious minutes of resuscitation. Several case reports and animal studies demonstrate that effective cardiopulmonary resuscitation (CPR) can be performed in the prone position [125]. The technique involves the placement of one hand over each scapula with compressions performed in a perpendicular motion toward the operating room table or floor. If the patient is on a specialized frame, the thoracic support underneath the patient will generally provide enough counter-pressure for effective changes in intrathoracic pressure. If the patient is on a frame where the chest and abdomen hang free, it may be necessary for another care provider to support the chest from underneath the table to allow for effective CPR.

KEY POINTS: INTRAOPERATIVE CARE

- Careful positioning is essential to avoid nerve and eye injuries, to avoid dislodgment of the endotracheal tube, and to enable the abdomen to hang free to reduce blood loss
- Remifentanil may lead to tachyphylaxis and increased postoperative pain; if used, then a long-acting opioid such as methadone can be given at the beginning of the case
- Postoperative visual loss is a rare but devastating complication of spine surgery; pressure on the globe, head down position, prolonged surgery with significant blood loss, and fluid administration are risk factors

Postoperative care including pain management

One of the keys to the successful care of the pediatric spine patient is to provide a smooth transition from the operating room to the ICU. This process begins with the preoperative preparation and education of the patient, preferably with a tour of the pediatric ICU. The patient should also be instructed regarding the correct use of incentive spirometry and patient-controlled analgesia (PCA) if the use of these devices is planned.

At the completion of the procedure, the majority of patients undergo tracheal extubation in the operating room. Given the prolonged prone positioning, lingual edema may be present and result in postoperative upper airway obstruction. Excessive lingual edema may mandate continuing mechanical ventilation into the postoperative period. When the cuff is deflated, an adequate airway leak should be present before tracheal extubation. An appropriate level of responsiveness should be obtained to allow for a neurological examination to demonstrate adequate upper and lower extremity function. In many institutions, idiopathic scoliosis patients are not routinely admitted to the pediatric ICU, but rather the inpatient ward. In such instances, a 2–4 h stay in the postanesthesia care unit is used to ensure hemodynamic respiratory stability.

Patients with co-morbid cardiac or respiratory disease are usually admitted to the pediatric ICU, and the decision to continue mechanical ventilation into the postoperative period is made on an individual basis. If there is any possibility for the use of postoperative mechanical ventilation or non-invasive respiratory support, this should be discussed preoperatively with the carers and the patient. The need for mechanical ventilation may be related to either the patient (neuromuscular disorder, preoperative pulmonary dysfunction) or the surgical procedure (blood loss of more than 1 blood volume). In specific cases, the best option may be to provide 2–4 h of postoperative mechanical ventilation to ensure cardiorespiratory stability, normal coagulation function, and correction of metabolic parameters. Once this is accomplished, the trachea can be extubated in the ICU setting. In patients with neuromuscular disorders, our practice is to consider tracheal extubation to a non-invasive ventilation technique (BiPAP). We have found that this may allow for rapid tracheal extubation following the procedure and yet limit the development of atelectasis or respiratory insufficiency.

Due to the significant length of the surgical incision and the degree of bony and soft tissue dissection required for such procedures, there may be significant postoperative pain. Effective analgesia is generally best provided using a multimodality approach, which includes analgesic agents, anxiolytic agents, and medications to control muscle spasms. Muscle spasms may be particularly problematic in patients with underlying cerebral palsy or neuromuscular disorders. Options for the provision of analgesia include the intravenous administration of medications and/or regional anesthetic techniques. For intravenous administration, we prefer the use of PCA. Although young patients or those with developmental disabilities may not be able to activate the device, nurse-controlled or parent-controlled analgesia may be provided. By using the device in this manner, the bedside nurse has ready access to a supply of opioid to provide an immediate dose to a patient who is in pain. Prior to instituting PCA, an appropriate level of analgesia must be achieved by the careful titration of opioid. This is generally done in the operating room at the completion of the surgical procedure. Once neurophysiological monitoring is completed, the remifentanil and propofol infusions are discontinued and desflurane or sevoflurane started to maintain the BIS at 50–60. After the onset of spontaneous ventilation, incremental doses of either hydromorphone (2–3 μg/kg) or morphine (20 μg/kg) are titrated based on the patient's respiratory rate. Once tracheal extubation is completed, additional complaints of pain are treated with additional bolus doses of opioid followed by the initiation of the PCA device to maintain analgesia. In patients who have received methadone as part of their intraoperative anesthetic technique, the PCA device is generally used in the bolus mode only without a continuous opioid infusion. Given the significant interpatient variability that may occur, age-appropriate pain scores as used to titrate the PCA doses up or down based on the patient's response.

To limit the total dose of opioid required and thereby opioid-related adverse effects, adjunctive agents can be used. There remains significant controversy regarding the potential adverse effects of NSAIDs on bone formation. Given these concerns, many centers choose not to use these agents following spinal surgery in children or at least to limit their use for the first 24 postoperative hours. Our preference is to administer intravenous acetaminophen every 4–6 h around the clock. Given the propensity of these patients to develop muscle spasms and the need, in some patients, to provide anxiolysis, benzodiazepines such as diazepam may be added to the postoperative regimen either as on an as needed basis or at fixed intervals. Alternatively, there may be a role for the α2-adrenergic agonists to provide anxiolysis as well as relief of muscle spasms. Given its limited effects on respiratory function and its ability to potentiate opioid-induced analgesia, dexmedetomidine may also have a role in the ICU setting to provide anxiolysis following major surgical procedures including spine surgery. The other class of agent that has gained popularity as an adjunct to opioid analgesia following spinal surgery are the γ-aminobutyric acid analogs such as gabapentin and pregabalin [126–129]. In a prospective study of 59 patients, 9–18 years of age, undergoing posterior spinal fusion, gabapentin significantly reduced total morphine consumption and pain scores in the postanesthesia care unit and on the first postoperative day [127]. In addition to working during the acute postoperative period, data from adult populations suggest more prolonged effects with decreased pain scores and improved functional outcomes 3 months after surgery [128].

Given successes in other surgical procedures, there is also significant interest in the potential use of regional anesthetic techniques as a means of controlling pain following spine surgery in children. Reports in the literature regarding the use of regional anesthesia following spine surgery have included several variations: (1) the dose of the medications used; (2) the route of delivery (intrathecal or epidural); (3) the mode of delivery (single dose, intermittent bolus dosing, or continuous infusion); (4) the number of catheters used (one versus two); (5) the medications infused (opioids or local anesthetics or both); (6) the opioid used (morphine, fentanyl, hydromorphone); (7) analgesic regimen of the control group if present (intermittent "as needed" morphine or PCA); (8) the type of surgery (short segment lumbar fusion, short segment laminectomy for dorsal rhizotomy, posterior spinal fusion, and anterior spinal fusion); and (9) the surgical approach (open versus thoracoscopic). The reader is referred to a review of the reports regarding the use of regional anesthetic techniques following spine surgery in pediatric-aged patients and a recent meta-analysis evaluating these techniques [130,131]. The evaluation of the efficacy of regional anesthetic techniques is clouded by the variation in the techniques, as previously outlined. Future trials are needed to determine the optimal postoperative analgesic regimens for these procedures.

KEY POINTS: POSTOPERATIVE CARE

- ICU care is frequently required after scoliosis surgery, particularly neuromuscular scoliosis. Patient preparation and through ICU hand-over of care are important for these complex patients
- Most patients are extubated in the operating room; however, for specific cases a 2–4 h period of mechanical ventilation may be prudent to ensure cardiorespiratory stability, normal coagulation function, and correction of metabolic parameters

- Extubation to BiPAP is appropriate for many neuromuscular spine patients with pulmonary involvement
- A multimodal analgesic approach, including opioid PCA, prevention of muscle spasm, and possible use of NSAIDs, α_2-adrenergic agonists, and γ-aminobutyric acid analogs is often required for pediatric spine surgery

Summary

There are many challenges facing the anesthesia provider during spine surgery in pediatric patients. As with any surgical procedure, patient care begins with a thorough preoperative evaluation to identify co-morbid features which are present in many of these patients. Although idiopathic scoliosis is still a common disease, many of these patients will have associated neurological or myopathic conditions that impact on anesthetic care. Intraoperative issues include techniques for airway management, vascular access, blood conservation techniques, patient positioning, intraoperative neurological monitoring, administration of blood and blood products, and maintenance of fluid and electrolyte homeostasis. There is also a need for a smooth transition to the postoperative period with ongoing monitoring to ensure stable cardiorespiratory function and an aggressive approach for the provision of effective postoperative analgesia.

CASE STUDY

A 14-year-old, 72 kg adolescent presented for posterior spinal fusion in the treatment of idiopathic scoliosis. His past medical history was unremarkable for co-morbid medical conditions or previous anesthetic care. Preoperative preparation included the administration of iron and two subcutaneous doses of erythropoietin. Preoperative coagulation function (PT, PTT, and INR) was within normal limits and the hemoglobin was 14.6 g/dL. The patient was held nil per os for 6 h and transported to the operating room where routine ASA monitors were placed. Core body temperature was monitored using a temperature probe incorporated into the Foley catheter. A gauze pad that had been rolled was placed in the mouth to prevent lingual damage from masseter muscle contraction during neurophysiological monitoring. Following the inhalation of nitrous oxide for 3 min, a large-bore peripheral intravenous cannula was placed followed by the intravenous administration of midazolam (2 mg) to provide anxiolysis. This was followed by anesthetic induction with 3 mg/kg of propofol and 5 μg/kg of fentanyl. Tracheal intubation was facilitated by rocuronium (0.4 mg/kg).

Following anesthetic induction, maintenance anesthesia consisted of desflurane (expired concentration 3–4%), intermittent doses of midazolam titrated to maintain the bispectral index at 50–60, and a remifentanil infusion at 0.1–0.3 μg/kg/min. To blunt the hyperalgesia related to remifentanil and provide postoperative analgesia, methadone (0.15 mg/kg) was administered. A second large-bore peripheral intravenous cannula and a radial arterial cannula were placed. Intraoperative monitoring with both somatosensory (SSEP) and motor (MEP) evoked potential monitoring was planned and the appropriate electrodes were placed over the extremities and scalp. A prone pillow was placed to prevent pressure to the eyes and face and the patient was turned prone onto a Jackson table. To facilitate SSEP and MEP monitoring, the concentration of desflurane was kept at 3–4%. No additional doses of a neuromuscular blocking agent were administered until the patient was turned prone and the first set of MEPs were obtained. The remifentanil was increased up to 0.3 μg/kg/min and a clevidipine infusion added as needed to maintain controlled hypotension with a MAP of 50–65 mmHg. Once positioned prone, a forced-air heating device was used to maintain normothermia. The antifibrinolytic agent, tranexamic acid, was administered as a bolus dose of 50 mg/kg followed by an infusion of 5 mg/kg/h until wound closure was started. Intraoperatively, blood salvage with a cell saver from the surgical suction devices was employed. With the desflurane–remifentanil technique, effective monitoring of SSEPs and MEPs was achieved. The technique was titrated to allow for a wake-up test or ankle clonus test should there be changes in neurophysiological monitoring that did not respond to the departmental protocol for loss of neurophysiological monitoring signals. Intraoperative arterial blood gas parameters and hemoglobin values were monitored.

The surgical hardware was placed without incident and the wound was closed. During wound closure, 400 mL of intraoperatively salvaged blood was washed and returned to the patient. Once monitoring of neurophysiological function was no longer indicated, the remifentanil infusion was discontinued with continuation of desflurane to maintain the BIS at 40–60. Once there was return of spontaneous ventilation, hydromorphone was administered in incremental bolus doses (0.1 mg) to achieve a respiratory rate of 8–12 breaths/min. Ondansetron (4 mg) and dexamethasone (4 mg) were administered to prevent postoperative nausea and vomiting. At completion of the surgical procedure, the desflurane was discontinued and the patient was turned supine.

Once there was eye opening and appropriate response to verbal commands, the patient's trachea was extubated. The patient was transported to the post-anesthesia care unit and then admitted to the inpatient orthopedic surgical ward for continued observation. Postoperative analgesia was provided by hydromorphone PCA with intravenous acetaminophen administered every 6 h. The hemoglobin value on postoperative day 1 was 11.6 g/dL. The remainder of the hospital course was unremarkable.

This case illustrates several of the basic tenets required for performance of anesthesia during spinal surgery. Of prime importance is tailoring of the anesthetic regimen to allow for effective monitoring of spinal cord function using SSEP and MEP modalities while ensuring the ability to achieve a rapid wake-up test in the event of changes. This generally includes

the comibed use of 0.5 MAC of desflurane and a synthetic opioid infusion (remifentanil or sufentanil). The desflurane is titrated up to 3–4% expired concentration to maintain the bispectral index at 50–60 with incremental doses of midazolam added if needed. During neurophysiological monitoring, if changes occur, immediate communication with the surgeon is necessary to allow for the reversal of any surgical intervention which may have resulted in these changes. This may include removal of recently placed hardware, wires, or pedical screws. In the event that the neurophysiological changes do not respond to surgical intervention or manipulations of hemodynamic parameters (increasing the blood pressure or the hemoglobin) and mechanical ventilation (increasing the inspired oxygen to 100% and ensuring normocarbia), the anesthesiologist must be ready to allow for a wake-up test. This will require a rapid decrease in the depth of anesthesia. A second component of anesthetic care during spinal surgery is the use of techniques to limit intraoperative blood loss, including basic maneuvers such as effective patient positioning to avoid abdominal compression and distention of epidural veins as well as maintenance of normothermia. Additional techniques may include isovolemic hemodilution, administration of an antifibrinolytic agent, intraoperative blood salvage, and controlled hypotension. The final component is the provision of effective postoperative analgesia with a multimodality approach including the use of patient-controlled analgesia and adjunctive agents (acetaminophen, NSAIDSs, dexmedetomidine, and gabapentin).

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A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 30
Anesthesia for Transplantation

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Introduction

Medical progress has made organ transplantation an accepted therapeutic modality for treating a variety of diseases affecting various organ systems in infants and children. Improvements in immunosuppressive therapy, surgical techniques, and organ preservation have permitted utilization of transplantation in a greater number of patients, and pediatric patients in particular have benefited from the growth of transplantation. The scope and magnitude of various transplant procedures in infants and children with underlying organ system disease will continue to challenge anesthesiologists caring for these patients. In addition, as more children undergo transplantation, anesthesiologists must be prepared to care for them following transplantation, including the management of post-transplant complications and procedures.

Anesthetic management of these procedures requires understanding the physiological implications of organ failure, as well as specific requirements of the transplant procedure [1]. To facilitate this discussion, issues related to the anesthetic care of children undergoing liver, renal, heart, heart–lung, lung, and multivisceral transplantation will be discussed separately. In addition, other chapters describe anesthetic care of infants and children with specific organ dysfunction who require surgery.

Perioperative anesthetic management of solid organ transplant procedures has a number of similarities. Because of the logistic constraints involving donor organ procurement and admission of patients awaiting transplantation, there is limited time available to the anesthesia team for preparation. During this time, the patient must be admitted to the hospital and an updated history and physical examination and laboratory studies must be obtained. The short period of preparation usually limits the duration of nil per os (NPO) status for most children, which has implications for the anesthesiologist. Anesthetic preparation and planning must incorporate the magnitude of these procedures. Because several vascular anastomoses are required, there is significant potential for hemorrhage. Adequate vascular access, invasive monitoring, and availability of adequate quantities of blood products are

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

required. Given the severity of underlying diseases, the physiological alterations they cause, and the frequency of intraoperative changes in the patient's condition, arterial blood gas and pH, blood chemistry profiles, and other hematological tests often are required during transplant procedures. When new transplantation programs are established, anesthesia departments should take an active role in defining the requirements and availability of these ancillary services to help in the care of these patients. Because of the urgent or emergent nature of most transplant cases, the resources must be available to the anesthesia team on a 24 h, 7 days a week basis.

Care of organ donors after neurological death

Once brain death has been established in a donor, and suitability of the donor organs has been established, the emphasis for patient care is directed toward organ preservation by maintaining cardiac output and oxygen delivery. After placement of the organs according to the United Network for Organ Sharing (UNOS) waiting list criteria in the USA, coordination of the arrival of the harvesting teams is done by the local organ procurement agency, and an operating room time selected. The anesthesia team needs to ensure preservation of oxygen delivery to the harvested organs by maintaining adequate ventilation, cardiac output, hemoglobin, and blood pressure within target ranges. Diabetes insipidus is often present, requiring close attention to urine output and electrolytes, replacement of losses, and 1-deamino-8-D-arginine vasopressin (DDAVP) administration. Because of loss of sympathetic outflow from the central nervous system, hypotension and cardiovascular compromise are a constant possibility during the preparation for harvest. Close communication with the surgical team, or teams for multiple organ harvests, will assure optimal organ retrieval.

Brain-dead donors do not experience pain; however, they may experience hemodynamic changes from spinal cord reflexes with surgical incision and should be treated with inhalational anesthetics or opioids. After wide abdominal exposure, the retrieval team will ask for heparin (200–400 units/kg). Organs are generally removed according to their susceptibility to ischemia, with the heart first and the kidney last. After the heart, great vessels, and lungs are dissected out, and the donor aorta is cross-clamped, the heart is perfused with a preservation solution such as standard crystalloid cardioplegia or Celsior® to provide both cardioplegia and organ preservation. The organs are then placed in ice for transport at 4°C.

Donation after cardiac death

Because of the ongoing shortage of donors for all organs, the concept of organ donation after cardiac death (DCD) is advocated. Families may request organ donation after withdrawal of mechanical ventilatory support in patients who are otherwise suitable for donation, with an irreversible neurological injury, who do not have brainstem death.

This condition must be confirmed by the patient's physicians and agreed to by the patient's next of kin. In order to optimize organ retrieval, patients and families are typically taken to the operating room where ventilatory and circulatory support is withdrawn. A physician not involved with the organ procurement determines an irreversible cessation of cardiac and respiratory function, and the organ recovery takes place. As of 2007 in the USA, transplant centers and organ procurement organizations are required to have policies and procedures in place for this process. DCD increased the number of donors (adult and pediatric) by over 600 in 2006 [2]. Despite increasing the pool of potential donors (an estimated 6–20% of pediatric deaths could potentially be DCD donors), a recent review of pediatric organ donation after cardiac death indicated that very few organs from DCD donors are implanted into pediatric patients annually. For example, in 2010 there were 137 pediatric DCD donor organs, but only nine of these organs were transplanted into pediatric patients (three livers, five kidneys, and one heart) [3]. Ethical issues, potential physician conflicts of interest, logistical issues, and concerns over warm ischemia time all have limited the application of DCD procedures. Pediatric renal and liver transplant outcomes after cardiac death are comparable to those following transplant from brainstem deceased donors, with minimal data about heart and lung transplant outcomes.

Immunosuppression for pediatric solid organ transplantation

Review of the history of solid organ transplantation demonstrates that successful outcomes are impossible without effective immunosuppression. The aim of immunotherapy is to minimize the risk of rejection and drug toxicity. Currently, pediatric solid organ transplantation protocols for induction, maintenance, and desensitization vary widely between centers. Even single organ transplant groups are far from consensus on the ideal approach to immunosuppression [4]. A general strategy is depicted in Figure 30.1 [4]. Most transplant patients require indefinite maintenance therapy, although

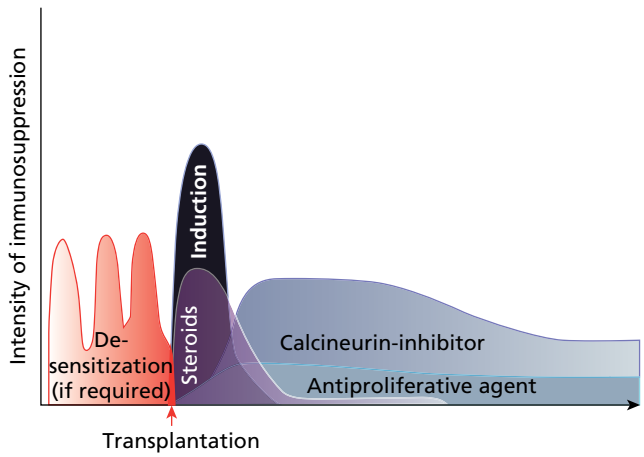


Figure 30.1 Time line showing the different approaches for immunosuppression in relation to the time of transplant. Pretransplant protocols are reserved for patients with specific risk factors (e.g. HLA sensitization or ABO-incompatible transplantation). Depending on the transplanted organ and center, the use of induction may or may not be part of the protocol. Furthermore, low-dose steroids may remain part of the maintenance therapy, supporting a regimen of one or two drugs of different classes. Additional treatments are used for treatment of rejection. *Source*: Reproduced from Urschel et al [4] with permission of Elsevier.

about 20% of pediatric liver transplant recipients and some kidney recipients have been successfully weaned from immunosuppression late after transplantation [5]. Figure 30.2 illustrates the cellular targets of immunosuppressive drugs, and commonly used drugs are detailed in Table 30.1 [4,6]. Discussion of individual agents is beyond the scope of this chapter and has been addressed recently [3,7–12].

It is important to monitor drug levels because co-existing disease and drug interactions can result in subtherapeutic or toxic drug effects. Nephrotoxic agents should be avoided even if renal function is normal. Cystic fibrosis patients have unreliable gastric absorption and hepatic clearance and are at risk for developing acute toxicity from oral medications like cyclosporine. Hepatic enzymes such as cytochrome P450 metabolize commonly used immunosuppressant drugs. Perioperative drugs (e.g. metoclopramide, amiodarone, antibiotics, barbiturates, phenytoin) may induce or inhibit cytochrome P450 and alter drug levels of calcineurin and mammalian target of rapamycin (mTOR) inhibitors. Newer immunosuppressant medications often do not include the liquid forms required for young children. Such liquid preparations must be compounded by local pharmacies and may have a short shelf-life, making them difficult to manage for patients not residing near a pediatric medical center. Moreover, absorption and pharmacokinetic data for infants and children often do not exist, often making dosing decisions in drugs that may have narrow therapeutic windows challenging [13].

Induction therapy

Induction immunotherapy is intense immunosuppression in the immediate perioperative phase of organ implantation to reduce the incidence of acute rejection in the early post-transplant phase [5,14,15]. Also, there are longer term benefits because chronic graft failure and decreased long-term survival correlate with the frequency of acute rejection. However,

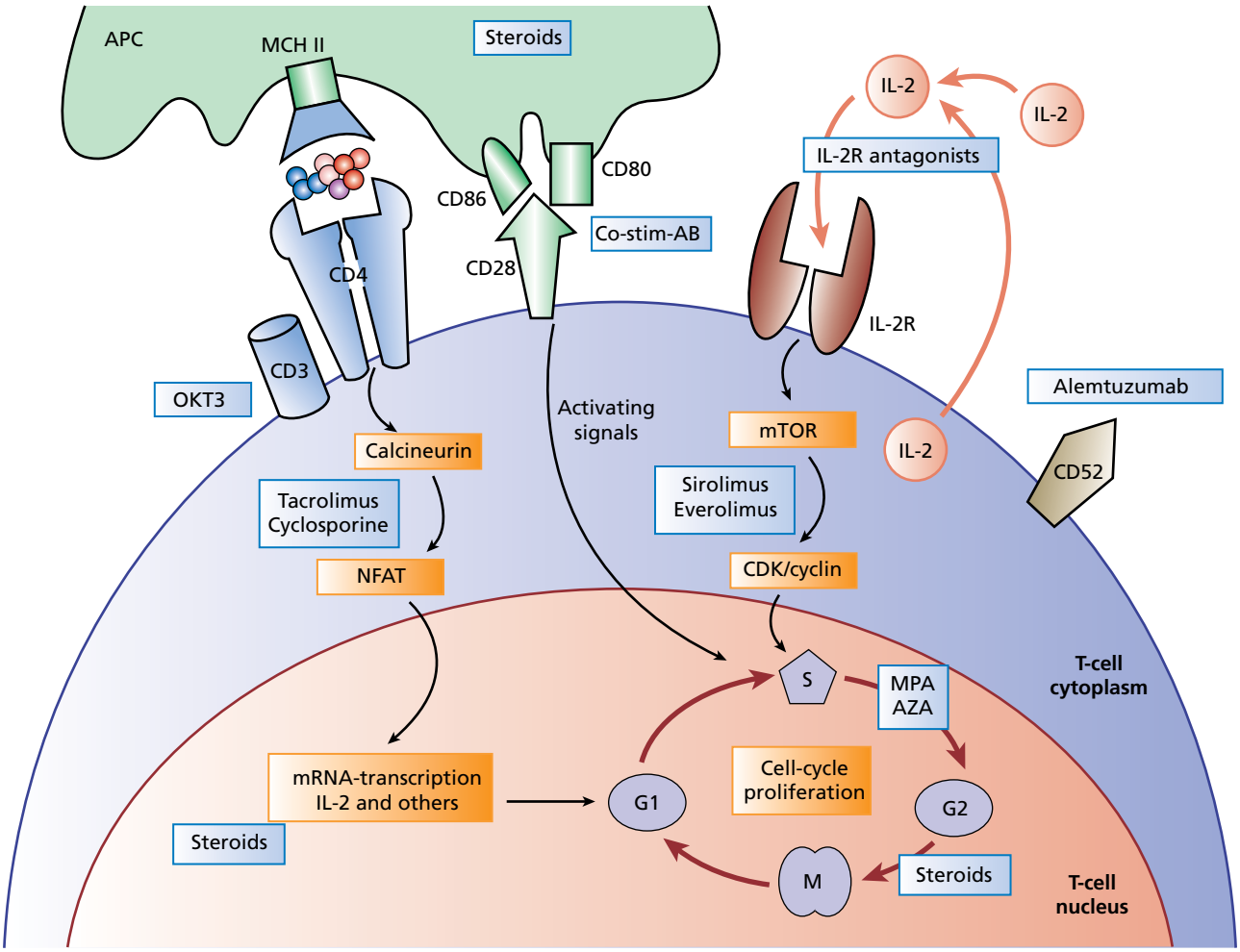


Figure 30.2 T-cell activation and proliferation results from presentation of a peptide fragment of the donor antigen in the major histocompatibility complex class II (MHC II) of the antigen-presenting cell (APC) and a co-signal from interaction from CD80/CD86 and CD28. This mechanism results in activation of calcineurin, which leads to production of interleukin-2 (IL-2). Autocrine stimulation by IL-2 results in cell proliferation by a pathway involving target of rapamycin (mTOR) and cyclin/cyclin-dependent kinase (CDK). Immunosuppressive agents exert their effects at a number of different targets to prevent T-cell proliferation. The CD80/CD86 and CD28 interaction is targeted by specific antibodies (Co-stim-AB) abatacept and belatacept. Basiliximab and daclizumab (IL-2R antagonists) target the receptor for IL-2, required for cell activation via mTOR, which is targeted by sirolimus and everolimus. Tacrolimus and cyclosporine interfere in the signal transduction from the T-cell receptor by inhibiting calcineurin nuclear factor of activated T-cells (NFAT). Mycophenolic acid (MPA), mycophenolate mofetil, and azathioprine (AZA) interfere in the cell cycle, preventing the T-cell as well as the B-cell from proliferation. Steroids target multiple sites in the interaction. Alemtuzumab and muronomab target specific lymphocytic surface structures to induce cytolysis; a similar principle is used for the antithymocyte globulins but with multiple targets on the surface. *Source*: Reproduced from Urschel et al [4] with permission of Elsevier.

Table 30.1 Immunosuppression therapies used in pediatric patients following organ transplantation

Drug class	Immunosuppression agents	Mechanism of action	Adverse effects
Calcineurin inhibitors	Tacrolimus	Calcineurin inhibitor blocking T-cell activation and proliferation	Nephrotoxicity, neurotoxicity, lymphomas and lymphoproliferative disease, cardiomyopathy, anemia, chronic diarrhea, onset of diabetes mellitus, electrolyte disturbances
	Cyclosporine	Interfering with activity and growth of T cells	Infection, malignancy, hypertension, dyslipidemia, post-transplant diabetes mellitus, renal failure, neurological effects, gingival hyperplasia, acne, hirsutism, hyperkalemia, hypomagnesemia
Mammalian target of rapamycin (mTOR) inhibitors	Sirolimus (rapamycin)	Binds to mTOR in T cells, suppressing T-cell proliferation by inhibiting progression from the G1 to S phase of the cell cycle	Hyperlipidemia, proteinuria, myelosuppression, poor wound healing, pneumonitis, hypersensitivity reactions
	Everolimus	A derivative of sirolimus with mechanism of action similar to sirolimus	Hypersensitivity reactions
Purine synthesis inhibitors	Mycophenolate mofetil	Targets an enzyme in the body called inosine monophosphate dehydrogenase that is important for the formation of DNA in cells	Gastrointestinal side-effects, neutropenia, opportunistic infections
	Azathioprine	Is converted into 6-mercaptopurine in the body where it blocks purine metabolism and DNA synthesis	Infection, malignancy, post-transplant diabetes mellitus, alopecia, nausea, vomiting, bone marrow suppression
	Cyclophosphamide	Cylotoxic effect on lymphocytes	Nausea, vomiting, bone marrow suppression, alopecia, joint pain, easy bruising and bleeding
Monoclonal antibodies	OKT3 (muromonab)	Binds to CD3 receptor (anti-CD3 monoclonal antibodies) of the T cell causing transient depletion of functional T cells from peripheral circulation	Cytokine release syndrome, opportunistic infections, post-transplant diabetes mellitus, gastrointestinal upset, bone marrow suppression, infusion-related reactions
	Basiliximab and daclizumab	Bind to the alpha chain of the IL-2 receptor (anti-CD25 antibodies) resulting in the inhibition of signal 3 of the T-cell activation pathway	Infection, malignancy, post-transplant diabetes mellitus, acute hypersensitivity reactions (rare)
	Rituximab	Anti-CD20 antibody that works by lowering the number of certain types of white blood cells (B cells) in the body	Severe infusion reaction, cardiac arrest, cytokine release syndrome, tumor lysis syndrome, causing acute renal failure, immune toxicity, malignancy, bowel obstruction and perforation
	Bebtacept (LEA29Y)	A fully human fusion protein with a binding affinity to CD86/CD80 on the antigen presenting cell, thus resulting in the blockade of T-cell activation	Anemia, diarrhea, urinary tract infection, peripheral edema, constipation, hypertension, pyrexia, graft dysfunction, cough, nausea, vomiting, headache, hypokalemia, hyperkalemia, leukopenia
	Eculizumab	A complete, humanized C5 monoclonal antibody that inhibits complement factor 5a, blocking terminal complement activation and the formation of membrane attack complexes	Life-threatening and fatal meningococcal infections, headache, and fever with nausea or vomiting
	Alefacept	It is thought to neutralize the effect of CD2-expressing T cells by complement-mediated lysis, interrupting the CD2 interaction with LFA-3, limiting helper T-cell adhesion to antigen-presenting cells, and disrupting effector T-cell receptor engagement with antigens and major histocompatibility complex molecules	Lymphopenia, malignancies, infections, hypersensitivity reactions, hepatic toxicity

(*Continued*)

Table 30.1 (Continued)

Drug class	Immunosuppression agents	Mechanism of action	Adverse effects
	Alemtuzumab (Campath-IH)	A monoclonal antibody targeting the CD52 antigen present on T and B lymphocytes, natural killer cells, and monocytes	Infection, malignancy, post-transplant diabetes mellitus, gastrointestinal effects
	Bortezomib	A proteasome inhibitor	Peripheral neuropathy, neutropenia, thrombocytopenia, gasrointestinal effects
Malononitrilamides	FK778(manitimus)	It inhibits both T-cell and B-cell functions by blocking *de novo* pyrimidine synthesis, inhibiting tyrosine kinase activity, and suppressing IgG and IgM antibody production	Anemia, angina pectoris, hyperlipidemia
Janus kinase inhibitors	Tofacitinib	These inhibit activity of the enzyme Janus kinase 3 (JAK3), by interfering with the JAK-STAT signaling pathway	Upper respiratory tract infections, diarrhea, headache
S1P-R agonists	FTY720 (fingolimod)	A sphingosine 1-phosphate receptor modulator. The exact mechanism is unknown, but is thought to work by reducing the immune system's attack on the central nervous system by retaining certain white blood cells (lymphocytes) in the lymph nodes	Bradycardia, encephalitis, macular edema
Polyclonal antibodies	Antithymocyte globulin	Causes depletion of T cells, modulation of various lymphocyte surface antigens, and interferes with the function of other immune effector cells	Cytokine-release syndrome, myelosuppression

Source: Reproduced from Malik et al [6] with permission of Wolters Kluwer.

the side-effects from induction agents are significant (polyclonal antibodies, opportunistic infections, post-transplant lymphoproliferative disorder, anaphylaxis, monoclonal antibodies, and hypersensitivity reactions). Induction therapy allows a delayed and gentle introduction of maintenance immunotherapy, thereby reducing the potential for harm (e.g. renal damage) from toxic drug concentrations [16,17].

Maintenance therapy

Steroids

Corticosteroids are used in most solid organ transplant protocols for induction, maintenance, and acute rejection. Their side-effects include hypertension, diabetes mellitus, osteopenia, poor wound healing, cataracts, emotional lability, hyperlipidemia, salt and water retention, Cushingoid habitus, weight gain, hirsutism, acne, and growth impairment. Steroid-free maintenance has been successfully achieved in liver, heart, and kidney but not lung transplantation [18–20].

Calcineurin inhibitors

Adult data comparing the two calcineurin inhibitors (CNIs) indicate that tacrolimus improved graft survival and prevented acute rejection more effectively than cyclosporine. Nephrotoxicity is an adverse side-effect common to both and is a major concern in pediatric solid organ transplant patients. Acute toxicity is dose dependent and can lead to chronic renal damage and transplantation. Renal-sparing strategies include the use of mycophenolic acid (MPA) and mTOR inhibitors. The side-effect profiles of CNI drugs are similar; generally hirsutism, hypertrichosis, gingival hyperplasia, hypertension, and hyperlipidemia are more likely with cyclosporine, and diabetes, tremor, peripheral neuropathy, alopecia, and gastrointestinal symptoms are commoner with tacrolimus. The seizures associated with CNI agents seem dose related and are thought to be due to ischemia from cerebral vasoconstriction. Autoimmune hemolytic anemia and leucopenia have been reported with both drugs, but may improve by switching to the other CNI.

Antiproliferative agents

The principle side-effect of azothioprine is bone marrow depression. Other concerns are an ultraviolet-dependent increase in skin cancers, pancreatitis, and hepatotoxicity. Azothioprine has largely been replaced by MPA-containing drugs such as mycophenolate mofetil (MMF), which have similar mechanisms of action but are more potent and have better efficacy [21]. The two main side-effects of MPA are gastrointestinal problems and marrow depression.

mTOR inhibitors

Mammalian target of rapamycin inhibitors such as sirolimus and everolimus cause an arrest in cell cycle and cell differentiation. Sirolimus inhibits vascular smooth muscle proliferation and hence may have a protective effect against coronary artery vasculopathy in cardiac allografts [22]. Adverse side-effects of mTOR inhibitors include renal dysfunction, hyperlipidemia (typically responds to statins), delayed wound healing, bone marrow suppression, ampthous ulcers, and systemic inflammatory response syndrome (e.g. pnuemonitis). The anti-CD20 monoclonal antibody rituximab may be added.

Acute rejection therapy

The usual first-line therapy is steroids, with the addition of polyclonal lymphocyte-depleting antibodies (antithymocyte globulin) in more severe cases of rejection. Maintenance immunosuppression might be switched from cyclosporine to tacrolimus. Antibody-mediated rejection is treated with plasmapheresis and IV immunoglobulin.

Newer agents

Normal immune tolerance to self-antigens involves central and peripheral mechanisms that potentially may be manipulated to allow recipient tolerance to alloantigens [23]. Anti-CD52 antibodies cause profound lymphocyte depletion and held promise as a tolerance-inducing agent but clinical studies to date are discouraging.

Abatacept and belatacept cause co-stimulation blockade of T-cell CD28 receptor binding to CD80/CD86 of the antigen-presenting cell and may allow less nephrotoxic maintenance regimens. Pediatric data are lacking.

KEY POINTS: IMMUNOSUPPRESSION FOR SOLID ORGAN TRANSPLANTATION

- Induction, maintenance, and desensitization protocols vary widely between centers; most transplant recipients receive indefinite maintenance therapy
- Induction immunotherapy is intense immunosuppression in the immediate perioperative phase of organ implantation to reduce the incidence of acute rejection in the early post-transplant phase
- The maintenance phase usually consists of corticosteroids, but many other agents such as calcineurin inhibitors, antiproliferative agents, mTOR inhibitors, and monoclonal antibodies may be used

Liver transplantation

Thomas E. Starzl performed the first human liver transplant in a 3-year-old child with biliary atresia in 1963. The attempt ended in failure from intraoperative hemorrhage, although Starzl performed the first successful liver transplant in a child in 1967. One-year survival after liver transplant remained below 50% until the introduction of cyclosporine in 1979. By 1983 pediatric liver transplantation was deemed the standard of care for hepatic failure or end-stage liver disease [24], and in 2002 the pediatric end-stage liver disease (PELD) and model for end-stage liver disease (MELD) scores were implemented to prioritize organ allocation to the sickest patients, rather than to those with the longest wait time, as had been the case. In addition, the PELD system conferred special status and protection to pediatric organs and recipients. Today pediatric liver transplantation is one of the most successful solid organ transplants. According to the US Organ Procurement and Transplantation Network (OPTN)/Scientific Registry of Transplant Recipients data, the 1-year patient survival rate is 88–94%, depending on the age at transplant [25]. The number of pediatric liver transplants per year has

remained steady in the last 10–15 years, averaging approximately 600 annually in the USA [25]. Currently, pediatric transplants account for about 10% of all liver transplants in the USA, and the majority of these transplants involve children less than 12 years of age. Liver transplantation is now performed on infants less than 3 months of age with graft survival and patient survival similar to that of older patients [26]. There is evidence that higher volume pediatric liver transplant centers (i.e. 10 or more transplants per year) have significantly lower wait list mortality, a higher likelihood of transplant, and higher survival at 5 and 10 years after transplant (91% and 89%, respectively) [27].

Indications

The indications and clinical characteristics for liver transplantation are listed in Table 30.2 [25]. Life-threatening complications secondary to hepatic failure or chronic end-stage liver disease are the primary indications for transplantation. Another indication is from progressive primary liver disease refractory to maximal medical management, before the development of life-threatening complications. A smaller number of liver transplants are performed for metabolic disease, in which liver replacement is curative, and for unresectable primary liver tumors. Fulminant hepatic failure is the indication for liver transplantation in approximately 11% of pediatric cases [28]. These children commonly present with rapidly developing life-threatening complications, and, therefore, the establishment of the underlying diagnosis is not always feasible. Approximately 13% of children undergo liver transplantation because of metabolic diseases [29–32], and these patients generally have excellent outcomes [31,33]. Pediatric patients with liver tumors represent a growing group of transplant recipients. Hepatoblastoma is the most common pediatric primary liver tumor. Resection in combination with systemic chemotherapy is the preferred method of treatment. If the tumor is unresectable after appropriate chemotherapy, transplantation may be offered if there has been a demonstrated response to therapy, even in the face of pulmonary metastases [34–36].

The MELD score (serum creatinine, bilirubin, sodium, and international normalized ratio (INR)) is calculated for patients age 12–17 years, and the PELD score (albumin, bilirubin, INR, growth failure, and age at listing) is used for patients under age 12 years.

Pathophysiology of end-stage liver disease

Patients with end-stage liver disease that results from many causes manifest similar pathophysiology (Table 30.3). The clinical manifestations of end-stage liver disease develop

Table 30.2 Clinical characteristics of pediatric liver transplant recipients, 2004–2006 and 2014–2016. Pediatric candidates aged 12–17years can be assigned model for end-stage liver disease (MELD) or pediatric end-stage liver disease (PELD) scores

Characteristic	2004–2006		2014–2016	
	N	%	*N*	%
Diagnosis				
Acute liver failure	213	12.3	157	9.3
Cholestatic biliary atresia	505	29.3	544	32.3
Other cholestatic	219	12.7	221	13.1
Hepatoblastoma	88	5.1	125	7.4
Metabolic	178	10.3	272	16.2
Other/unknown	523	30.3	364	21.6
Blood type				
A	582	33.7	553	32.9
B	209	12.1	232	13.8
AB	70	4.1	70	4.2
O	865	50.1	828	49.2
Medical condition				
Hospitalized in ICU	484	28.0	307	18.2
Hospitalized, not ICU	274	15.9	293	17.4
Not hospitalized	968	56.1	1073	63.8
Hospitalization unknown	0	0.0	10	0.6
Medical urgency				
Status 1A/1B	573	33.2	590	35.1
MELD/PELD ≥35	168	9.7	393	23.4
MELD/PELD 30–34	192	11.1	181	10.8
MELD/PELD 15–29	471	27.3	339	20.1
MELD/PELD <15	315	18.3	178	10.6
Unknown	7	0.4	2	0.1
Any MELD/PELD exception	419	24.3	673	40.0
All recipients	1726	100.0	1683	100.0

Source: Reproduced from Kim et al [25] with permission of John Wiley and Sons.

Table 30.3 Pathophysiology of end-stage liver disease

Organ system	Common findings
Cardiovascular	Hyperdynamic circulation; increased cardiac output, decreased systemic vascular resistance, increased stroke volume and ejection fraction
	Expanded plasma volume
	Arteriovenous shunting
Pulmonary	Restrictive pulmonary function secondary to ascites
	Hypoxemia secondary to ventilation/perfusion mismatch, impaired hypoxic pulmonary vasoconstriction, intrapulmonary shunting
	Pulmonary hypertension
	Hepatopulmonary syndrome
Central nervous system	Encephalopathy
	Cerebral edema with fulminant hepatic failure
Gastrointestinal	Hepatic dysfunction: synthetic, metabolic, excretory aspects
	Portal hypertension (esophageal varices, portal hypertensive gastropathy)
	Delayed gastric emptying
Renal	Renal dysfunction from prerenal azotemia (secondary in diuretics)
Hematological	Elevated PT
	Thrombocytopenia
	Anemia
	Hypofibrinogenemia, dysfibrinogenemia
	Fibrinolysis
	Disseminated intravascular coagulation
Fluids, electrolytes, acid–base status	Intravascular volume depletion (secondary to diuretics)
	Hypokalemia, hyponatremia
	Metabolic alkalosis
	Metabolic acidosis (especially fulminant hepatic failure)

PT, prothrombin time.

from the loss of hepatocytes and resulting fibrosis. The loss of hepatocytes results in the development of coagulopathy, hypocholesterolemia, hypoalbuminemia, and encephalopathy. Hepatocellular injury results in fibrosis and destruction of the portal triad with increased resistance to liver blood flow leading to portal hypertension manifest by varices (esophageal, bowel), hemorrhoids, ascites, spontaneous bacterial peritonitis, splenomegaly with thrombocytopenia, and hepatic encephalopathy.

The cardiovascular system undergoes marked changes as the child develops cirrhosis and end-stage liver disease. Patients frequently have a hyperdynamic circulation, decreased systemic vascular resistance, increased cardiac output, and a slightly decreased arterial blood pressure. The pathophysiology producing peripheral vasodilation remains obscure, and the "humoral factor" theory is the most widely accepted explanation [37]. In cirrhosis, increased intrahepatic resistance induces portosystemic collateral formation, allowing gut-derived humoral substances (endocannabinoids and nitric oxide) to directly enter the systemic circulation without detoxification by the liver. The hyperdynamic circulation of the patient has important implications for the anesthesiologist, including a decreased sensitivity to catecholamines and vasoconstrictors, an increase in mixed venous oxygen saturation, with a decreased arteriovenous oxygen difference. Because of the vasodilated state, anesthetics may cause severe hypotension in this patient population.

Patients with end-stage liver disease also manifest significant changes in the pulmonary system and are frequently hypoxemic. Many patients with chronic liver disease have abnormal pulmonary mechanics and some degree of alveolar hypoventilation. The presence of ascites and increased infra-abdominal pressure alter the respiratory mechanics and often reduce functional residual capacity. Atelectasis produces ventilation/perfusion mismatch and is common in patients with ascites, hepatosplenomegaly, and/or pleural effusions. Hepatopulmonary syndrome is characterized by hypoxia from intrapulmonary arteriovenous shunting and intrapulmonary vascular dilation [38]. The diagnosis is predicated on either arterial hypoxia (PaO_2 <70 mmHg) or an alveolar–arterial gradient greater than 20 mmHg in the setting of pulmonary vascular dilation. Intrapulmonary vascular dilation can best be demonstrated on echocardiography or by macroaggregated albumin perfusion scan [39]. Again, the most likely explanation for the development of hepatopulmonary syndrome is related to systemic absorption of nitric oxide from the gut without detoxification in the liver. Supplemental oxygen therapy is the mainstay of supportive therapy and definitive treatment is liver transplantation. A case series of seven children with hepatopulmonary syndrome and severe hypoxemia were successfully transplanted and recovered from hepatopulmonary syndrome on average within 24 weeks of their liver transplant [40].

Portopulmonary hypertension (PPH) is defined as pulmonary artery hypertension (pulmonary systolic pressure ≥25 mmHg) in the setting of normal pulmonary capillary wedge pressure and portal hypertension [41]. The incidence of PPH is 0.2–0.7% in adults with cirrhosis and is present in 3–9% of adults undergoing liver transplantation [42]. The incidence in children is probably lower, and occurrences are limited to case reports and one case series. The signs and symptoms of PPH on presentation include a new heart murmur, dyspnea, and syncope. Echocardiography can diagnose pulmonary hypertension, and is one reason why routine screening of potential liver transplant candidates includes a baseline echocardiogram [43]. The largest retrospective review of 43 adult patients found mean pulmonary artery pressure (MPAP) to be predictive of outcome. Those patients with a MPAP <35 mmHg did not have increased mortality after orthotopic liver transplantation. In contrast, those with a MPAP of 35–45 mmHg had a mortality of 50%, and those with a MPAP >50 mmHg had 100% mortality [44]. Among children with PPH, early identification is essential. And if PPH is suggested by screening echocardiography, a cardiac catheterization should be performed to confirm the diagnosis, measure the pulmonary pressures, and assess the response to nitric oxide and epoprostenol. Children who respond to medical management may be candidates for liver transplantation [45]. Severe PPH is generally a contraindication for liver transplantation because of the high mortality.

Hepatic encephalopathy is a significant neurological complication of liver disease that may be acute, as seen in fulminant hepatic failure, or chronic. Table 30.4 presents the staging of hepatic encephalopathy [46]. Cerebral edema is a feature of both acute and chronic encephalopathy; however, it is more severe and happens more rapidly in acute hepatic encephalopathy commonly leading to increased intracranial pressure (ICP). The pathogenesis is thought to be due to hyperammonemia that more readily crosses the blood–brain barrier and will cause astrocytes to swell, leading to low-grade cerebral edema [47]. Blood ammonia levels develop from catabolism of endogenous protein and gastrointestinal absorption. Ammonia is formed when bacteria break down nitrogen-containing products in the gut which are then absorbed into the portal circulation. Therefore, blood ammonia levels increase from increased catabolism due to infection, increased gut absorption from high protein diets, and gastrointestinal bleeding and renal failure. Arterial ammonia levels over 200 μg/dL have been strongly correlated with cerebral herniation and death. Other factors that may contribute to cerebral edema include benzodiazepines, hyponatremia, and inflammatory cytokines. Management typically focuses on reducing gastrointestinal production and absorption of ammonia. Lactulose is often prescribed to create an osmotic diuresis and

Table 30.4 Classification of the severity of acute and chronic hepatic encephalopathy

Grade 0	Minimal hepatic encephalopathy, lack of detectable changes in personality or behavior; no asterixis
Grade 1	Trivial lack of awareness, shortened attention span, sleep disturbance, altered mood, slowing the ability to perform mental tasks; asterixis may be present
Grade 2	Lethargy or apathy, disorientation to time, amnesia of recent events, impaired simple computations, inappropriate behavior, slurred speech; asterixis is present
Grade 3	Somnolence, confusion, disorientation to place, bizarre behavior, clonus, nystagmus, positive Babinski sign; asterixis usually absent
Grade 4	Coma, lack of verbal, eye, and oral response to stimuli

Source: Reproduced from Zafirova and O'Connor [46] with permission of Wolters Kluwer.

to acidify the lumen of the gut to trap ammonia and minimize absorption, yet it has not been shown to improve survival [46]. Antibiotics (e.g. neomycin and metronidazole) are sometimes used to kill the gastrointestinal bacteria involved in metabolizing nitrogen products to ammonia.

As hepatic encephalopathy progresses, the child's ability to manage the airway should be carefully assessed. Children with grade 3 and 4 disease commonly require endotracheal intubation to protect their airway and to maintain oxygenation and ventilation. Increased ICP occurs in 38–81% of adult patients with fulminant hepatic failure [48] and brain computed tomography (CT) is recommended in those with grade 3–4 hepatic encephalopathy. Simple therapeutic measures, which can be performed on all patients, include elevation of the head of the bed to 30° and minimizing stimulation. Acute hyperventilation fails to reduce episodes of cerebral edema, and it does not delay onset of herniation [48]. ICP monitors may help to diagnose intracranial hypertension and optimize management, although their use remains controversial [49,50]. Non-randomized trials have shown no survival advantage. Medical management to reduce ICP includes intravenous administration of sodium thiopental or propofol to minimize stimulation and to directly reduce ICP. Mannitol can be administered if ICP remains increased. Hypothermia has also been used to treat increased ICP. In a trial of 14 patients with fulminant hepatic failure, ICP was significantly reduced by mild hypothermia to 32–33°C [49]. Corticosteroids have no role in this setting [51], and orthotopic liver transplantation remains the definitive treatment.

The gastrointestinal system undergoes many changes when patients have end-stage liver disease, including abnormal synthetic, metabolic, and excretory functions of the liver and portal hypertension. Complications of portal hypertension include: (1) altered hepatic and intestinal lymph flow and decreased plasma oncotic pressure, which facilitate the development of ascites; and (2) gastrointestinal bleeding from esophageal and gastric varices or from portal hypertensive gastropathy.

Renal failure commonly complicates acute and chronic liver disease in adults; however the incidence in children is considerably lower [52]. Renal insufficiency is common and may be caused by prerenal azotemia, acute tubular necrosis, or hepatorenal syndrome. Prerenal azotemia may develop from the use of diuretics, gastrointestinal bleeding, splanchnic pooling, and sepsis. Acute tubular necrosis develops when the kidney becomes ischemic from these same etiologies. Hepatorenal syndrome is characterized by renal insufficiency or failure in the setting of liver failure and portal hypertension. The pathophysiology of hepatorenal syndrome is thought to be secondary to intense renal vasoconstriction from activation of the renin–angiotensin, arginine–vasopressin, and sympathetic nervous systems [53]. However, hepatorenal syndrome presents as prerenal azotemia (increased creatinine, decreased urine sodium); a fluid challenge will not improve renal function. Rapid progression of renal failure from hepatorenal syndrome is classified as type 1, and is characterized by a rapid progression of renal failure with a 100% increase in creatinine in less than 2 weeks. This form usually occurs in acute liver failure. In type 2, renal failure progresses over weeks to months. Dopamine, diuretics, and octreotide have all been used to remove excess volume and optimize renal perfusion; however orthotopic liver transplantation remains the definitive therapy because renal failure is reversible if the liver is replaced [54]. Combined liver–kidney transplantation is an option for children with both liver and renal disease.

Hematological abnormalities occur with liver disease because the synthesis of fibrinogen and factors II, V, VII, IX, and X decreases [55]. Because of the decreased synthesis of these factors, the prothrombin time (PT) and the partial thromboplastin time (PTT) are increased. Thrombocytopenia is common when patients develop hypersplenism in response to portal hypertension. Also, anticoagulant factors (protein C and S, antithrombin III) are reduced in patients with end-stage liver disease. The altered hemostasis increases the risk of inserting vascular catheters and nasogastric tubes, and increases the potential for excessive bleeding from surgical wounds. Antifibrinolytics such as aprotinin and aminocaproic acid have been reported to reduce blood loss; however, there are insufficient data to recommend their use.

Electrolytes and acid–base balance often are altered in chronic liver disease by renal dysfunction and/or the use of diuretics. Acid–base changes may be due to renal dysfunction or to changes in ventilation. The intravascular volume status may be difficult to assess in patients with liver disease due to the presence of ascites, peripheral edema, and anasarca. The effective plasma volume is often inadequate. Consequently, intraoperative measurement of central filling pressures is required during transplantation.

Extracorporeal liver support

In recent years, extracorporeal liver support has been utilized in pediatric patients with acute severe liver failure as a bridge to transplant. One of the commonly used systems is the Molecular Adsorbent Recirculating System (MARS®, Gambro, Inc., Lakewood, CO, USA), utilizing albumin dialysis, which was introduced in the 1990s in adult patients [56].

A large-bore, double-lumen catheter similar to a hemodialysis catheter is placed in a large central vein; and via a circuit primed with human albumin and two special filters, the patient's blood is circulated through the MARS machine, removing protein-bound and water-soluble toxins that have accumulated as a result of liver failure. The water-soluble substances are subsequently removed from the albumin dialysate via a conventional hemodialysis filter. Albumin-bound substances are adsorbed onto a charcoal filter and an anion exchanger placed in series in the albumin dialysate circuit. Adult and pediatric (<25 kg) sized filters are available. MARS dialysis can be performed continuously, or once daily for 8–10 h sessions.

Indications for MARS therapy include acute liver failure with significant hepatic encephalopathy, high indirect bilirubin, coagulopathy, hemodynamic instability, hepatorenal and hepatopulmonary syndromes, and plasma ammonia >200 mMol/L [56]. In a series of 20 pediatric patients averaging 7 years of age and awaiting liver transplant, or suffering from acute graft failure after transplant, all were mechanically ventilated and 19 or 20 required vasopressors [57]. Thrombocytopenia and significant bleeding were frequent, and death occurred before transplant in four patients – two from cerebellar herniation and two from cardiorespiratory failure. The 3-month survival for MARS-treated patients was

65%. This therapy is likely to be used more commonly in the future for pediatric liver transplant patients with acute liver failure.

KEY POINTS: INDICATIONS FOR LIVER TRANSPLANT AND PATHOPHYSIOLOGY

- Biliary atresia is the most common indication for liver transplant in children
- Portal hypertension, coagulopathy, hepatic encephalopathy, hyperdynamic circulation, ascites, hyperbilirubinemia, and renal dysfunction are all common in hepatic failure
- Extracorporeal liver support (MARS) is increasingly used for "liver dialysis" as a bridge to liver transplantation

Anesthetic management

Preoperative evaluation

Most transplant centers utilize a multidisciplinary approach for the evaluation of patients for liver transplantation. Typical laboratory studies include blood typing, blood chemistries, liver and renal function tests, coagulation profiles, and viral serologies. Cardiac and pulmonary systems are assessed through electrocardiogram (ECG), chest x-ray, and echocardiography. A careful neurological examination should be performed to detect any problems present in the preoperative period. Anatomical assessment of the native liver typically includes abdominal ultrasound and/or CT or magnetic resonance imaging (MRI). A liver biopsy may be indicated to confirm the diagnosis or severity of the liver disease. Also, an assessment of the psychosocial and financial situation of the child's family is performed. Following the initial evaluation, the patient's history and data are presented to a selection committee, which decides if the patient is a candidate for transplantation. Patients approved for transplantation are then activated on the transplant center's recipient list. In situations of acute hepatic failure or rapid decompensation of chronic liver disease, the evaluation process can be condensed to a few hours. Contraindications to liver transplantation are listed in Box 30.1 [58].

Referral to the transplant center and acceptance of the child as a transplant candidate allows the transplant center physicians the opportunity to optimize the patient's medical condition while the child awaits transplantation. Medical therapy to control ascites, infection, and encephalopathy is initiated. Nutritional assessment and diet modification are frequently performed. Endoscopy and sclerotherapy may be performed to treat gastrointestinal bleeding. If the patient has cardiopulmonary disease, additional studies, including arterial blood gases, response to inhaled oxygen, and cardiac catheterization may be indicated. Vitamin K may be administered to improve hemostatic function. Prophylactic dental work or dental extraction and tonsillectomy and adenoidectomy are performed if required prior to transplantation and initiation of immunosuppression. A summary of the preoperative evaluation is presented in Box 30.2 [58].

Perioperative period

In general, patients are admitted from home when a potential donor is identified. Because of the logistic complications associated with scheduling, performing donor surgery, and transporting the donor organ to the transplant center, often only 8–12 h notice is provided to the patient, family, and transplant team members. Upon admission to the hospital, interval history and physical examination are performed to seek evidence of new changes and complications since the original pretransplant evaluation. Whenever possible, the child is made NPO prior to surgery. In addition to routine blood tests, multiple additional blood samples are obtained for serologic studies, and specialized immunotesting is undertaken. A peripheral intravenous line is usually started and maintenance fluids administered. Disease-specific anesthetic considerations are listed in Table 30.5 [58].

Following arrival of the donor organ at the hospital, final inspection and possible biopsy and frozen section of the liver are performed. Following notification from the transplant surgeon that the liver is appropriate for transplantation, the child is transported to a warm operating room. In some children, especially those who are older, premedication may be required with either intravenous or oral midazolam. Children with hepatic encephalopathy should not receive premedication because midazolam may produce significantly greater central nervous system depression among these patients and may potentially increase ICP. Routine monitors (pulse oximetry, ECG, arterial blood pressure) are applied prior to induction of anesthesia. One hundred percent oxygen is administered by

Box 30.1: Contraindications to pediatric liver transplantation

- Rapidly progressing hepatocellular carcinoma with metastasis
- Extrahepatic malignancy
- Uncontrolled systemic infection
- Severe multisystem mitochondrial disease
- Niemann–Pick type C
- Severe portopulmonary hypertension not responsive to medical therapy
- Mean pulmonary artery pressure (MPAP) greater than 35 mmHg despite therapy

Source: Reproduced from Wasson et al [58] with permission of Elsevier.

Box 30.2: Summary of preoperative evaluation for pediatric liver transplantation

- Cause of liver failure and reason for transplant
- Coagulation status (prothrombin time, partial thromboplastin time, international normalized ratio, fibrinogen, platelets)
- Sequelae of portal hypertension (e.g. esophageal varices, significant ascites)
- Current liver and renal function
- Cardiopulmonary co-morbidities: review of recent cardiology evaluation and any imaging studies (e.g. echocardiography, stress test)
- Acid–base status
- Electrolytes and blood glucose (e.g. Na^+/K^+)
- Temperature irregularities
- Prior surgeries or procedures
- Any other existing co-morbidities and their anesthetic implications

Source: Reproduced from Wasson et al [58] with permission of Elsevier.

Table 30.5 Disease-specific anesthetic considerations for pediatric liver transplantation

Diagnosis	Anesthetic considerations
Autoimmune hepatitis	Preoperative immunosuppression
Alagille syndrome	Congenital heart disease
Hyperoxaluria	Hypertension, renal failure, heart failure
Alpha-1-antitrypsin	Pulmonary disease
Wilson disease	Increased sensitivity to neuromuscular blockade
Hemochromatosis	Diabetes, cardiomyopathy, anemia
Familial intrahepatic cholestasis	Malnutrition
Cystic fibrosis	Lung disease, malnutrition

Source: Reproduced from Wasson et al [58] with permission of Elsevier.

facemask. Because of concerns that these patients have a full stomach and may aspirate gastric contents, cricoid pressure is applied and a rapid sequence induction of anesthesia is performed for most patients. Those who present for elective transplant to correct a metabolic disease may undergo inhalational induction. Since patients with significant ascites are likely to have a reduced functional residual capacity, adequate preoxygenation is required. Once the airway is secure, mechanical ventilation with an increased inspired concentration of oxygen and positive end-expiratory pressure is initiated. Cuffed endotracheal tubes are favored because they make a reliable seal between the tracheal tube and the tracheal mucosa and reduce the risk of inadequate ventilation and monitoring of ventilation from a leak around the endotracheal tube.

Following tracheal intubation, vascular access is obtained and monitoring catheters are inserted. Ideally, two large-bore intravenous lines are placed in the upper extremities (20–22 gauge for infants, 18–20 gauge for a young child, and larger for older children). Adequate venous access is critical during any liver transplant procedure because the anesthesia team must be able to respond rapidly to surgical hemorrhage. The fluid delivery system must allow for sufficient control over the volume and rate of fluid and blood product administration in small children to prevent overhydration. An arterial catheter is inserted, preferably in a radial artery, because the aorta may be cross-clamped during reconstruction of hepatic arterial inflow. A multi-lumen central venous catheter is inserted after induction. One lumen is used for central venous pressure monitoring, and the other lumens used for infusion of medications and/or volume. The surgical team may decide to insert a tunneled central line if long-term access is likely to be needed in the postoperative period. Measuring pulmonary artery pressures may facilitate the perioperative management of patients with cardiac disease or associated pulmonary hypertension. Except for these rare cases, central venous pressure monitoring is sufficient in infants and children for liver transplant. See Chapter 19 for more detail about vascular access procedures. Many adult centers use transesophageal echocardiography to monitor cardiac function and filling during liver transplantation; however, this is much less common in the pediatric setting [59].

Particular attention is paid to maintaining normal body temperature during pediatric liver transplantation. Numerous factors facilitate development of unintentional hypothermia: exposure of the abdominal contents to air, duration of surgery, rapid administration of cool intravenous fluids and blood products, and implantation of the cold liver graft and washout of the cold storage solution during reperfusion of the organ. Rigorous attention is paid to warming the operating room and to the use of insulated wrapping of exposed extremities, forced-air warming blankets, humidified anesthesia circuit, and warming of all intravenous fluids.

No particular anesthetic regimen has proven superior in liver transplantation. A combination of potent inhaled anesthetic, bolus doses of opioids or an infusion, provides a relatively stable intraoperative course during liver transplantation. Higher concentrations of inhaled anesthetics reduce splanchnic blood flow and should probably be avoided. Sevoflurane, isoflurane, and desflurane are commonly used with success when added to a balanced anesthetic technique with opioids. Nitrous oxide should not be used in order to avoid bowel distension. A comparison of right ventricular function in adult patients undergoing liver transplantation found no difference between propofol and isoflurane [60]. Even though the primary metabolic pathway for propofol is hepatic, there appears to be extrahepatic metabolism in the lung, kidney, and intestine [61,62].

Intravenous opioids have been used extensively in the anesthetic management of adult and pediatric patients undergoing liver transplant. Although end-stage liver disease is likely to affect the distribution and plasma clearance of opioids, the functioning newly transplanted liver graft will improve opioid clearance. Opioid analgesics undergo hepatic biotransformation via mixed function oxidase (e.g. fentanyl) and glucuronosyltransferase (e.g. morphine). Because the hepatic extraction of morphine and fentanyl is high, plasma clearance is less affected by alterations in hepatic function than by alterations in hepatic blood flow. Morphine, fentanyl, and sufentanil appear to have unchanged plasma clearance and volumes of distribution in patients with end-stage liver disease, which may reflect the ability of the large volume of distribution to buffer any decrease in drug metabolism. In contrast, alfentanil, with its volume of distribution approximately 25% that of the other opioids, has a decreased plasma clearance and an increased free fraction of drug in patients with cirrhosis. The impact of large changes in and replacement of intravascular volume during the course of a lengthy liver transplant procedure is not known.

Liver disease affects the duration of action of non-depolarizing muscle relaxants. The action of pancuronium is prolonged in patients with liver disease. The duration of action of vecuronium depends on the extent of liver disease and on the dose of vecuronium. Vecuronium in a bolus of 0.1 mg/kg has the same pharmacokinetics in both patients with normal livers and those with liver disease [63]. In more advanced liver disease, a dose of 0.2 mg/kg of vecuronium may have a prolonged duration of action [64,65]. Similarly, rocuronium will have prolonged duration of action after repeated doses despite a normal onset of action for the first dose [66]. Redistribution of the drug within the body may be important for the termination of the drug's effect in patients with liver disease, but when larger doses of drug are administered, reduced hepatic clearance becomes more evident. Studies suggest that the liver graft with normal function rapidly resumes its role of drug metabolism.[67,68]. Despite the overall uncertainty of anesthetic drug metabolism in the

perioperative period following liver transplantation, delayed recovery from anesthetic drugs and neuromuscular blockade rarely poses a clinical problem. The timing of extubation of the trachea varies among centers; however, immediate postoperative extubation has gained acceptance and is practiced more commonly. In the authors' institutions, tracheal extubation in the operating room is performed in over 50% of patients. Most commonly, the decision to extubate the patient early is based on the presence or absence of co-morbidities.

Because of the duration of the procedure and the potential for hypoperfusion of the skin and extremities, positioning is critical to prevent injuries. All extremities should be padded, and all cables and wires need to be wrapped and protected from the skin. The head should be turned and repositioned periodically to prevent pressure sores and alopecia.

KEY POINTS: PREOPERATIVE EVALUATION AND PERIOPERATIVE PERIOD FOR LIVER TRANSPLANTATION

- Careful physical exam, lab studies, echocardiography, radiography, and ultrasound/CT/MRI are necessary before transplant listing
- Arterial and central venous access are required for liver transplant surgery
- A variety of anesthetic regimens can be used; avoiding drugs with extensive hepatic metabolism is important

Surgical procedure

Liver transplantation is usually divided into four stages: dissection (preanhepatic), anhepatic, reperfusion, and biliary anastamosis. During the dissection period, the liver is mobilized via a large bilateral subcostal incision (Fig. 30.3) [69]. All perihepatic adhesions are lysed; the suprahepatic vena cava, infrahepatic vena cava, and structures in the porta hepatis (portal vein, hepatic artery, and common bile duct) are identified and mobilized. Lysis of dense adhesions following a Kasai portoenterostomy or other previous surgery usually prolongs the dissection time and increases blood loss during this period. Adequate replacement of blood components during this time is essential. Common problems and goals of the preanhepatic phase are summarized in Table 30.6 and Box 30.3 [58].

Prior to implantation, the donor organ is stored in preservation solution, most commonly University of Wisconsin solution. Because of the high potassium content (120 mEq/L), the donor organ is perfused with a cold crystalloid or colloid solution to remove the preservation solution from the liver before the liver is implanted. In the case of reduced-size liver transplants, the partial hepatectomy of the donor liver is performed on the back table prior to implantation. When the dissection phase is complete in the recipient, the preservation solution is flushed out of the donor liver, and it is brought onto the operative field. However, flushing the donor liver with large volumes of fluid does not always remove all of the potassium, air, and particulate matter. Consequently, when the donor organ is reperfused, the recipient will be subjected to a bolus of hypothermic solution, and may be subjected to hyperkalemia and thrombotic and air emboli. Bradycardia and increases in pulmonary artery pressure are common, and, occasionally, there is a hyperkalemic cardiac arrest at the time the donor organ is reperfused.

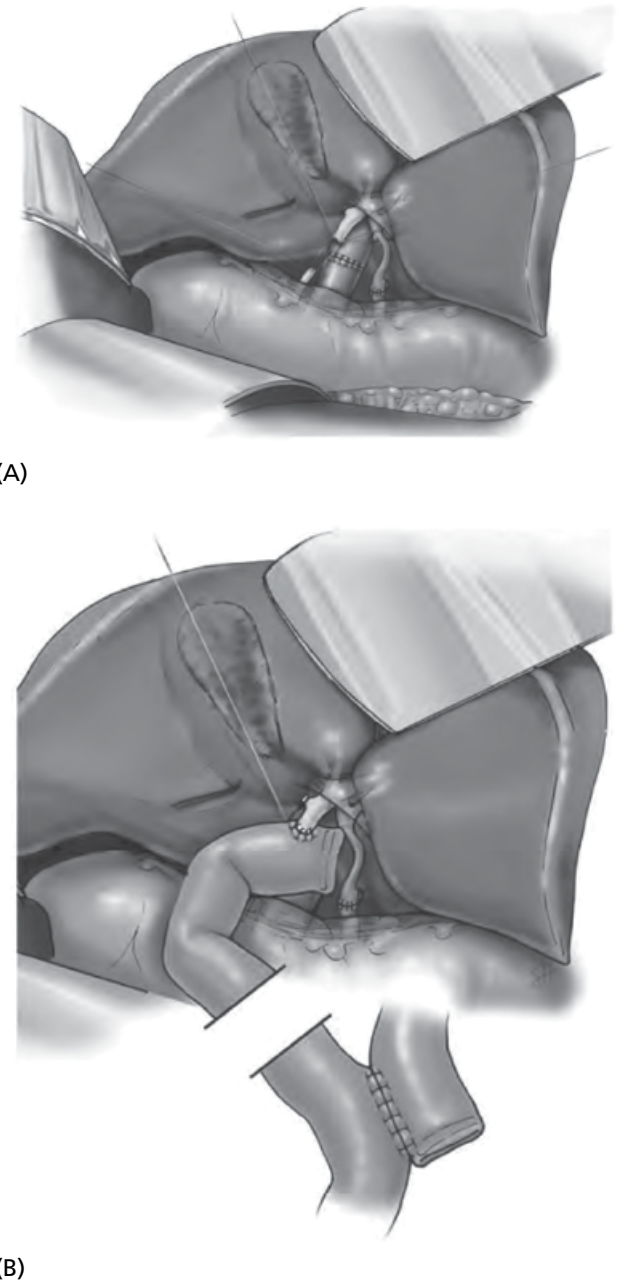


Figure 30.3 Surgical technique for liver transplantation. (A) Whole allograft with choledocholedochostomy showing completed portal venous (central) and hepatic arterial (right) anastomoses. The donor and recipient bile ducts have been aligned with the corner sutures in place for anastomosis. (B) Whole allograft with completed hepaticojejunostomy. Biliary anastomosis is in the foreground, whereas the portal venous and hepatic arterial anastomoses are in the background. Caval anastomoses are not seen. *Source*: Reproduced from Cotton et al [69] with permission of Wolters Kluwer.

The anhepatic stage begins with cross-clamping the suprahepatic vena cava, infrahepatic vena cava, portal vein, and hepatic artery. This surgical approach will significantly reduce preload from cross-clamping the inferior vena cava. However, patients with chronic cirrhosis develop collateral circulation, and an inferior vena cross-clamp is generally well tolerated.

Table 30.6 Common complications during the preanhepatic (dissection) period

Problem	Risk factors	Treatment
Massive hemorrhage Hypotension	Impaired synthetic function Prior abdominal surgery Bleeding Large-volume ascites drained Acidosis	Transfuse as necessary Vasopressors 5% albumin for ascites May need vasopressor infusions

Source: Reproduced from Wasson et al [58] with permission of Elsevier.

Box 30.3: Anesthetic goals during the preanhepatic (dissection) period

- Maintenance of hemodynamic stability
- Replacement blood or volume losses
- Avoidance of significant acidosis
- Avoid electrolyte derangements (K^+ or Ca^{2+})
- Normothermia and normoglycemia

Source: Reproduced from Wasson et al [58] with permission of Elsevier.

Table 30.7 Anesthetic goals during the anhepatic period

Goal	Target or treatment
Maintenance of intravascular volume and hemodynamic stability	Hematocrit 24–27% (hemoglobin 8–9 g/dL) CVP 6–10 mmHg Use vasopressor infusions as necessary
Maintain normoglycemia	May need dextrose bolus or infusion
Maintain normothermia	Bair Hugger™, warmed fluids, heat–moisture exchanger, low-flow anesthesia
Maintenance of acid–base balance	Hyperventilation Sodium bicarbonate boluses (1–2 mEq/kg)
Maintain normal calcium and low–normal potassium levels	Replace Ca^{2+} as necessary Treat any hyperkalemia

Source: Reproduced from Wasson et al [58] with permission of Elsevier.

Partial clamping of the inferior vena cava is used for reduced size grafts, or when inferior vena cava cross-clamping produces cardiovascular instability. Using the piggy-back technique [70], the liver is dissected away from the inferior vena cava, the short hepatic veins, portal vein, and left, right, and middle hepatic veins. The infrahepatic vena cava of the donor is oversewn, and the suprahepatic vena cava is anastomosed to the native hepatic veins. In addition, a portocaval shunt can be established for children who do not tolerate clamping of the portal vein. Typically, these recipients have not developed collateral flow secondary to portal hypertension (e.g. metabolic liver disease and acute fulminant hepatic failure). During the anhepatic period, the native liver is completely excised, bleeding is controlled in the retrohepatic area, and the donor liver is sutured in place. The liver is most commonly reperfused with venous inflow, which accounts for approximately 80% of liver blood flow. The anhepatic period ends with restoration of blood flow to the new liver. A summary of anesthetic goals during the anhepatic phase is presented in Table 30.7 [58].

Following restoration of blood flow into the new liver, the final stage of the operation, reperfusion, has started. The surgical goals during this time include completion or revision of the hepatic artery anastomoses and establishment of biliary drainage. In infants and children, reconstruction of the hepatic arterial inflow may be more difficult and frequently includes reconstruction via a patch graft from the recipient aorta, or donor saphenous vein graft to the celiac trunk, hepatic artery, or aorta. Biliary drainage may occur via a direct choledochocholedochostomy, or more commonly in children, via a Roux-en-Y choledochojejunostomy. A major goal during the early reperfusion period is the control of bleeding. This period requires close communication between surgeons and anesthesiologists to determine the presence of a coagulopathy (common in the early reperfusion period) as opposed to defined surgical bleeding (common following total hepatectomy of the native liver and multiple vascular anastomoses and following previous abdominal surgery). The operating team uses a variety of clinical observations (color, texture, bile production) and laboratory measurements (prothrombin time, metabolic acidosis, ionized calcium, glucose concentration) to document the status and quality of liver graft function. The anesthetic goals of the reperfusion phase are presented in Table 30.8 [58].

Occasionally, infants who have cardiac anomalies and intracardiac shunts require liver transplantation. This is especially dangerous because when the graft is reperfused there is the likelihood of air, clot, and other debris entering the systemic circulation. If this occurs, there is the danger of coronary artery or cerebral artery embolism. One method used to reduce this risk is to leave the vena cava above the liver clamped and to open the vena cava below to allow the initial blood entering the liver from the portal vein to exit the vena cava into the abdomen. This often means that one-fourth to one-third of the blood volume is lost via this route. This period of phlebotomy requires rapid replacement of blood, but is effective in reducing the risk of systemic embolization.

Table 30.8 Anesthetic goals during the reperfusion period

Goal	Treatment
Correct calcium	Calcium chloride (central) 10–20 mg/kg IV
Prevent or treat hyperkalemia: low–normal (K^+ 3.5–4.0)	Hyperventilation Calcium chloride boluses Sodium bicarbonate Insulin or dextrose Inhaled albuterol Furosemide Epinephrine
Normothermia: expect ~1°C drop	Warm room Bair Hugger™ Warm fluids
Normotensive	Vasoactive infusions ready as needed Dopamine and/or epinephrine
Normal heart rhythm	Treat as above Defibrillation pads attached to defibrillator

Source: Reproduced from Wasson et al [58] with permission of Elsevier.

KEY POINTS: SURGICAL PROCEDURE FOR LIVER TRANSPLANTATION

- Surgery is divided into four stages: pre-anhepatic, anhepatic, reperfusion, and biliary anastomosis
- The anhepatic phase reduces preload from inferior vena cava cross-clamping; this is generally well tolerated because of collateral venous return
- Reperfusion can introduce acidemic blood or perfusate with air or particulate material entering the circulation

Intraoperative management issues

Hemodynamics

Periods of hemodynamic instability are common during liver transplantation. In the earlier portions of the anesthetic (e.g. during line placement, preparing and draping the skin), the general debilitating effects of end-stage liver disease and the reduced blood volume induced by diuresis may limit the patient's ability to compensate for the hypotensive effects of anesthetics. In response to abdominal incision and dissection around the native liver, surgical stimulation may overcome light levels of anesthesia and produce hypertension and tachycardia.

A more common scenario is the development of hypotension at various points during the operation. Massive blood loss must always be entertained in the differential diagnosis for hypotension. Given the site of surgery, the presence of extensive abdominal and retroperitoneal collateral vessels, and scar tissue from previous surgeries, bleeding may be significant during the dissection phase of surgery. It should always be kept in mind that splenic bleeding is a possibility. The changes in hemodynamics during the anhepatic period are frequently the most complicated to understand. With application of the venous clamps to the portal vein and to the infrahepatic and suprahepatic vena cava, there is an abrupt decrease in venous return to the right side of the heart and subsequently to the left side of the heart. Although there may be a brief period of hypotension in response to application of the clamp, infants and children appear to tolerate moderate hypovolemia and maintain normal systemic arterial pressures. Stimulation may produce hypertension and tachycardia if the anesthesia level is light. Reflex tachycardia, reduction in central venous pressure (CVP), dampening of the arterial waveform during positive pressure ventilation, and development of a metabolic acidosis are all consistent with significant hypovolemia. In addition, this same hemodynamic picture may develop from surgical manipulation resulting in compression of the inferior vena cava or right ventricle.

In adult patients, the cardiac index may decrease 30–50% when the venous clamps are applied, but systemic arterial pressure is only slightly decreased because there is a compensatory increase in systemic vascular resistance. Volume administration during the anhepatic period is guided by CVP, systemic arterial pressure, and by the arterial pressure waveform. While surgical attention is focused on the vascular anastomoses during the anhepatic period, significant bleeding may continue from areas behind the liver and at other sites of collateral flow. In rare situations, vasopressin (0.1–0.3 units/min IV) may be required to decrease splanchnic blood flow while the anastomoses are being completed. Fluid administration may include crystalloid, colloid, or blood products, depending upon the hemoglobin, PT, and preference of the surgeon and anesthesiologist. Colloid solutions may have particular benefit during the anhepatic period and at the end of the dissection period. Care should be taken not to administer excessive fluid during the anhepatic phase because when the blood is returned to the central circulation with unclamping of the inferior vena cava, a high CVP will impair hepatic venous drainage. Typically a CVP of 8–10 mmHg is adequate to maintain arterial pressure at the time of reperfusion with little need for vasopressors.

Because the portal vein is clamped during the anhepatic period, portal venous hypertension develops. Because of the increased venous pressure, there is a tendency toward fluid translocation and bowel edema during the anhepatic period. Administration of colloid solutions during the dissection and anhepatic period may reduce the amount of bowel edema that develops and facilitate closure of the abdomen at the end of the operation. In addition, the extent of bowel edema may influence the duration of impaired intestinal motility following the operation. Because large volumes of hydroxyethyl starch are associated with coagulopathy, albumin solutions are routinely utilized for colloid administration. Patients with persistent hypotension may require cardiovascular support with dopamine or epinephrine during this time.

Infants and children commonly have normal urine outputs during the anhepatic period, apparently because there are other pathways by which venous blood can return to the central circulation. However, low urine output during the anhepatic phase is not an indication for fluid administration because of the potential adverse effects of high CVP, and the routine recovery of urine output after removal of the venous cross-clamp. The CVP is a better indicator of hydration status.

Completion of the anhepatic period restores venous return from the lower extremities and splanchnic bed. Despite adequate intravascular volume, hypotension is a common finding following graft reperfusion. Numerous factors are felt to contribute to the hemodynamic changes associated with reperfusion. Immediately upon reperfusion, a combination of hypotension, bradycardia, and supraventricular and ventricular dysrhythmias may develop. Prior to reperfusion, a small bolus of fluids may be administered to optimize ventricular filling. Acid–base status is checked approximately 5–10 min before reperfusion. Sodium bicarbonate and calcium are administered to achieve a high–normal pH and calcium levels prior to cross-clamp release. At the moment of reperfusion, attention must be divided between the cardiac monitor and the surgical field. Evidence of life-threatening hemorrhage requires the immediate infusion of blood products while the surgeons control the bleeding. Inspection of the cardiac monitor will detect ECG changes consistent with profound bradycardia and/or hyperkalemia. Bradycardia may result from the sudden atrial stretch occurring with restoration of normal venous return and/or influx of cold storage flush solution, with profound alterations in pH and electrolyte content. If the heart rate decreases by 30–40%, atropine should be administered, and warm solutions should be instilled into the abdominal cavity.

ECG evidence of hyperkalemia includes development of peaked T waves (rare in babies), QRS widening, and

sine-wave formation. Inspection of the arterial waveform trace will confirm the loss of mechanical activity. The occurrence of hyperkalemia at the time of reperfusion represents systemic toxicity of organ preservation solution that was not removed when the organ was flushed. Acute interventions for hyperkalemia include administration of calcium and bicarbonate, and circulatory support with closed chest cardiac massage and epinephrine. Because the surge in serum potassium is transient, treatment is directed towards decreasing the concentration of serum potassium and restoring the cardiac rhythm. The potassium concentration increases 0.5–1.5 mEq/L at the time of reperfusion in almost all patients. Because this increase in potassium is expected during reperfusion, care should be taken to prevent increases in potassium concentrations during the dissection and anhepatic periods. Forced diuresis (renal dose dopamine, fenoldepam, diuretic administration) can help lower the potassium level. In addition, insulin and glucose administration effectively decreases the serum potassium concentration during the anhepatic period. Following the abrupt increase at reperfusion, potassium concentrations tend to decrease during the remainder of the operation. Urinary losses of potassium account for some of the decrease, while potassium uptake by muscle cells and allograft liver cells also contribute to the decreases in serum potassium. Potassium administration is indicated if the serum potassium concentration decreases and the urine output remains adequate in the post-reperfusion period.

Other factors, including transient hypocalcemia, acidosis and hypothermia, contribute to hypotension following graft reperfusion. Studies in adult transplant patients suggest that approximately 30–40% of patients develop a "post-reperfusion" syndrome consisting of decreased arterial blood pressure and profound vasodilation. A study utilizing transesophageal echocardiography (TEE) found right ventricular dysfunction (paradoxical motion of interventricular septum, right atrial enlargement, right-to-left interatrial deviation) following reperfusion [70]. In addition, the pulmonary circulation is known to be sensitive to acute alterations in temperature and pH. Perfusion of the lungs with ice-cold, hyperkalemic, acidic blood may increase pulmonary vascular resistance and cause right ventricular dysfunction. Embolization of air, clot, and cellular debris can occur at the time of graft reperfusion, as was shown by the TEE study just mentioned.

Perturbations of hemodynamics at reperfusion can affect other organs and systems. The liver graft is sensitive to increased levels of central venous and pulmonary artery pressure. Vascular engorgement of the liver is common following reperfusion of the liver, especially if the CVP was greater than 10 mmHg before the liver was reperfused. Because the arterial blood supply to the liver may still be compromised (e.g. during the hepatic arterial reconstruction), excessive passive engorgement of the liver may deprive some areas of the liver of oxygen and cause poor restoration of graft function. Anesthetic management must attempt to prevent liver graft engorgement. If the systemic arterial pressure is adequate, infusion of nitroglycerin may reduce elevated central blood volumes and graft swelling or engorgement. Specific treatment for pulmonary hypertension includes increased ventilation, correction of acid–base status, and normalizing body temperature.

Hemostasis

Intraoperative hemostasis is a complex issue during orthotopic liver transplantation [55,68]. The hemostatic system is often impaired as a result of intrinsic liver disease and as a result of the transplant procedure. Based upon preoperative diagnosis and coagulation testing, several groups have attempted to predict the risk of intraoperative bleeding during liver transplantation [72]. However, a predictive score that indicates a low likelihood of bleeding is not a reason to decrease the level of preparedness. Blood products should be immediately available for transfusion. Low potassium units of blood should be used (less than 2 weeks since collection) or it is prudent to wash units of packed red blood cells to remove the excess potassium. Once the initial extent of dissection and coagulopathy is determined, the need for additional crossmatching of blood and/or preparation of fresh frozen plasma (FFP), cryoprecipitate, and platelets can be determined. In the event of significant hemorrhage, the blood bank must be notified of anticipated increased requirements for blood products.

The anesthesia team is responsible for maintaining adequate hemostasis during liver transplant procedures. Central to this role is the ability to rapidly monitor coagulation status intraoperatively. For the monitoring system to be effective, the anesthesiologist must have rapid access to the results of these tests so that the abnormalities can be corrected immediately. Routine coagulation testing should include measurement of PT, activated PTT, platelet count, hemoglobin concentration, and fibrinogen concentration. Thromboelastography (TEG) and thromboelastometry, specific types of whole blood viscoelastic coagulation monitoring, have been used successfully by some clinicians during liver transplantation [73]. TEG is a test of clot strength, and requires a 30–60 min recording of clot formation and lysis. It gives an indication of clotting factor activity, platelet function, and fibrinolysis. Since significant fibrinolysis is less common in children, TEG monitoring is not routinely utilized in most centers [59].

Intraoperative management of coagulopathy during liver transplantation includes the administration of blood products and potential pharmacological interventions. The principal blood product administered is FFP, which will correct clotting factor deficiencies. Because hepatic artery thrombosis is one of the most common causes of graft failure in pediatric patients, FFP is administered to correct and maintain at values for PT and PTT close to 1.5 times prolonged from normal, depending on the amount and severity of intraoperative bleeding. Cryoprecipitate is administered when the infusing FFP does not correct a low fibrinogen concentration (<80–100 mg/dL). In the post-reperfusion period, intravascular filling pressures may be elevated. Consequently, the decreased volume of cryoprecipitate is better tolerated.

Thrombocytopenia is a common finding during liver transplantation. Many patients have decreased platelet counts because portal hypertension has induced hypersplenism. Intraoperative thrombocytopenia may develop or worsen due to replacement of blood loss during the dissection phase with non-platelet-containing solutions. Platelet counts decrease slightly during the anhepatic period and decrease significantly upon reperfusion of the graft. Platelet entrapment within the grafted liver has been demonstrated in a porcine model of liver transplantation; in addition, platelet activation and consumption increase following reperfusion of the graft.

Platelet counts of 50,000–100,000/L commonly develop and are not an indication for platelet transfusion in the absence of excess bleeding. Over transfusion of platelets may also increase the risk of hepatic artery thrombosis. Platelet transfusion is indicated if thrombocytopenia is present and there is a clinical impression of abnormal hemostatic function.

Severe post-reperfusion coagulopathy occurs in some patients who undergo liver transplantation, possibly because of the reperfusion-initiated disseminated intravascular coagulation. Studies indicate that primary fibrinolysis may develop during liver transplantation due to changes in the circulating concentration of tissue-type plasminogen activator. Both ε-aminocaproic acid (EACA) and aprotinin have been utilized to pharmacologically reduce the severity of fibrinolysis during orthotopic liver transplantation. EACA improves the TEG findings of fibrinolysis during liver transplantation; however, prophylactic use of EACA has not been demonstrated to be of value. Administration of aprotinin, a protease inhibitor of kallikrein, decreases the laboratory abnormalities associated with fibrinolysis and reduces transfusion requirements during liver transplantation [74]. The worldwide marketing of this agent was suspended in 2008 due to complications in the adult cardiac surgery population – including thrombosis, stroke, and renal failure – and it is not available in the USA. Children are hypercoagulable after liver transplantation because of a decrease in protein C and antithrombin III [75], and they may be more likely to develop hepatic artery thrombosis or emboli [76–78]. Therefore, antifibrinolytics are not routinely used in most pediatric transplant centers.

Hepatic artery thrombosis may result from disorders of the coagulation system and/or technical factors in hepatic arterial reconstruction. Intraoperative and postoperative Doppler ultrasound examinations of the hepatic arterial and portal vein anastomoses are commonly used to assess patency of the anastomoses. Because of the potential for graft loss with vessel thrombosis, a slightly anticoagulated state is maintained in infants and small children following liver transplantation. This includes avoiding fully correcting the heparin effect in the operating room, maintaining a slightly higher PT, and early administration of aspirin. At the Texas Children's Hospital, our practice is to start a heparin infusion in the operating room once hemostasis has been achieved after reperfusion and to continue this infusion for the first few days postoperatively. In addition, hyperviscosity from overtransfusion of red cells should be avoided. Maintaining the hemoglobin between 8 and 10 mg/dL provides adequate oxygen-carrying capacity.

Metabolic control (K^+, Ca^{2+}, acid–base, glucose)

Acute changes in acid–base status, potassium concentration, ionized calcium, and glucose are common, both before and during liver transplantation. Concomitant renal dysfunction promotes acid–base changes and exacerbates electrolyte problems. Diuretic therapy can cause electrolyte imbalance (hyponatremia, hypokalemia, hypocalcemia) and prerenal azotemia. A common pattern of electrolyte changes develops in most patients. Consequently, an anticipated treatment plan can be developed. Routine intraoperative monitoring of arterial blood gases, electrolytes, and glucose concentrations will define the need for and further refine intraoperative electrolyte therapy. Because of the multiple factors contributing to hemodynamic instability in these patients, these parameters are more tightly controlled than in other operations.

Many patients who present for surgery have hyponatremia due to prerenal azotemia and the use of diuretics. Care should be taken to avoid a rapid rise in sodium concentrations during surgery from the use of salt-containing solutions, sodium bicarbonate, and blood products. Also, both hypo- and hyperkalemia are frequently encountered during surgery (see earlier discussion).

Patients undergoing liver transplantation are particularly susceptible to the development of ionized hypocalcemia. Although total calcium concentrations are decreased in patients with chronic liver disease, ionized calcium concentrations are normal. Intraoperative administration of blood products decreases ionized calcium and magnesium concentrations because citrate-based anticoagulant solutions used in collection and storage of blood products bind these ions. Citrate usually is metabolized rapidly by the liver. In normal patients, low ionized calcium concentrations only occur following massive and rapid administration of blood products. Patients with end-stage liver disease are particularly sensitive to the administration of citrate-containing blood products, and the administration of moderate amounts of FFP can significantly decrease ionized calcium concentrations. Profoundly low ionized calcium concentrations, particularly during the anhepatic period, may cause myocardial depression and hypotension. Given the potential for dramatic changes in the ionized calcium concentration, direct measurement of ionized calcium is particularly useful during liver transplantation. Calcium replacement therapy during the dissection and anhepatic phases can be achieved with either bolus administration or constant infusion of calcium. Calcium chloride and calcium gluconate are equally effective in increasing the ionized calcium concentration during the anhepatic period [79]. Calcium requirements are expected to increase (often markedly) during the anhepatic period and to quickly decrease following reperfusion of the hepatic allograft. With restoration of blood flow to the liver graft, metabolism of citrate proceeds at a much faster rate than that which occurred with the native liver or during the anhepatic phases. A reduction in calcium requirement following reperfusion is consistent with adequate hepatic allograft function. As mentioned earlier, normal ionized calcium concentrations at the end of the anhepatic period may protect against the cardiovascular effect of abrupt increases in potassium from the reperfused liver. Measurement of ionized calcium 5 min before graft reperfusion and administration of calcium prior to reperfusion is suggested.

Metabolic acidosis is extremely common during orthotopic liver transplantation. Numerous factors contribute to its development, including tissue hypoperfusion; decreased or absent metabolism of lactate, citrate, and other metabolic acids by the liver; rapid administration of acidic blood products; associated renal impairment; and acidic effluent from the liver allograft. During the dissection period, a development of acidosis most commonly reflects global tissue hypoperfusion. The administration of additional intravascular volume and restoration of adequate blood pressure and cardiac output often corrects the acidosis. The anhepatic period in particular is associated with rapid development of acidemia. The contribution of decreased tissue perfusion (caused

by the abnormal hemodynamics associated with vena cava and portal vein occlusion) and the absence of hepatic function are unknown. Sodium bicarbonate is used to treat metabolic acidosis during the anhepatic period, and the amount of bicarbonate administered is based on the rapidity and severity of changes in the acid–base balance. In general, with base deficits greater than 5–8 mEq/L, or pH less than 7.35 ($PaCO_2$ <40 mm Hg), bicarbonate should be administered to create a relatively normal pH immediately prior to reperfusion of the graft. Arterial blood gases and pH measurements obtained approximately 5 min prior to reperfusion will determine the amount of bicarbonate required.

Following reperfusion of the liver graft, metabolic acidosis frequently recurs. Treatment of severe metabolic acidosis at this point is indicated when there is concomitant myocardial depression and/or there are signs of persistent hyperkalemia. Normally, the exacerbation of metabolic acidosis quickly abates during the post-reperfusion period; this abatement is one of the early signs that the graft is functioning. The liver allograft usually resumes metabolic function rapidly, and hepatic metabolism of lactate and citrate frequently leads to the development of a metabolic alkalosis in the later portions of the operation and in the postoperative period. Resolution of metabolic acidosis (and development of alkalosis) is indicative of adequate allograft function, although the sensitivity and specificity of these findings are not known. The extent of the metabolic alkalosis is related to the amount of intraoperative transfusion, and not to the amount of bicarbonate administered.

Glucose balance is complicated by liver transplantation. Hypoglycemia may be present in patients with fulminant liver failure or severe chronic liver disease and may necessitate preoperative administration of dextrose-containing fluids. It usually is necessary to administer glucose to these patients before the graft is reperfused. In theory, the anhepatic period should pose a greater risk of hypoglycemia because there is no liver in the circulation. Numerous factors are present that help maintain a relatively normal glucose concentration in the blood during the anhepatic period: stress response to surgery, steroid administration, dextrose-containing blood products, and reduced glucose utilization due to hypothermia. Since organ preservation solutions and flush solutions frequently contain dextrose, glucose concentrations commonly increase after reperfusion of the graft. Hyperglycemia in the reperfusion period also has been suggested as a marker for allograft function. Small infants may have markedly decreased glycogen stores when presenting for liver transplantation and are frequently at increased risk for developing hypoglycemia. Preoperative and frequent intraoperative glucose determinations are the best methods of detecting abnormal glucose levels. Dextrose should be administered if hypoglycemia is present. Persistent hyperglycemia, glucose greater than 250 mg/dL, is treated with insulin administration.

Temperature maintenance

Hypothermia is common during liver transplantation, despite utilization of multiple methods to conserve body heat. The long intra-abdominal operation, massive fluid and blood product administration, and implantation of a graft that has a temperature near zero, all contribute to the development of hypothermia. There is usually a 1–2°C decrease in body temperature when the ice-cold donor liver is placed in the abdomen. There also may be an abrupt decrease in core temperature of 1–2°C with reperfusion when cold flush solution is infused into the systemic circulation. Profound hypothermia carries significant risk, including cardiac depression, arrhythmias, abnormalities in clotting function, and decreased renal function. Because of these risks, specific efforts are directed at maintaining core temperature. Heating the operating room is imperative for infants and small children. A forced-air warming blanket is placed beneath the child, and the exposed extremities are wrapped. Forced-air warming is useful over the legs and/or upper extremities in larger patients. Intravenous fluids and blood products are warmed prior to their administration. Lowering of fresh gas flows and using a humidifier will reduce the heat loss caused by the use of cold dry inspired gases.

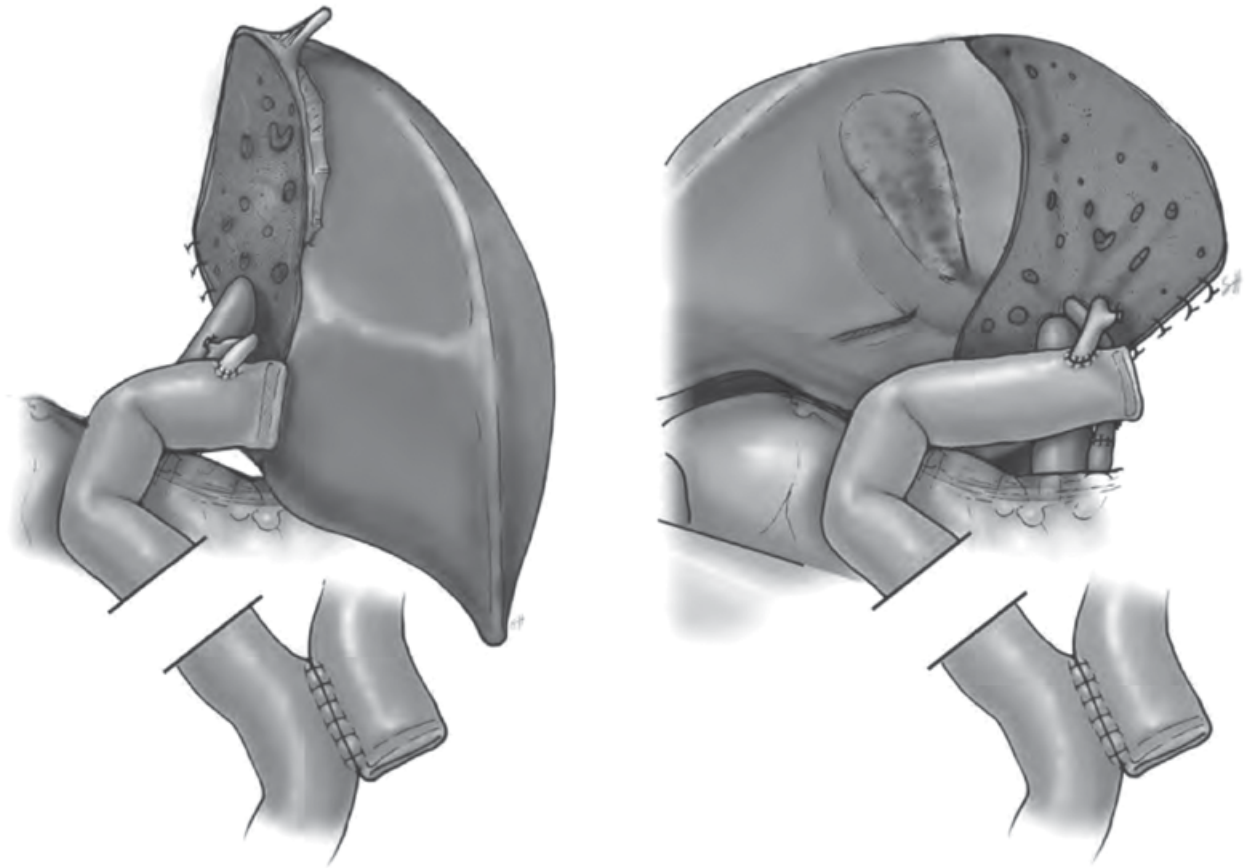
KEY POINTS: INTRAOPERATIVE MANAGEMENT DURING LIVER TRANSPLANTATION

- Hemodynamics are often unstable due to massive blood loss, reperfusion, hyperdynamic circulation, or occasional pulmonary hypertension
- Hemostasis is challenging because of poor liver synthetic function and massive blood loss; care should be taken not to overcorrect coagulopathy because of the risk of hepatic artery thrombosis
- Metabolic control can be challenging, and particular attention must be paid to potassium, calcium, and glucose concentrations, and acid–base status

Special techniques

Three advances in surgical technique have improved the number of available grafts for children: using a reduced-size graft (pare-down), dividing the liver allowing two grafts for two recipients, and living donor transplantation. The surgical technique most commonly used to split the liver is performed while still *in vivo* (in the heart-beating donor) as compared with *ex vivo* (splitting performed after the graft is removed from the donor) (Fig. 30.4) [69]. This decreases cold ischemia time and facilitates hemostasis of the liver edge. This technique results in improved child and graft survivals [80,81]. The Studies in Pediatric Liver Transplantation (SPLIT) group is an excellent source of data regarding pediatric liver transplantation in North America. This group represents 46 pediatric liver transplant centers across America and Canada and reflects the results of programs with a strong pediatric emphasis. A review of the SPLIT database reveals patient survival rates of 91.4% and 86.5%, at 1 and 5 years following liver transplantation, respectively [82].

Living related transplantation has greatly benefited the pediatric transplant population, particularly in countries in which there is limited availability of deceased donor grafts for cultural or even legal reasons [83]. In this procedure a left lateral segmentectomy (segments 2 and 3) is performed in the donor and transplanted in a similar fashion to a whole-organ transplant. Approximately 300 living donor liver transplants



(A) (B)

Figure 30.4 Surgical technique for split-liver graft. (A) Left lateral segment allograft with completed hepaticojejunostomy. Of note, the portal venous anastomosis in the background contains an extension donor iliac vein allograft. The hepatic venous anastomosis is not seen. (B) Right trisegment allograft with completed hepaticojejunostomy. Of note, the arterial inflow is elongated with donor iliac artery conduit. *Source*: Reproduced from Cotton et al [69] with permission of Wolters Kluwer.

are performed annually and 20% of these are in child recipients. Despite the success of this technique for the recipients there is considerable risk to the donor. Complications include exposure to blood products, peripheral nerve injuries, biliary leakage, abdominal wall defects, pleural effusions, pneumonia, pulmonary emboli, and death [84,85].

Retransplantation

Hepatic retransplantation is performed to treat primary nonfunction of the allograft, allograft dysfunction resulting from thrombosis of the hepatic artery or portal vein, rejection unresponsive to aggressive medical therapy, or recurrent or primary disease in the transplanted liver. Retransplantation rates are currently at 10–20%. Because of the dense adhesions around the transplanted liver, significant hemorrhage may occur during the dissection phase. In addition, if the liver has sustained an ischemic insult, disruption of the vascular anastomoses may occur and produce catastrophic hemorrhage. There must be adequate vascular access to allow massive volume resuscitation. Sufficient blood products must be available in the operating room to rapidly instill one blood volume in the patient. Most reports indicate that patient survival following retransplantation of the liver is worse than it is following the primary transplant. However, a 2010 study found graft and patient survival after retransplantation to be similar to that of primary liver transplantation [86].

Renal transplantation

Indications

Renal transplantation is the optimal therapy for children with chronic renal insufficiency and end-stage renal disease (ESRD). Despite the availability of dialysis for children, transplantation is the preferred long-term management for children with ESRD to allow the best chance for normal growth, activity, and development. Also, the risk for death is more than four times higher with dialysis than with renal transplantation [87]. The incidence of ESRD in children 0–19 years of age is between 5 and 12 per million. The incidence increases with age and males are more likely to develop ESRD than females secondary to the higher rate of congenital urological anomalies. The etiologies of ESRD, and therefore the disease processes leading to transplant, differ depending on the age of the patient. For children under 5 years of age, congenital lesions (renal dysplasia/aplasia, obstructive uropathy, complex urogenital malformations, congenital nephrosis) are responsible for the majority of pediatric transplants. Over 5

years of age, glomerulonephritis (e.g. focal glomerulosclerosis, membranoproliferative glomerulonephritis) and recurrent pyelonephritis are major causes of ESRD (Fig. 30.5). The North America Pediatric Renal Trials and Collaborative Studies registry reported that from 1987 to 2013, in 12,189 transplants, 47.2% were over 12 years of age, 32.6% were 6–12 years of age, 14.7% percent were 2–5 years, and only 5.4% were under 2 years of age [88].

The improving outcome of renal transplantation in children and overall graft survival rate is encouraging (Table 30.9) [88]. In recent years, survival after a living donor graft is over 93%, and after a deceased donor graft is over 90%, at 3 years. Of note, 64 ABO-incompatible pediatric renal transplants (0.6% of total) have been reported, with a current 3-year graft survival of 78.2%, which is not different from ABO-compatible transplants; 50.3% of transplants were from living donors, with 80% from a parent; and 2.6% were from unrelated donors.

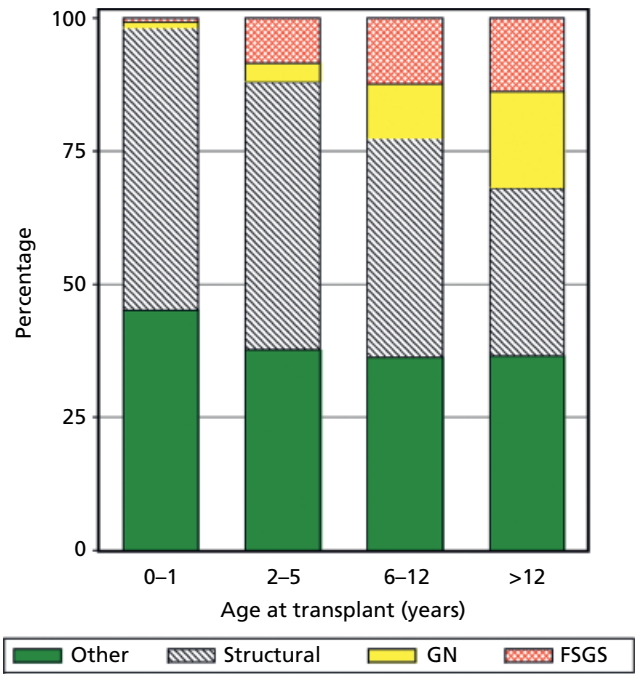


Figure 30.5 Primary diagnosis of pediatric renal transplant recipients by age. FSGS, focal segmental glomerulosclerosis; GN, glomerulonephrosis. *Source*: Adapted from North American Pediatric Renal Trials and Collaborative Studies [88].

Pathophysiology

A patient's fluid and electrolyte balance is dramatically altered by renal failure. Hypervolemia, hypovolemia (after dialysis), hyponatremia, hyperkalemia, hypocalcemia, hyperphosphatemia, and metabolic acidosis are common. Because the failing kidney may not excrete adequate free water, hypervolemia is frequent and is a cause of hypertension. Hypovolemia can occur after aggressive dialysis. Hyponatremia occurs when water retention exceeds sodium retention, or when there is salt wasting plus an inability to concentrate urine. Hyperkalemia may be a major problem due to its effects on the cardiac conduction system, and it may require treatment before general anesthesia can be safely induced. Hypocalcemia is secondary to the hyperphosphatemia that results from the kidney's inability to excrete phosphates. Metabolic acidosis develops because the failing kidney cannot excrete the body's daily production of metabolic acids.

Many organ systems are affected by ESRD. Hypertension, increased cardiac output, pericarditis, arrhythmias, and cardiomyopathy are manifestations of the altered cardiovascular system. Hypertension occurs secondary to fluid overload or to alterations in the renin–angiotensin–aldosterone system. Patients with anemia compensate for their decreased oxygen-carrying capacity by increasing their cardiac output. The use of recombinant erythropoietin has decreased the incidence of severe anemia in ESRD patients. Congestive heart failure due to hypertension and volume overload, a uremia-induced cardiomyopathy, and pericardial disease may complicate the management of children with ESRD. Pulmonary edema can develop as a result of fluid overload, hypoproteinemia, and altered pulmonary capillary permeability.

Anemia develops due to decreased erythropoietin production and decreased erythrocyte lifespan, despite normal reticulocyte counts. Uremic toxins decrease red blood cell lifespan and suppress bone marrow function. The anemia is normocytic and normochromic, despite renal failure-induced deficiencies in folate and vitamin B12. There is an increased concentration of 2,3-diphosphoglycerate, which, in conjunction with the metabolic acidosis, shifts the oxygen–hemoglobin dissociation curve to the right. This shift and an increased cardiac output partially compensate for the decreased oxygen-carrying content caused by the anemia. Coagulation is often altered in uremic patients by residual heparinization following dialysis and by abnormal platelet function. Platelets are usually normal in number and lifespan but have a reversible functional defect secondary to accumulation of guanidinosuccinic

Table 30.9 Graft survival rates for pediatric renal transplantation by cohort year, and living versus deceased donor

	Graft survival rates					
	Living donor			Deceased donor		
Cohort group	1 year	3 years	5 years	1 year	3 years	5 years
1987–1991	90.3	82.4	76.3	76.4	65.3	56.9
1992–1996	92.1	87.0	81.6	87.0	77.9	70.9
1997–2001	95.4	91.4	86.3	93.1	84.5	78.3
2002–2006	96.3	92.0	86.4	94.4	84.1	79.2
2007–2013	96.4	93.4	–	95.8	90.4	–

Source: Adapted from North American Pediatric Renal Trials and Collaborative Studies [88].

acid, which inhibits adenosine diphosphate-induced activation, of platelet factor III, which is needed for normal platelet adhesion [89].

Renal failure induces numerous neurological effects. Uremic encephalopathy manifests as a global depression that is reversible with dialysis. Uncontrolled hypertension may lead to either focal neurological deficits or seizures, so hypertension must be controlled. Seizures may also occur with rapid electrolyte changes (e.g. hyponatremia). Peripheral neuropathies are common in patients with renal failure and usually consist of axonal degeneration with segmental demyelination. The median and common peroneal nerves are frequently involved. Autonomic dysfunction develops in children with ESRD. Baroreceptor activity may be abnormal and lead to hypotension that is unresponsive to intraoperative volume administration.

Nutrition is generally poor in ESRD. Uremia causes anorexia, leading to poor calorie intake and growth retardation. Despite the need for protein and calories, protein intake must be carefully controlled to prevent worsening metabolic acidosis. Renal osteodystrophy, aluminum toxicity, altered somatomedin activity, and insulin and growth hormone resistance are all associated with the growth failure [90]. Delayed gastric emptying is common in children with renal failure. Therefore, patients undergoing a renal transplant may have an increased risk of aspiration of gastric contents regardless of the NPO interval.

KEY POINTS: INDICATIONS AND PATHOPHYSIOLOGY OF RENAL TRANSPLANTATION

- In young children, congenital malformations and lesions are the most common indication for renal transplant; in older children glomerulosclerosis and glomerulonephritis are most common
- Dramatic alterations in fluid balance, potassium, sodium, and calcium balance and levels, and in renin–angiotensin–aldosterone systems are seen in ESRD
- Transplantation offers better growth, survival, and quality of life than long-term dialysis

Preoperative assessment and preparation

There are two sources for kidneys for transplantation into children: cadaver and living donors. Because living donor transplants are elective operations, there is adequate time to optimize the nutritional, hydration, and metabolic status of the patient.

Evaluation of the fluid and electrolyte status of the patient is of primary importance. If the patient has been recently dialyzed, a review of the dialysis records is often helpful. Changes in weight, blood pressure, and electrolyte concentrations before and after dialysis should be noted. The patient's dry weight is the minimum weight not associated with hypotension or cardiovascular instability; the current weight compared to the dry weight will indicate the volume status of the patient. Because there are significant changes in electrolytes (e.g. Na^+, K^+) after dialysis, serum electrolytes should be determined after dialysis. Hypertension in patients with ESRD is common and frequently indicates hypervolemia. However, many patients also require antihypertensive medications, which should be continued until the time of surgery to avoid intraoperative rebound hypertension.

The physical examination should assess the airway and cardiopulmonary status of the patient and determine if a functioning arteriovenous shunt is present. If so, it must be protected during the operation. Patients with nephrotic syndrome or those who have been on steroids may be edematous, which could make tracheal intubation more challenging. Due to the delayed gastric emptying of patients with ESRD, the use of an antacid or anti-H_2 agent and metoclopramide may be useful before anesthesia induction.

Surgical technique

Pediatric renal transplantation employs more than one surgical technique. In older children (weighing >20 kg), the standard surgical approach is similar to that of adults, that is, a lower abdominal incision with extraperitoneal placement of the donor kidney in the iliac fossa. Vascular anastomoses are usually to the iliac vein (end-to-side) and iliac or hypogastric arteries (end-to-side or end-to-end). For infants and small children (weighing <20 kg), a midline incision is made and the kidney placed intra-abdominally, although extraperitoneal placement is also possible (Fig. 30.6) [91]. The vascular anastomoses are made to the inferior vena cava and the lower abdominal aorta. The aorta and vena cava are cross-clamped while the anastomoses are being completed. In addition, the donor organs for most small children are from older children or adults with obvious size implications.

Anesthetic management

Premedication with midazolam is usually safe and may allay anxiety if needed. Standard American Society of Anesthesiologists (ASA) monitors are used, and because of the potential for acute blood loss, large-bore peripheral intravenous access and a blood warmer are indicated. Because the patient's volume status is difficult to determine and may vary considerably during the operation, measurement of the CVP helps guide appropriate fluid management. The CVP catheter can also be used to obtain blood samples for laboratory tests and to administer vasoactive medications into the central circulation. However, preservation of sites for long-term vascular access in patients who may need hemodialysis in the future should be considered, and the subclavian veins are generally avoided for this reason. Larger, older children can usually be adequately managed with peripheral IV access alone. Also, an indwelling arterial catheter is not routinely used for adults or older children, but it may be quite helpful for smaller children, especially if the aorta is to be cross-clamped. One must be careful not to risk the patency of an existing arteriovenous shunt or to compromise future placement of such a shunt.

Anesthesia for renal transplantation is usually induced with intravenous drugs because the patients frequently have an IV catheter already in place. For patients without an IV catheter, inhaled induction of anesthesia is a viable alternative.

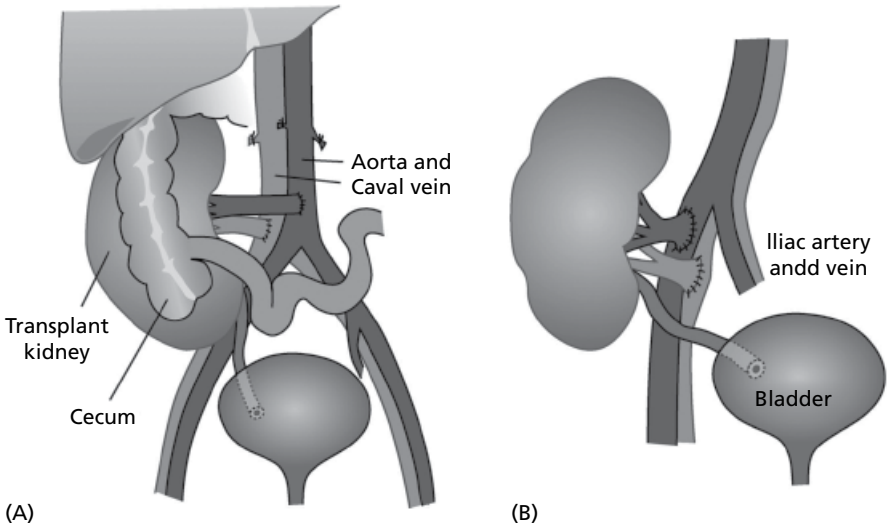


Figure 30.6 Renal transplantation in infants. The kidney is placed intra-abdominally instead of in the iliac fossa because of size considerations. In infants, the kidney graft can be placed intraperitoneally (A) or extraperitoneally (B). *Source*: Reproduced from Jalanko [91] with permission of Springer Nature.

The pharmacokinetics and pharmacodynamics of anesthetic drugs are altered in patients with ESRD, and this must be taken into account when administering drugs to induce anesthesia. Propofol will produce vasodilation and potentially hypotension in patients who are hypovolemic. Ketamine can also be used as an IV induction agent for patients with ESRD, but its sympathomimetic effects may exacerbate pre-existing hypertension. To blunt the autonomic response to laryngoscopy and tracheal intubation, opioids or lidocaine can be given intravenously. As with all sick children, careful titration of anesthetic drugs to the desired effect is always the safest approach.

The choice of muscle relaxant for tracheal intubation continues to generate discussion. Because delayed gastric emptying is common in patients with renal failure, patients undergoing renal transplantation may be at increased risk for regurgitation and possible aspiration of gastric contents. This situation makes a rapid-sequence intravenous induction of anesthesia with an intravenous induction agent, cricoid pressure, and succinylcholine theoretically advantageous. However, the administration of succinylcholine may cause serum potassium concentrations to rise 0.5–0.75 mEq/L in normal patients [92]. A number of conditions can lead to an exaggerated rise of serum potassium and subsequent hyperkalemic cardiac arrest. Patients with ESRD are at risk for hyperkalemia if they have uremic neuropathy or if they have not been dialyzed recently [93]. An alternative to succinylcholine is to perform a modified rapid-sequence intravenous induction of anesthesia using an intravenous agent, a non-depolarizing muscle relaxant, cricoid pressure, and controlled ventilation. The non-depolarizing muscle relaxant used should not depend on renal pathways of elimination. Two categories that fit this requirement are the atracurium/*cis*-atracurium family, whose elimination is by Hoffman degradation and ester hydrolysis, and the steroid-based muscle relaxants that are predominantly metabolized by the liver. The steroid-based muscle relaxants vecuronium and rocuronium have some dependence on renal excretion, perhaps 10–25%, that will lead to some prolongation of onset and duration of action of the drugs when used in patients with ESRD.

Maintenance of general anesthesia during renal transplantation is usually provided by a combination of potent inhaled anesthetic agents and opioids. Nitrous oxide can be used, but it may distend the intestines and make it more difficult to close the abdomen at the end of the operation. Sevoflurane has the theoretical problem of producing a metabolite, compound A, that has been associated with renal concentrating defects, and although useful for inhaled induction of anesthesia, should probably not be the first choice for maintenance of anesthesia [94]. If sevoflurane is used, fresh gas flows should be maintained above 2 L/min. Fentanyl is the most widely used opioid for renal transplantation; no active metabolites are excreted by the kidneys, and there is extensive experience with its use in children without significant complication. The metabolites of morphine are excreted by the kidney so probably should not be the first choice for intraoperative analgesia.

If the patient has an arteriovenous shunt, the extremity with the shunt must be positioned so that the shunt is protected and available to allow the anesthesiologist to periodically determine that the shunt is functional. A blood pressure cuff should not be used on that extremity. At the very least, the shunt should be checked both at the beginning and the end of the operation for a thrill or bruit and the presence of either or both documented on the anesthetic record.

Fluid management during renal transplantation is challenging owing to reduced preoperative renal function and to blood loss and third space fluid losses during the operation. Preoperative fluid status is discussed earlier. Interstitial fluid losses (third space) and blood losses are determined in the usual fashion (see Chapters 11 and 19). Fluid administration should be based on estimates of need and clinical criteria, including vital signs and CVP when utilized. It should be recognized that hypovolemia should be avoided, and fluid administered to produce normovolemia to hypervolemia with adequate blood pressure to the new organ. An isotonic crystalloid solution is a suitable choice of fluid. Theoretically, lactated Ringer solution should be avoided due to the potassium (4 mEq/L) that it contains. On the other hand, normal saline is hypernatremic (154 mEq/L) and can lead to a

hypernatremic metabolic acidosis if given in large quantities. Intermittent measurements of the serum electrolyte and glucose concentrations should be done to follow the metabolic status of the patient. If a blood transfusion is required, washed or fresh packed red blood cells are preferred due to the small volume and the minimal amount of potassium present after washing. The blood should also be irradiated to minimize graft-versus-host reactions in an immunocompromised host.

The surgeons may request a higher than normal mean arterial pressure to ensure adequate perfusion of the new kidney. Whenever a new kidney is placed into a small recipient (<20 kg), it is possible that the aorta will be cross-clamped to perform the arterial anastomosis. When the aorta is subsequently unclamped, the blood pressure may decrease dramatically secondary to reduced afterload and the return of acidotic blood from the lower extremities. Furthermore, a large quantity of blood is diverted to the renal allograft, which will decrease the arterial blood pressure if the intravascular volume is inadequate. The anesthesiologist must be prepared to treat abrupt changes in arterial pressure with fluid and vasopressors. It must be remembered that these changes occur with patients who usually have baseline hypertension. Vascular thrombosis is a potential cause of graft failure in the smallest of recipients so the outcome may depend on the reperfusion management. After completion of the vascular anastomosis, mannitol and furosemide may be administered to facilitate diuresis.

The anesthesiologist will also be involved with the administration of immunosuppressant medications, antibiotics, diuretics, and other drugs during the operation. The surgeon or nephrologist should notify the anesthesiologist of the doses and timing of these medications. It is helpful to find out common side-effects of these drugs that may impact anesthetic management. Antilymphocyte antibodies include muromonab-CD3 (OKT3), alemtuzumab (Campath), antithymocyte globulin (Atgam), and antithymocyte globulin (thymoglobulin) (see Table 30.1). The infusion of these agents causes a cytokine response. This cytokine response can include fever, chills, rigors, and malaise that should be pretreated with acetaminophen, corticosteroids, and diphenhydramine [95,96]. Anti-interleukin-2 antibodies include basiliximab, and daclizumab. These medications do not cause a cytokine response. Side-effects from anti-interleukin-2 antibodies are comparable to placebo except for an acute hypersensitivity reaction that can occur with basiliximab [95].

At the end of the operation, a determination should be made whether the patient's trachea will be extubated. If so, residual neuromuscular blockade should be antagonized. Prolongation of the action of neuromuscular blockers is matched by prolongation of action of the reversal agents. The patient should be awake when the trachea is extubated. If there is evidence of pulmonary edema, or a relatively large kidney is placed into the abdomen of a small child, tracheal extubation can be delayed and the patient transported to a pediatric intensive care unit (ICU) and the patient's condition allowed to stabilize.

Postoperative pain control is most commonly achieved by the administration of intravenous opioids. Epidural analgesia can be used, but the association with possible hypotension has tended to limit its widespread use as well as the alterations in coagulation status of patients with ESRD.

KEY POINTS: ANESTHETIC MANAGEMENT DURING RENAL TRANSPLANTATION

- Close attention to the most recent dialysis and lab studies is crucially important
- Vascular access in older children usually can be accomplished with large-bore IV lines, while central and arterial access are reserved for special situations
- Avoiding drugs with extensive renal metabolism, maintaining high blood pressure and volume status for the transplanted kidney, and keeping current with immunosuppressant and antibiotic regimens are all important

Follow-up

Follow-up protocols vary by age and institution; techniques include renal ultrasound, MRI including diffusion-weighted imaging, creatinine clearance, and experimental urinary and blood biomarkers [97]. Ultrasound-guided renal biopsy is not routine in transplantation surveillance and is undertaken only if graft dysfunction is indicated. Rejection episodes are treated with increased doses of corticosteroids and other immunosuppressants. Surveillance for opportunistic infection and secondary malignancies including post-transplant lymphoproliferative disorder is important in renal transplant patients [58].

Heart transplantation

History

On 6 December 1967, just 3 days after Christian Barnard stunned the world with the first human heart transplant, the first pediatric heart transplant was performed in Brooklyn, New York, by Adrian Kantrowitz and associates [98]. The recipient was 17 days old with Ebstein's anomaly and the donor an anencephalic infant. The recipient only survived a few hours and died of apparent acute graft dysfunction [99]. Cyclosporine became available in 1978 and the first successful infant cardiac transplant was subsequently completed by Cooley and associates at the Texas Children's Hospital in 1984 [99,100]. The number of pediatric heart transplants worldwide increased throughout the 1980s and early 1990s to approximately 400 transplants annually and remained relatively constant up until 2009 [101]. The last decade, however, has seen a progressive increase in the number of transplants performed annually, with 684 reported in 2015 compared with 442 in 2004 [102].

Indications

Evidence-based indications for heart transplantation

The most recent evidence-based review of indications for pediatric heart transplant were published in 2007 following a working group assessment from the American Heart Association [103]. These indications incorporated the A–D pediatric heart failure staging system (Table 30.10) and are based mainly on consensus clinical opinions of experts (level C evidence) [103]. Class I indications (general agreement of usefulness and efficacy) include stage D heart failure in

Table 30.10 Heart failure staging in pediatric cardiac disease

Stage	Interpretation	Clinical example
A	At risk for developing heart failure	Congenital heart defects Family history of cardiomyopathy
B	Abnormal cardiac structure and/or function No symptoms of heart failure	Anthracycline exposure Univenticular hearts Asymptomatic cardiomyopathy Repaired congenital heart defects
C	Abnormal cardiac structure and/or function	Repaired and unrepaired congenital heart diseases
D	Past or present symptoms of heart failure Abnormal cardiac structure and/or function Continuous infusion of intravenous inotropes or prostaglandin E1 to maintain patency of a ductus arteriosus Mechanical ventilatory and/or mechanical circulatory support	Cardiomyopathies Same as stage C

Source: Reproduced from Canter et al [103] with permission of Wolters Kluwer.

Table 30.11 Evidence-based indications for pediatric heart transplantation

Indications	Level of evidence
Class I	
Stage D heart failure associated with systemic ventricular dysfunction in pediatric patients with cardiomyopathies or previously repaired/palliated CHD	B
Stage C heart failure associated with severe limitation of exercise and activity. If measurable, such patients would have a peak maximum oxygen consumption <50% predicted for age and sex	C
Stage C heart failure associated with systemic ventricular dysfunction in patients with cardiomyopathies or previously repaired/palliated CHD when heart failure is associated with significant growth failure attributable to the heart disease	B
Stage C heart failure in pediatric heart disease with associated near sudden death and/or life-threatening arrhythmias untreatable with medications or an implantable defibrillator	C
Stage C heart failure in pediatric restrictive cardiomyopathy disease associated with reactive pulmonary hypertension	C
Class IIA	
Stage C heart failure in pediatric heart disease associated with reactive pulmonary hypertension and a potential risk of developing fixed, irreversible elevation of pulmonary vascular resistance that could preclude orthotopic heart transplantation in the future	C
Certain anatomical and physiological conditions likely to worsen the natural history of CHD in infant patients with a functional single ventricle, which can lead to use of heart transplantation as primary therapy, including: (1) severe stenosis (stenoses) or atresia in proximal coronary arteries; (2) moderate to severe stenosis and/or insufficiency of the AV and/or systemic semilunar valve(s); and (3) severe ventricular dysfunction	C
Several anatomical and physiological conditions likely to worsen the natural history of previously repaired or palliated CHD in pediatric patients with stage C heart failure that may lead to consideration for heart transplantation without severe systemic ventricular dysfunction, including: (1) pulmonary hypertension and a potential risk of developing fixed, irreversible elevation of pulmonary vascular resistance that could preclude orthotopic heart transplantation in the future; (2) severe aortic or systemic AV valve insufficiency that is not considered amenable to surgical correction; (3) severe arterial oxygen desaturation (cyanosis) that is not considered amenable to surgical correction; and (4) persistent protein-losing enteropathy despite optimal medical/surgical therapy	C

AV, atrioventricular; CHD, congenital heart disease.
Source: Reproduced from Thrush and Hoffman [104] with permission of Nancy International Ltd Subsidiary AME Publishing Company.

patients with cardiomyopathies or congenital heart disease (CHD), stage C heart failure with severe growth/activity limitation or refractory life-threatening arrhythmias or restrictive cardiomyopathy with reversible pulmonary hypertension (Table 30.11) [104].

Contraindications to pediatric heart transplant (class III: risks outweigh the benefits) include previous infection with hepatitis B/C or human immunodeficiency virus (HIV), history of substance abuse, significant behavioral or cognitive disorders, history of non-compliance, poor family support structure, irreversible multisystem disease, fixed severely elevated pulmonary vascular resistance (PVR), or severe hypoplasia of the central branch pulmonary arteries or veins.

Indications for cardiac retransplantation (Table 30.12) in pediatrics are mainly based on non-randomized studies and registries (level B evidence) [104]. Contraindications for retransplantation include primary transplant within 6 months and ongoing acute allograft rejection.

Diagnostic indications for heart transplantation

Primary diagnosis is an important factor affecting post-transplant survival [102]. Diagnostic indications for pediatric heart transplantation (<18 years of age) are categorized into four major groups: congenital heart disease, dilated cardiomyopathy, retransplantation, and "other" (Table 30.13). CHD and dilated cardiomyopathy (DCM) are the most prevalent indications, contributing to over 80% of pediatric heart transplants [102]. Although the distribution of diagnoses has remained relatively constant over time, there are significant differences with age (Fig. 30.7) and geographical location (Fig. 30.8) [102]. In infants <1 year of age the most common indication for transplant is CHD (55%), whereas in the 11–17-year age group the most common diagnosis is DCM (54%). CHD is a more common indication in North America (42%) than in Europe (23%), whereas cardiomyopathies represent the majority of cases in Europe (59%) and other areas (71%). Figure 30.9 illustrates the frequency of transplant by age [102].

Dilated cardiomyopathies

Dilated cardiomyopathy accounts for over 50% of pediatric cardiomyopathies in the USA, with the majority being idiopathic in nature [104]. Other causes of pediatric cardiomyopathy include viral myocarditis, neuromuscular

Table 30.12 Evidence-based indications for pediatric heart retransplantation

Indications	Level of evidence
Class I	
In children with abnormal ventricular function and at least moderate graft vasculopathy	B
Class IIA	
Indicated in children with normal ventricular function and at least moderate graft vasculopathy	B

Source: Reproduced from Thrush and Hoffman [104] with permission of Nancy International Ltd Subsidiary AME Publishing Company.

Table 30.13 Categorization of diagnosis for pediatric heart transplants

Category	Diagnoses in category
Congenital heart disease (CHD)	Congenital heart defect, HLHS uncorrected, with surgery, without surgery, previous surgery unknown, or valvular heart disease
Dilated cardiomyopathy (DCM)	Dilated myopathy due to adriamycin, alcohol, familial, idiopathic, myocarditis, post-partum, viral, or other reasons
Retransplant (RETX)	Retransplant due to acute rejection, chronic rejection, coronary artery diseases, hyperacute rejection, non-specific, primary failure, restrictive/constrictive causes, or other reasons
Other	Arrhythmogenic right ventricular dysplasia, cancer, coronary artery disease, myopathy-ischemia, hypertrophic cardiomyopathy, muscular dystrophy, reactive cardiomyopathy (any reason), or other cardiac disease

HLHS, hyperplastic left heart syndrome.
Source: Reproduced from Rossano et al [102] with permission of Elsevier.

disease, and genetic causes. The overall unadjusted survival is better after transplant for DCM patients when compared with CHD or retransplant patients [102] and the post-transplant outcomes are reported to be better than for other forms of cardiomyopathies [102,104,105]. Patients with DCM have a relatively low wait-list mortality (11%) but mechanical ventilation and arrhythmias increases the risk of death whilst waiting [106].

Congenital heart disease

The CHD group represents a diverse group of diseases (Table 30.14) that may affect the perioperative and post-transplant course in different ways. Suitability for transplant takes into account degree of allosensitization, PVR, and hepatic reserves [107]. Approximately one-third of these patients are palliated single-ventricle patients [105] who may not have "heart failure" in the traditional sense of systolic dysfunction, and may be listed for transplant due to severe diastolic dysfunction or high PVR leading to high Fontan pressures, cyanosis, protein-losing enteropathy, ascites, and plastic bronchitis. There are emerging data to suggest that failing Fontan patients with preserved ventricular systolic function have more perturbed Fontan physiology and a higher cardiac transplant mortality than those with systolic dysfunction [108]. General indications for transplant in patients with CHD are listed in Box 30.4.

Retransplantation

Coronary artery vasculopathy is a chronic low-grade rejection phenomenon that results in gradual vascular occlusion and occurs in 11% and 17% of recipients at 5 years and 10 years, respectively, after transplant [90]. Coronary artery vasculopathy results in listing for retransplantation if ventricular function deteriorates, or significant dysrhythmias or heart block ensue. These patients usually do not experience angina because of the denervated state of the transplanted heart and are at risk for sudden death. Although cardiac retransplantation is uncommon, it is associated with increased mortality and morbidity [101,102].

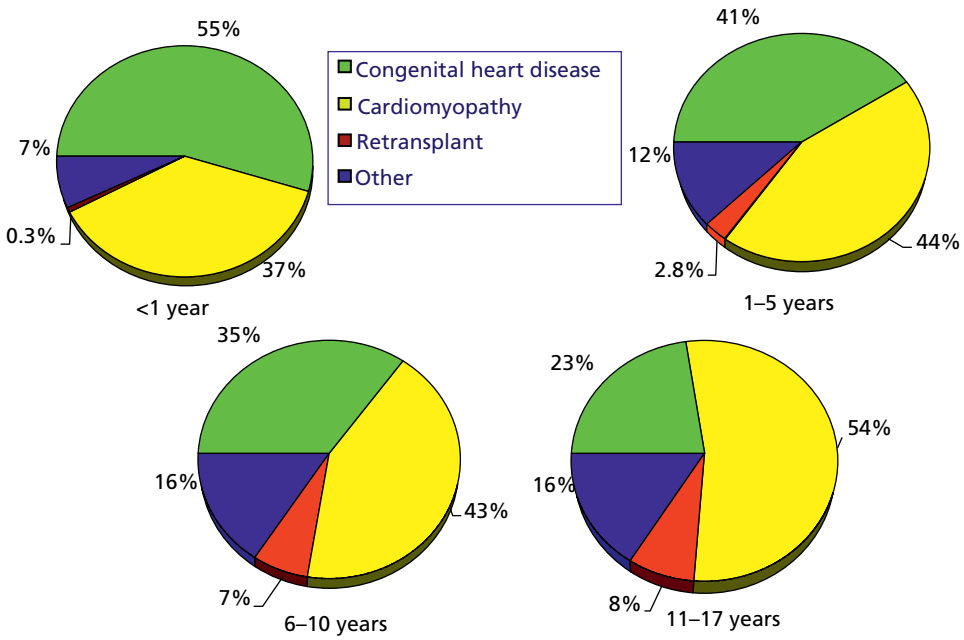


Figure 30.7 Heart transplant recipient diagnosis by age, 2009–2016. *Source*: Reproduced from Rossano et al [102] with permission of Elsevier.

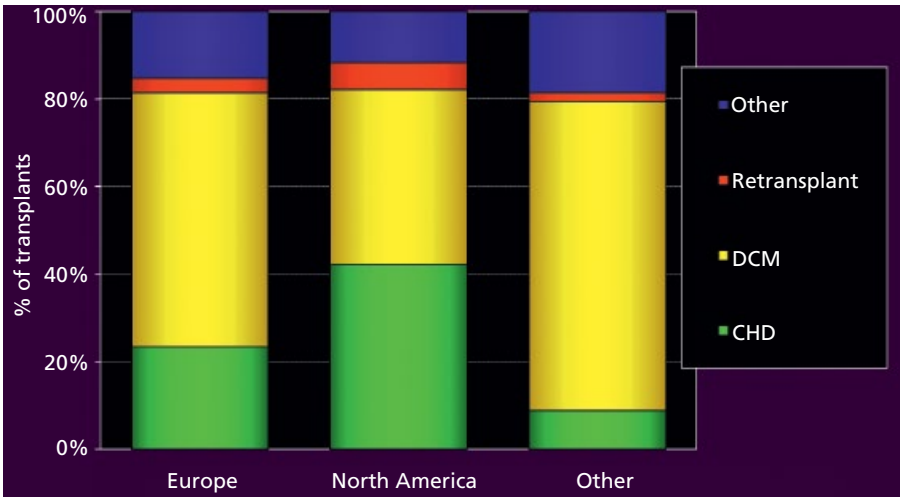


Figure 30.8 Pediatric heart transplants by location, 2004–2016. CHD, congenital heart disease; DCM, dilated cardiomyopathy. *Source*: Reproduced from Rossano et al [102] with permission of Elsevier.

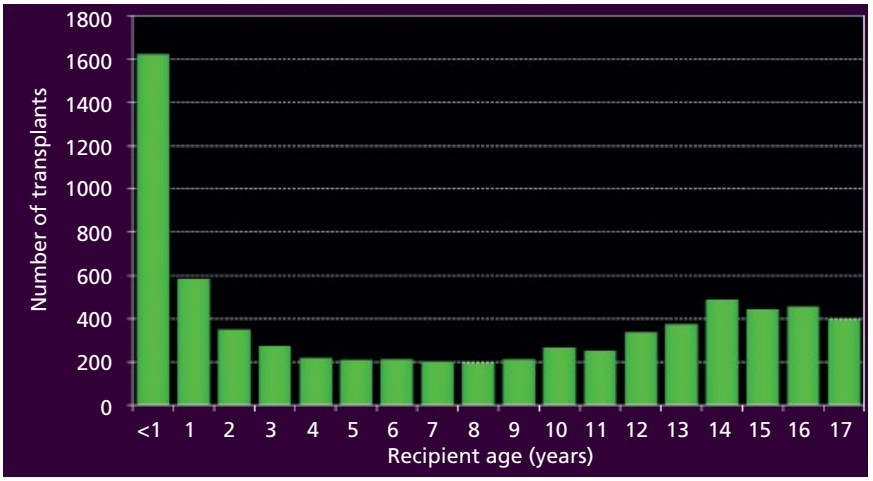


Figure 30.9 Pediatric heart transplants by recipient age distribution, 2004–2016. *Source*: Reproduced from Rossano et al [102] with permission of Elsevier.

Table 30.14 Diagnosis in pediatric cardiac transplant recipients with congenital heart disease

Diagnosis	*n* (*N* = 488)	%
Single ventricle	176	36
D-transposition of the great arteries	58	12
Right ventricular outflow tract lesions	49	10
Ventricular/atrial septal defect	38	8
Left ventricular outflow tract lesions	38	8
L-transposition of the great arteries	39	8
Complete AV canal	37	8
Other	53	11

AV, atrioventricular.
Source: Reproduced from Lamour et al [105] with permission of Elsevier.

Other

This group includes restrictive cardiomyopathies, hypertrophic cardiomyopathies, and arrhythmogenic right ventricular dysplasia. Hypertrophic cardiomyopathy only accounts for 5–6% of pediatric heart transplants and has a diverse spectrum of etiologies, including idiopathic, familial, and inborn errors of metabolism. Restrictive cardiomyopathies are uncommon, and are characterized by diastolic dysfunction with normal ventricular size and wall thickness and biatrial enlargement. These patients account for approximately 5% of cardiomyopathy transplants [103]. Historically, restrictive cardiomyopathy patients have a poor prognosis with a high incidence of pulmonary hypertension and sudden death, and are not amenable to other surgical or medical therapy. Given the natural progression of restrictive cardiomyopathy, early listing for heart transplant is recommended [104].

KEY POINTS: DIAGNOSTIC INDICATIONS FOR HEART TRANSPLANTATION

- CHD and DCM are the two main indications for pediatric heart transplant
- Primary diagnosis is an important factor affecting post-transplant survival
- Survival is better for DCM patients than for CHD, other forms of cardiomyopathies, and retransplantation

Box 30.4: General indications for heart transplanation in patients with congenital heart disease

- Patients with stage D heart failure refractory to medical therapy, who will not benefit significantly from surgical, interventional, or electrophysiological intervention
- Patients having congenital heart disease (CHD) with associated near-sudden death or life-threatening arrhythmias refractory to all therapeutic modalities
- Patients with stage C heart failure associated with reactive pulmonary hypertension and a potential risk of developing fixed, irreversible elevation of pulmonary vascular resistance that could preclude orthotopic heart transplantation in the future
- Stage C heart failure associated with systemic ventricular dysfunction in pediatrie patients with previously repaired or palliated CHD when heart failure is associated with significant growth failure attributable to the heart disease
- Pediatric patients with CHD with normal ventricular function when the following anatomical and physiological conditions are present and not amenable to surgical intervention:
  - Severe stenosis (stenoses) or atresia in proximal coronary arteries
  - Moderate to severe stenosis or insufficiency of the atrioventricular or systemic semilunar valve(s)
  - Symptomatic arterial oxygen desaturation (cyanosis) that is not considered amenable to surgical correction
  - Persistent protein-losing enteropathy despite optimal medical and surgical therapy

Source: Reproduced from Kirklin et al [107] with permission of SAGE.

Pretransplant recipient selection and optimization

The decision to list a patient for cardiac transplant is made by a multidisciplinary group led by the medical transplant team, the patient's primary cardiologist, and the surgical transplant team. A formal structured evaluation focuses on four main areas [103]:

- Cardiovascular anatomy and hemodynamics
- Dysfunction in other organ systems
- Human leukocyte antigen (HLA) sensitization
- Psychosocial assessment of patient and family.

Cardiovascular anatomy and hemodynamics

Cardiac catheterization, often in conjunction with CT or MRI, is used to accurately delineate the patient's cardiac anatomy, an important consideration in patients who have been palliated for CHD. A critical hemodynamic parameter that needs to be assessed pretransplant listing is PVR. All patients with elevated PVR (>3 Woods unit (Wu) in biventricular patients or 2 Wu in single-ventricle patients) should have their PVR measured during cardiac catheterization at baseline and after administration of oxygen, inhaled nitric oxide, or other pulmonary vasodilators. Ideally PVR should be <6 Wu prior to transplant listing. More experienced centers may accept higher PVR values if it is reactive to vasodilator therapy. Patients with irreversibly elevated PVR may need to be considered for heterotopic heart transplant, or heart–lung transplant.

Dysfunction in other organ systems

The severity of dysfunction in other organ systems has an impact on post-transplant survival and outcomes, e.g. a need for renal dialysis at the time of transplant is a risk factor for 1-year mortality [102,109] and estimated glomerular filtration rate is a continuous risk factor for 1-, 5-, and 10-year mortality [102]. There is an increasing trend to treat irreversible moderate–severe renal dysfunction and end-stage heart failure with a combined heart–kidney transplant. Similar strategies of combined heart–liver transplant are being used in the presence of irreversible hepatic dysfunction.

HLA sensitization

A panel reactive antibody (PRA) screen is performed to determine the level of antibodies to red blood cell antigens from prior blood transfusions. Highly sensitized patients (allosensitization) are those who have a PRA >10%. Cardiac transplantation for highly sensitized patients has increased morbidity and mortality [102]. The use of cryopreserved allograft material for prior congenital heart surgery also induces a HLA immune response.

High levels of antibodies to specific antigens may prevent transplant from a donor with those antigens, and a "virtual cross-match" is performed for donor and recipient red cell antigens before accepting the organ. A strongly positive cross-match for specific antigens may prevent transplantation from a donor with those antigens. Other strategies for patients with high PRA titers include preoperative plasmapheresis, thymoglobulin, and cyclophosphamide treatment to reduce titers [110]. HLA prospective cross-matching is not routinely performed because of time constraints and limited availability of donor organs.

Psychosocial assessment of patient and family

This includes the capacity to comply with the complicated regimens needed for ongoing care [111]. Although substance abuse, psychosocial problems, and non-compliance have been associated with increased morbidity and mortality after adult heart transplantation, there are limited studies to assess its impact in pediatric patients [103]. Developmental delay is also commonly encountered in pediatric transplant patients, especially those with CHD. Consensus opinion is that the selection of these patients for heart transplant listing should be considered on a case-by-case basis rather than arbitrary denial [103].

United Network for Organ Sharing waiting list

In the United States, organ donation and allocation is managed by UNOS [112]. UNOS maintains the waiting lists for each type of transplant, and determines the rules for organ allocation, which depend on patient status and, to some extent, proximity to the donor. Once listed for transplant, the patient is designated a status dependent on priority for transplant (Table 30.15) [113]. The median waiting time for pediatric heart transplant is 60–80 days [113]. Wait-list mortality in pediatric heart transplant remains significant and can be as high as 23% in infants 6 months after listing for transplant [114,115]. Other factors associated with increased wait-list mortality include the need for extracorporeal membrane oxygenation (ECMO) or mechanical ventilation, status 1A listing, diagnosis of CHD, the need for dialysis, and weight <3 kg [104,114,115].

Table 30.15 Status designation for pediatric heart transplantation. Status 7 refers to a listed patient who is temporarily off the transplant list, i.e. for infection or other reversible cause, who can be reinstated once the condition is treated

Status 1A (at least one of the criteria below)	Status 1B (at least one of the criteria below)	Status 2
Continuous mechanical ventilation and is hospital inpatient	Needs one or more inotrope infusions but does not qualify for 1A	<18 years old at time of listing but does not meet requirements for 1A or 1B
Ductal-dependent systemic or pulmonary circulation and is hospital inpatient	Has hypertrophic cardiomyopathy or restrictive cardiomyopathy *and* is <l year old	
Hemodynamically significant congenital heart disease and is an inpatient on multiple inotropes or high-dose single inotrope		
Dependent on mechanical circulatory support		
NB status 1A must be recertified every 14 days	*Can remain IB for unlimited period without recertification*	*Status 2 does not need recertification*

Source: Adapted from Organ Transplant and Procurement Network [113].

KEY POINTS: HEART TRANSPLANT RECIPIENT SELECTION

- Evaluation of four main areas (cardiovascular anatomy and hemodynamics, other organ dysfunction, HLA sensitization, and psychosocial assessment of patient and family) is required prior to listing for heart transplant
- Most centers require a PVR <6 WU prior to transplant listing. High PVRs should be reactive to pulmonary vasodilator therapy
- Highly sensitized patients with a PRA >10% have a higher transplant morbidity

Anesthesic management

Pre-bypass period

The basic anesthetic considerations for transplantation do not differ from the normal preparation for congenital cardiac surgery (see Chapter 27 for a detailed discussion of pathophysiology). A summary of intraoperative considerations for pediatric cardiac transplantation is presented in Box 30.5. A thorough preoperative evaluation and consultation with the patient and family and explanation of the anesthetic procedures is performed. The preoperative condition may vary from a deconditioned, hospitalized, status 1A patient dependent on multiple inotropes or ventricular assist devices to status 1B patients called in from home. The timing of entrance into the operating room (OR) must be planned and communicated with frequent updates due to difficulties in coordinating harvesting teams and donor hospital OR time. It is preferable to err on the side of having the patient in the OR too early than too late; prolonged ischemic time will affect graft function and 1-year survival [102,104]. Allowing adequate time to place invasive vascular access lines and extensive surgical dissection for multiple re-entry sternotomies must be considered when deciding an OR time. At Lucille Packard Children's Hospital, Stanford we organize a multidisciplinary huddle hours before bringing the patient into the OR. This involves discussion between the heart failure team, transplant surgeon, cardiovascular ICU, and anesthesia team and reviews the patient's current medical condition, any anticipated perioperative problems such as vascular access, rescue plans for cardiopulmonary decompensation, renal protection, and immunosuppressive regimens.

Patients presenting for cardiac transplantation have limited cardiopulmonary reserve and the anesthesia induction should be tailored to the condition and the specific physiology of the patient. While most patients will require some form of anxiolysis the timing, route, and location should be determined by the patient's cardiorespiratory state. The timing of immunosuppressive regimens varies between institutions – some start soon after arrival to the OR and others after separating from cardiopulmonary bypass (CPB) when bleeding is controlled. Although having invasive arterial monitoring in place prior to induction is ideal, this is not always possible for younger patients where standard non-invasive monitoring for induction may have to suffice. Continuous transthoracic echo monitoring during induction can also be considered provided there are skilled and dedicated personnel to obtain and interpret the images. Transthoracic echo monitoring may be useful for monitoring function, left ventricular outflow tract obstruction, and PVR changes during anesthesia induction. Most pretransplant patients are at significant risk of developing dysrhythmias or cardiovascular collapse with the induction of general anesthesia and positive pressure ventilation. Therefore, methods of resuscitation must be immediately at hand to support the patient. This includes pharmacological agents, defibrillator, and the ability to rescue the patient with emergent CPB. Intravenous induction can often be accomplished with gradual titration of midazolam 0.05–0.1 mg/kg per dose, and fentanyl 1–5 μg/kg per dose, followed by muscle relaxation. Another option for intravenous induction includes etomidate 0.1–0.3 mg/kg, which has little or no hemodynamic effect [116]. Ketamine 1–2 mg/kg IV can also be used. However, one should be aware of the potential for direct myocardial depression with the use of ketamine in patients receiving continuous infusions of β-adrenergic agonists where the patient's endogenous catecholamine stores may be depleted [117,118]. Bolus propofol should generally be avoided because of its venous and arterial vasodilating properties.

Assisted mask ventilation is assumed, taking care to limit intrathoracic pressure and minimize changes to the PVR. Among patients with pulmonary hypertension, increases in pulmonary arterial pressure can be minimized by the use of

Box 30.5: Summary of intraoperative anesthetic considerations for pediatric cardiac transplantation

Pre-bypass period
- Consider pathophysiology of congenital heart disease and/or reduced myocardial function (see Chapter 27)
- Induction and maintenance agents to preserve function
- Maintain preoperative inotropes, increase doses preinduction if needed
- Mechanical circulatory support (MCS): MCS specialist, preinduction arterial line, and NIRS if non-pulsatile
- Resuscitation drugs, bypass machine, and perfusionist and surgeon immediately available
- Interrogate/convert pacemaker/ICD functions as indicated (DOO pacing, defibrillator off)
- Efficient vascular access with ultrasound: arterial, central venous, large-bore peripheral IV lines; minimize ischemic time
- Prepare for possible emergency femoral vessel cannulation for bypass
- Adequate blood products and heparin in OR
- Antifibrinolytic agents: tranexamic acid or ε-aminocaproic acid
- Thromboelastography/elastometry for coagulation monitoring
- TEE to assess function, filling, air, and postoperative anatomy

Bypass period
- Exchange transfusion as bypass initiated for ABO-incompatible or high panel reactive antibody patients
- Cooling on bypass will depend on surgical needs; usually moderate hypothermia
- Deep hypothermic bypass or circulatory arrest may be necessary for aortic arch reconstruction or pulmonary vein repair in congenital heart disease
- Left atrial and aortic anastomosis done with aortic cross-clamp. A donor ischemic time of <5 h is desirable
- Lidocaine, magnesium sulfate, or amiodarone may be needed for ventricular fibrillation
- Inotropic support varies; low-dose epinephrine, milrinone, and low-dose isoproterenol are commonly used
- Inhaled nitric oxide for elevated pulmonary vascular resistance
- Atrial and ventricular pacing wires for heart rate support in denervated heart

Post-bypass period
- Significant bleeding with repeat sternotomy or VAD patients: platelets, cryoprecipitate/fibrinogen concentrate, and fresh frozen plasma/coagulation factor concentrate/activated factor VII are often necessary
- TEE to assess anastomoses and cardiac function
- Maintain inotropic support, pacing, and iNO as needed
- Usually will not extubate in OR, but stable patients can be extubated in 12–24 h
- Full hand-over report from anesthesia/surgical team to ICU team

DOO, asynchronous atrial/ventricular pacing; ICD, implantable cardiac defibrillator; ICU, intensive care unit; iNO, inhaled nitric oxide; IV, intravenous; NIRS, near-infrared spectroscopy; OR, operating room; TEE, transesophageal echocardiography; VAD, ventricular assist device.

larger doses of opioids, 100% oxygen, and mild hyperventilation prior to tracheal intubation. If a pulmonary hypertensive crisis develops, treatment with systemic vasopressors and pulmonary vasodilators, including inhaled nitric oxide, is immediately undertaken.

In addition to invasive monitoring (arterial and central venous), adequate large-bore access should be secured especially for repeat sternotomy patients. Some complicated re-entry sternotomy patients may require predissection arterial and venous access via femoral or neck vessels that could be used to rapidly transition to extracorporeal support if needed.

Many patients especially those with CHD may have implantable pacemakers or cardioverter-defibrillators in place and these should be reprogrammed appropriately prior to incision and the use of surgical diathermy.

Almost a third of pediatric heart transplant patients are on a form of mechanical circulatory support (MCS) (see section "Bridge to transplant"), most often a left ventricular assist device (LVAD). The anesthesiologist must be familiar with the many types of devices in current use; the presence of an MCS specialist is essential to operate and troubleshoot the device. Patients on a continuous flow ventricular assist device may have reduced or no cardiac and arterial pulsatility, rendering conventional pulse oximetry and oscillometric blood pressure monitoring non-functional. A preinduction arterial line with ultrasound guidance, or near-infrared spectroscopy, combined with maintaining ventricular assist device flow parameters in normal ranges, is often necessary in these patients.

Additional monitoring includes TEE to assess post-transplant cardiac function and integrity of cardiac and great vessel anastomoses. We routinely utilize near-infrared spectroscopy measurement of cerebral oxygen saturation because of the high risk of cerebral oxygen desaturation from a low cardiac output state in these patients. Early detection and treatment of cerebral oxygen desaturation may lead to improved neurological outcomes. Although patients with poor cardiac function undergoing transplant are at higher risk for anesthesia awareness, processed electroencephalographic monitoring for depth of anesthesia will not reliably prevent this significant problem and is not recommended for use in this situation, particularly in young children [119].

Because many of these patients have undergone previous sternotomies and are at greater risk for intra- and postoperative hemorrhage, antifibrinolytic agents are often utilized. These include EACA or tranexamic acid. Antibiotic prophylaxis, often cefazolin in uncomplicated transplants, is given 30–60 min before incision, repeated after institution of bypass, and every 3–4 h thereafter while in the OR.

Patient positioning, preparation, draping, and sternotomy are accomplished as efficiently as possible. The mediastinal,

heart, and great vessel dissection and preparation is then undertaken prior to donor organ arrival in order to minimize donor ischemic time. Pre-bypass anesthetic management is carried out according to the pathophysiology of the patient's underlying cardiac disease and response to surgical and anesthetic interventions. Maintenance of anesthesia is often achieved with large doses of opioids such as fentanyl, and amnestic agents such as midazolam. Low doses of volatile anesthetic agents are often employed and there are some data that suggest isoflurane may preserve cardiac output better than other volatiles [120,121].One should also consider using a trigger-free anesthetic regimen, when possible, for patients with neuromuscular disease (e.g. Duchenne or Becker muscular dystrophy) who may be at risk for malignant hyperthermia-type symptoms or anesthesia-induced rhabdomyolysis.

Bypass period

Standard CPB techniques are used for cardiac transplant, including heparin 300–400 units/kg for anticoagulation, and anticoagulation monitoring with celite activated clotting time, and heparin level assay or TEG/thromboelastometry, according to institutional practice. Aorto-bicaval cannulation is utilized. General principles of bypass management for CHD are followed (see Chapter 26 for further details). Recent data suggest that pH stat blood gas management, and maintaining higher hematocrits of 30–35%, result in better long-term neurological outcomes [122]. Maintaining full flow CPB of 150 mL/kg/min for patients under 10 kg, and 2.4–2.8 L/min/m^2 for those over 10 kg, may improve outcomes as well [123]. Moderate hypothermia to 25–28°C is commonly employed and deep hypothermic (<22°C) circulatory arrest (DHCA) is avoided; however, complex reconstruction of pulmonary venous or aortic anatomy may require DHCA. If possible, DHCA periods should be limited to less than 30 min; reperfusing for a short period and then reinstituting DHCA may be required, utilizing cerebral oximetry to guide the bypass [123–127]. Ultrafiltration on CPB is very useful to achieve hematocrit goals and to remove excess fluid and inflammatory mediators. Alternatively, modified ultrafiltration after CPB can be used to achieve the same goals.

In patients where high levels of PRAs are measured, or in ABO-incompatible transplants (see later in this chapter), an exchange transfusion is performed when CPB is initiated. A double CPB prime volume is prepared, with packed red blood cells and FFP. Upon institution of CPB, the patient's calculated blood volume is drained into a separate collection bag, bypassing the venous reservoir, and discarded. This process will reduce the red cell antibody concentration, and limit the possibility of acute rejection [128].

The most common surgical technique involves orthotopic transplantation [129], where the donor heart is completely excised except for a cuff of left atrial tissue containing all four pulmonary veins (Fig. 30.10) [130]. Donor weight is ideally 80–160% of the recipient's weight. It is important for the surgical team to know the details of the donor's demise (while appropriately preserving patient confidentiality), donor cardiac function (ejection fraction) and inotropic support, and any donor structural abnormalities such as atrial septal defect or patent foramen ovale. The entire right atrium is removed, leaving the superior and inferior vena cavae for anastomosis. After arrival of the donor heart, the ABO and rH type of both the donor and recipient are checked and independently verified by two people including the transplant surgeon. The donor heart is typically preserved with a solution such as crystalloid cardioplegia or Celsior® and stored on ice at 4°C. The heart is placed in the mediastinum, and the left atrial anastomosis is performed first. Then, the aortic anastomosis is performed. The aortic cross-clamp is usually removed at this point to minimize the donor heart ischemic time and to allow sufficient time for donor heart reperfusion. Donor ischemia time is the time from donor heart cross-clamp during retrieval until the cross-clamp is removed during recipient implantation. Ideally, an upper limit of 5 h of donor ischemic time is desired. This limits donor organ transport time to 3.5–4 h. Although transplantation of hearts with longer ischemic times are reported, it is believed that after 5 h of ischemia, graft function worsens, and long-term graft function may be compromised [101,102]. After the aortic cross-clamp is removed, the donor heart commonly experiences ventricular fibrillation due to ischemia and/or electrolyte imbalance, and must be defibrillated (initial energy 2–10 J) until sinus rhythm is achieved. Lidocaine, 2 mg/kg into the CPB circuit, is given 5 min before aortic cross-clamp removal, and a repeat dose of 1 mg/kg can be given if more than 1–2 defibrillations are required. Magnesium sulfate 25–50 mg/kg is often helpful, as is a lidocaine infusion at 20–40 μg/kg/min. Rarely, amiodarone 5 mg/kg load, repeated up to two additional doses, may be required. With the cross-clamp removed and the heart beating, the bicaval anastomoses and the pulmonary artery anastomoses are completed. The surgeon must pay particular attention to the anatomy of CHD recipients. There may be a need for extensive aortic arch reconstruction, requiring a long length of donor aorta in patients with hypoplastic left heart syndrome, or the need for a long length of donor superior vena cava in the case of single-ventricle patients with cavopulmonary anastomoses.

With the establishment of sinus rhythm and completion of the anastomoses, rewarming is accomplished. Additional intravenous anesthetics and muscle relaxant are administered. During this period inotropic support is instituted, according to institutional preference, taking into account ischemic time, systemic and pulmonary vascular resistance, and appearance of the myocardial function on visual inspection and TEE. Low-dose epinephrine, 0.03–0.05 μg/kg/min, is a common choice in this setting. Milrinone, 0.25–0.75 μg/kg/min, with or without a loading dose of 25–75 μg/kg over 15–30 min, is also useful in this situation for its inotropic and pulmonary and systemic vasodilator properties, as well as low propensity for arrhythmogenicity. Because the denervated heart has limited capacity to alter heart rate, and sinus node discharge of the donor heart often slows with edema, inflammation, or hypothermia, an isoproterenol infusion in low doses of 0.01–0.03 μg/kg/min is often very useful to maintain adequate heart rate. Some institutions opt for temporary atrial pacing to augment heart rate instead of pharmacotherapy. Recipients with pulmonary hypertension, and situations where the donor is smaller than the recipient (the donor right heart may have insufficient ability to overcome the recipient PVR), the right heart can be supported with milrinone, or inhaled nitric oxide, at 10–20 ppm [131]. Additional transthoracic monitoring catheters, such as right and left atrial lines,

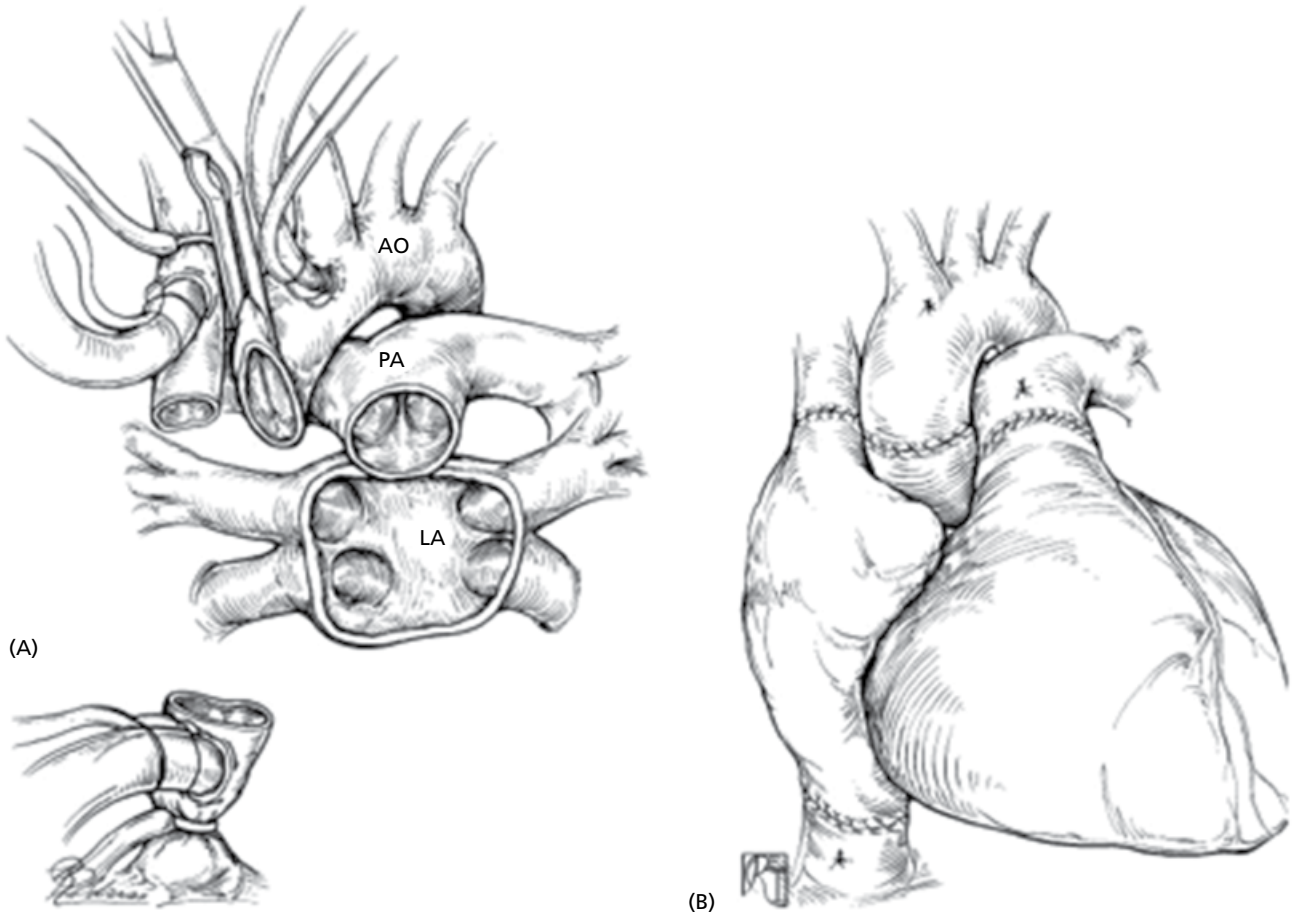


Figure 30.10 Surgical technique for "bicaval" cardiac transplantation. (A) The recipient cardiectomy has been completed. Note that the entire recipient right atrium has been removed. (B) The completed implant. The sequence of anastomoses is: (1) left atrial (LA), (2) aortic (Ao) (cross-clamp removed and heart perfused), (3) inferior vena cava, (4) pulmonary artery (PA), and (5) superior vena cava. *Source*: Reproduced from Rossano et al [130] with permission of John Wiley and Sons.

and occasionally pulmonary artery lines, are placed by the surgeon, along with temporary atrial pacing wires, which may be needed to support the denervated heart. Ventilation is commenced with 100% oxygen, designed to produce mild hypocarbia with a $PaCO_2$ of 32–35 mmHg. Once heart rate and rhythm, hematocrit, ventilation, and electrolytes are optimized, CPB is weaned slowly with gradual volume loading of the heart, using TEE monitoring to assess for intracardiac air, as well as biventricular function. After separation from CPB, cardiac function is assessed with TEE, as is the status of the anastomoses of the aorta, pulmonary artery, vena cava, and left atrium, with particular attention to any pulmonary venous obstruction. After ensuring a period of adequate hemodynamics and cardiac function, protamine 1–1.3 mg per mg of heparin in the original dose is administered, to neutralize the anticoagulation. The TEE probe is removed if no longer needed, and surgical hemostasis is achieved. Platelets and cryoprecipitate (rich in fibrinogen) are often required to achieve hemostasis, particularly with repeat sternotomy and complicated great vessel reconstruction [132]. Patients who are supported with ventricular assist devices before heart transplant are typically on intensive preoperative anticoagulation to prevent thrombosis and embolization, and this group of patients more commonly develop uncontrollable hemorrhage after bypass. There appears to be an increasing trend for the use of prothrombin complex concentrates to control refractory bleeding after cardiac surgery although the data in the pediatric population are limited.

Post-bypass period

In a few unstable patients, particularly small infants, the sternum may be left open for a period of 24–48 h to allow bleeding and myocardial performance to improve; these patients must have the sternum closed as soon as possible to reduce the risk of infection in the immunosuppressed patient. After bypass, attention is directed to the need for additional antibiotic or corticosteroid/immunosuppressive medications. Extubation of pediatric cardiac transplant patients in the OR is typically avoided, as many patients have an ongoing risk for myocardial dysfunction, arrhythmias, bleeding, and pulmonary hypertension. If the patient is stable, tracheal extubation can often be achieved in 12–24 h after ICU admission. Upon transfer to the ICU, a thorough patient hand-over report is given, including the surgical team discussing surgical issues, the anesthesia team giving a complete perioperative report to the attending ICU physician, and bedside nurses and the heart failure team clarifying the patient's postoperative immunosuppressive therapy. A standardized hand-over note, verbal communication, along with an opportunity to answer any questions, is recommended practice for the effective transfer of care in these complicated patients.

KEY POINTS: HEART TRANSPLANT PERIOPERATIVE MANAGEMENT

- Successful perioperative outcomes are dependent on careful multidisciplinary discussion, communication, and planning
- Many pretransplant patients are at high risk for cardiovascular collapse and therefore plans for resuscitation and extracorporeal support should be clearly organized
- Perioperative complications include massive bleeding, cardiac dysfunction, and arrhythmias
- In pediatric patients, 30% are bridged to transplant with MCS and are more prone to perioperative bleeding and vasoplegia

Post-transplant rejection surveillance

The mainstay of post-transplant surveillance for rejection is myocardial biopsy, with the first biopsy often performed 7–10 days after transplant to assess for acute rejection. Biopsies are performed most frequently in the first year after transplant, often every 3 months for uncomplicated cases. Thereafter, biopsy every 6 months is usually performed, along with thermodilution cardiac output measurement. Coronary angiography is added to the yearly regimen after 1–2 years, to assess the development of coronary artery vasculopathy. Five to seven biopsies of the right ventricle are obtained, and rejection is usually assessed according to the International Society for Heart and Lung Transplantation (ISHLT) scale according to the degree of lymphocytic infiltration and myocyte damage in the specimen [133]. Rejection is classified as either cellular, primarily lymphocyte infiltration, or humoral, a predominance of antibody–antigen and complement complexes, which is often observed in patients with high PRA titers. Signs of acute rejection can range from low-grade fever and malaise, and gastrointestinal symptoms, to poor myocardial function and cardiovascular collapse. Treatment for acute rejection often begins with large doses of corticosteroids, and higher doses of maintenance immunosuppressants. Other agents such as antithymocyte globulin, antilymphocyte globulin, or interleukin-2 receptor antagonists may also be added according to institutional practice. Plasmapheresis may be used for humoral rejection to reduce the antibody titers until immunosuppressants have an effect. Patients in acute rejection may need additional therapy, including inotropic and ventilatory support, or even MCS with ventricular assist devices or ECMO. If all of these measures fail to reverse the rejection, retransplant is the only remaining treatment option.

Morbidity and mortality after cardiac transplant

The median survival post transplant is 22.3 years in infants less than 1 year old and 13.1 years for those aged 11–17 (Fig. 30.11) [102]. The decreasing median survival in older patients is thought to be multifactorial, including a relatively immature immune system in infants with a lack of preformed antibodies, increased sensitization in older children from previous cardiac surgeries, and increased risk taking behavior in older children such as poor medication compliance [104].

The highest mortality rate remains during the first year post transplant [102] (Fig. 30.11) and improvements in 5-year survival over different eras (Fig. 30.12) are primarily due to improvements in early survival in the first year [101,102]. Early mortality is significantly increased for patients on ECMO, those with a CHD diagnosis, those undergoing retransplantation, and those requiring ventilatory support immediately prior to transplant (Fig. 30.13) [102]. Continuous risk factors associated with 1-year mortality include donor ischemic time, donor–recipient height difference, estimated glomerular filtration rate, and pediatric center volume (Table 30.16). The leading causes of death in the first 30 days are: graft failure in 35%, infection in 15%, and multiorgan failure and acute rejection in 12% each. Categorical risk factors for 5-, 10-, and 15-year mortality include CHD, ECMO, and PRA >10%. Continuous risk factors for late mortality are also displayed in Table 30.16.

The leading cause of late mortality is graft failure, responsible for 30–40% of deaths beyond 3 years after transplant (Fig. 30.14) [102]. Retransplantation is most commonly

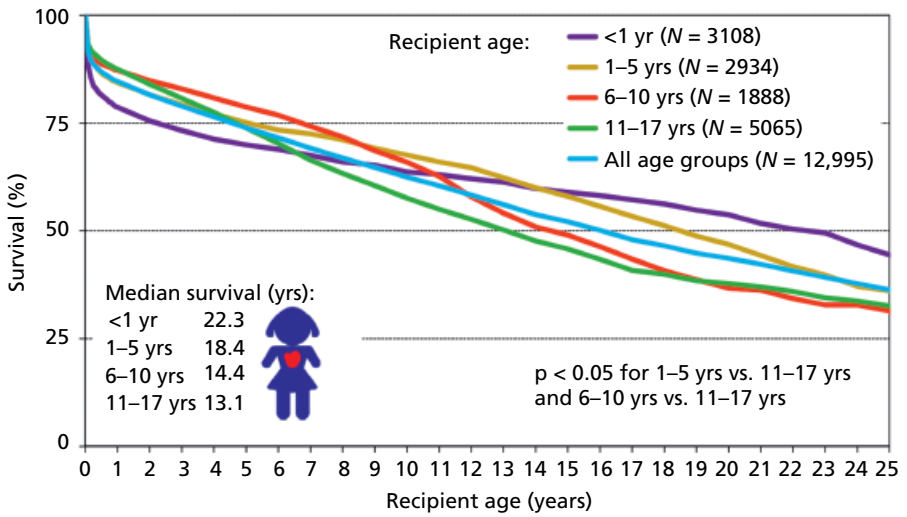


Figure 30.11 Pediatric heart transplant survival by age. *Source*: Reproduced from Rossano et al [102] with permission of Elsevier.

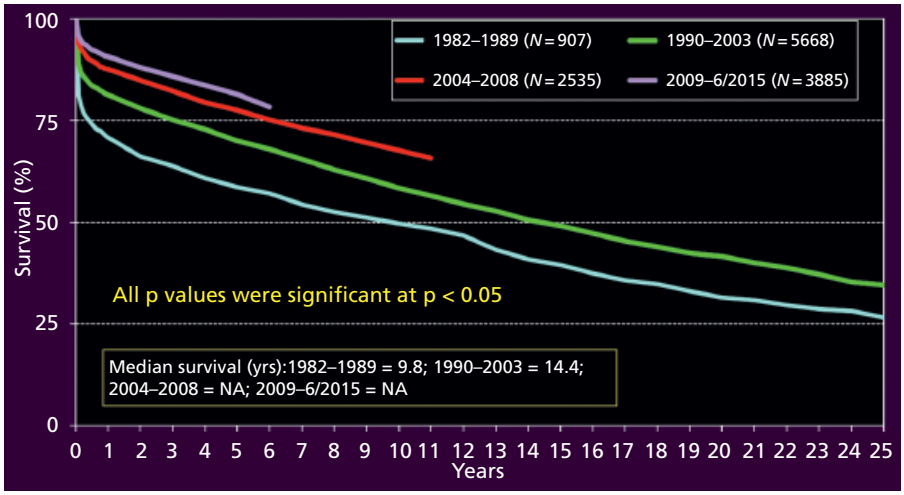


Figure 30.12 Pediatric heart transplant survival by era, 1982–2015. *Source*: Reproduced from Rossano et al [102] with permission of Elsevier.

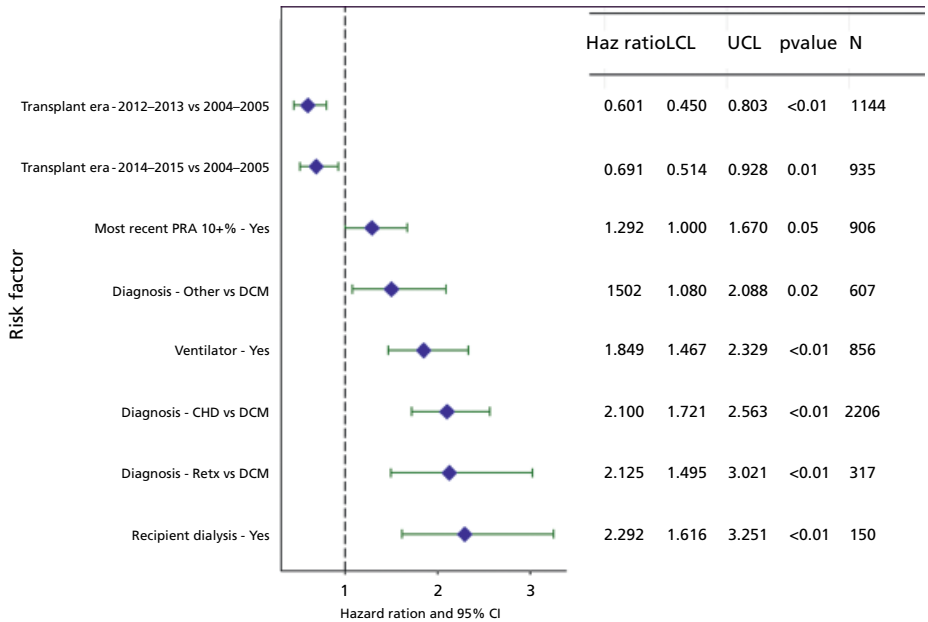


Figure 30.13 Risk factors for 1-year mortality in pediatric heart transplants, 2004–2015. CHD, congenital heart disease; CI, confidence interval; DCM, dilated cardiomyopathy; LCL, lower confidence level; PRA, panel reactive antibody; Retx, retransplant; UCL, upper confidence level. *Source*: Reproduced from Rossano et al [102] with permission of Elsevier.

performed because of severe coronary artery vasculopathy (CAV) or graft failure, and carries a higher risk of mortality, with a 5-year survival of about 67% in the modern era versus 77% for primary transplantation [134].

Morbidities in cardiac transplant recipients at 5 years after transplant include hypertension in 63% (primarily associated with corticosteroid use), hyperlipidemia in 26%, CAV in 11%, and renal dysfunction in 9% [101,102]. Thus a substantial number of these patients will be taking antihypertensive medications, and some will be taking statins or other cholesterol-lowering drugs. Renal function requires assessment before anesthetic, to avoid or minimize the use of agents with primary renal excretion, in appropriate patients. Infection and lymphoma are seen in a very small percentage of pediatric cardiac transplant recipients. Early CAV in the first 3 years after transplant is associated with a significantly higher risk of rejection.

KEY POINTS: HEART TRANSPLANT MORTALITY

- The highest mortality rate occurs during the first year post transplant
- Mortality risk factors include pretransplant ECMO or mechanical ventilation, CHD, retransplantation, renal dialysis, PRA >10%, and donor ischemic time
- The leading cause of early mortality is graft failure and of late mortality is coronary artery vasculopathy

Anesthetic management

Endomyocardial biopsy

All cardiac transplant recipients require myocardial biopsy. Access is gained either via the right internal jugular vein or

Table 30.16 Multivariable analysis of continuous risk factors for mortality after pediatric cardiac transplantation

Variable	p value
1-year mortality (transplants: January 2004 to June 2015)	
Ischemic time	0.0003
Recipient body mass index	0.0072
Donor body surface area	0.0038
Donor–recipient height difference	0.0119
Recipient estimated glomerular filtration rate	0.0117
Center volume: number of pediatrie transplants in previous year	0.0004
Recipient total bilirubin	0.0170
5-year mortality (transplants: January 2001 to June 2011)	
Recipient age	0.0002
Donor age	0.0434
Ischemic time	0.0048
Recipient weight	0.0403
Recipient estimated glomerular filtration rate	0.0006
Center volume: number of pediatrie transplants in previous year	0.0026
10-year mortality (transplants: January 1996 to June 2006)	
Recipient age	0.0010
Donor age	0.0006
Recipient height	0.0023
Recipient estimated glomerular filtration rate	0.0143
Transplant center volume	0.0084
15-year mortality (transplants: January 1990 to June 2001)	
Donor age	0.0137
Donor weight	0.0016
Donor body mass index	0.0038
Center volume: number of pediatrie transplants in previous year	0.0236

Source: Reproduced from Rossano et al [102] with permission of Elsevier.

the femoral vein. One advantage of jugular vein access is a faster post-biopsy recovery without a mandatory "lying flat" period, whereas femoral vein access may simplify the anesthetic and sedation management because the access site is remote from the airway. Some older teenage patients are mature and cooperative enough to receive intravenous sedation and local anesthesia to the access site without requiring the presence of an anesthesiologist. However, many older patients are very anxious due to the lifelong nature of their medical interventions, and require higher doses of sedative medications and associated deeper sedation in order to perform the catheterization. In stable outpatients without signs or symptoms of rejection or CAV, moderate or deep IV sedation with a variety of agents can be used, including benzodiazepines, opioids, and propofol. Patients with known or suspected rejection or CAV must be approached with great care. These patients may have significantly compromised cardiac function, or very severe CAV with marginal myocardial perfusion. They have very limited reserves if the myocardial oxygen supply–demand balance is upset. Whatever technique is used, these patients should not be subjected to significant reductions in preload or afterload as myocardial perfusion depends on blood pressure. Bolus administration of agents such as propofol or thiopental should be avoided, blood pressure monitored closely, and hypotension treated immediately. Tachycardia should also be avoided. If general anesthesia is chosen, positive pressure ventilation must be instituted carefully so as not to excessively decrease venous return. Airway and oxygenation may be supported with nasal cannulae, facemask, laryngeal mask airway, or endotracheal intubation.

Non-cardiac surgery

Cardiac transplant recipients may undergo surgical and diagnostic procedures, unrelated to the transplant. In addition to the assessment of cardiac and non-cardiac problems, the anesthesiologist should determine the results of the most recent cardiac biopsy, cardiac output, signs of rejection, and whether there is a suspicion of CAV. Ideally there should be a cardiology evaluation, including an echocardiogram, within 6 months of the procedure. The hemodynamic goals noted

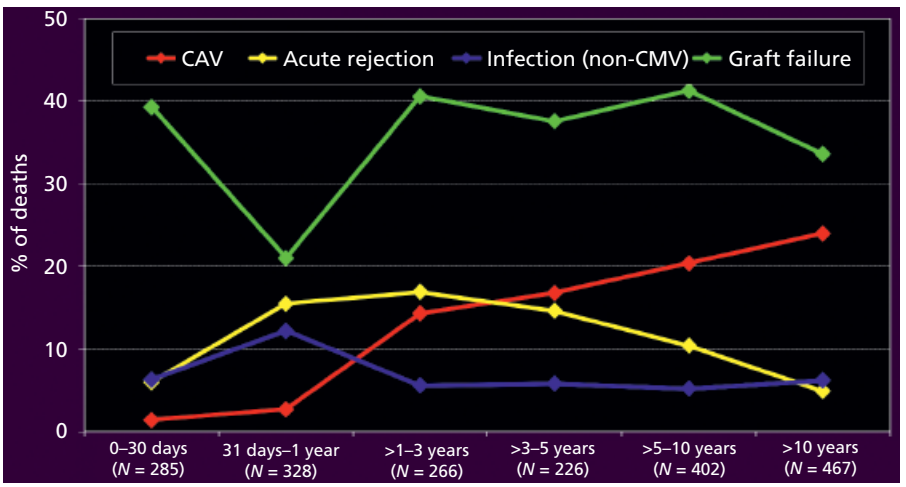


Figure 30.14 Relative incidence of leading causes of death in pediatric heart trasnsplants, 2004–2016. CAV, coronary artery vasculopathy; CMV, cytomegalovirus. *Source*: Reproduced from Rossano et al [102] with permission of Elsevier.

above for endomyocardial biopsy are the same for non-cardiac surgery. The denervated heart does not respond to vagolytic agents, so bradycardia requires treatment with a direct acting β1-agonist such as isoproterenol or epinephrine. Infective endocarditis prophylaxis guidelines have been significantly revised, and limit the need for prophylaxis to transplant recipients who develop valvulopathy and undergo dental and airway procedures where the respiratory mucosa is breached.[135]. Prophylaxis is no longer recommended for gastrointestinal and genitourinary procedures unless there is active infection. Care should be taken with the reversal of non-depolarizing muscle relaxants using neostigmine. Variable parasympathetic reinnervation, along with humoral or cellular rejection, may produce unpredictable responses to neostigmine and glycopyrrolate, which have been reported to produce severe sinus bradycardia and asystole [136]. Stress dose corticosteroids should be administered as appropriate for significant surgical procedures, where adrenal suppression is suspected.

ABO-incompatible transplantation

The number of infants listed for cardiac transplantation exceeds the number of donors by approximately 3:1, and there is significant mortality for infants waiting for transplant. Many infant heart transplant recipients who survive the first year after transplant are remarkably free of rejection. In 2001 West and colleagues described a series of infant cardiac transplants in patients up to age 14 months, with ABO-incompatible donors [128]. Anesthetic and surgical management of the transplant does not differ, except that an exchange transfusion, as described earlier, is performed upon institution of CPB. In addition, transfused blood products are selected to avoid antibodies to the donor heart. Midterm survival and rejection rates were not different to those of ABO-compatible transplants, and the waiting list mortality was reduced from 58% to 7% for infant transplants [128]. This technique has been adopted by more institutions, as evidence develops that overall survival of infants listed for transplant improves in the long term [137,138]. UNOS recently changed the priority listing for ABOi heart transplants to give them equal organ priority to ABO-compatible listed patients [111,112]. In recent years the ABO-incompatible approach has been extended to patients less than 2 years of age, with similar outcomes as for ABO-compatible transplants [139]. Many programs now offer these transplants, and the ABO-incompatible approach has now been reported in pediatric lung, liver, and kidney transplantation.

Bridge to transplant

Due to the shortage of donor organs, an increasing number of pediatric patients (approximately 30%) undergo MCS as a bridge to transplant (Fig. 30.15) [102]. In the past 10–15 years this has been the biggest change in the field of pediatric cardiac transplantation; the percentage of transplant patients on a ventricular assist device (VAD) has approximately tripled, while the percentage on ECMO support has declined significantly with improvement in techniques and devices for VAD support. Recent data show a similar overall survival in pediatric patients bridged to transplant with a VAD or total artificial heart (TAH) compared with no MCS (Fig. 30.16) [102]. However, patients bridged to transplant with ECMO had a significantly worse survival when compared to those bridged with VAD/TAH or those without MCS. The greatest risk of death in the ECMO group occurred in the first 6 months post transplant [102]. In 2011, the PediMACS registry was developed as a comprehensive registry of temporary and durable VADS in pediatric patients. Durable devices include pulsatile flow devices such as the Berlin Heart Excor® and continuous flow devices such as the HeartMate® (Thoratec, Pleasanton, CA, USA) and HeartWare™ (Medtronic, MA, USA) devices. Overall pediatric survival on a durable device is approximately 72% at 6 months [140]; ranging from 47% in patients <1 year to 81% in patients 11–19 years of age. Approximately 50% all patients were transplanted by 6 months on a device; 81% of patients were supported with LVAD alone whereas 15% required biventricular support. Common adverse events post-VAD implantation include bleeding, infection, device malfunction, and neurological events [140]. The frequency of MCS varied significantly according to the indication for transplant [102]. From 2009 to 2015, 47% of patients with DCM

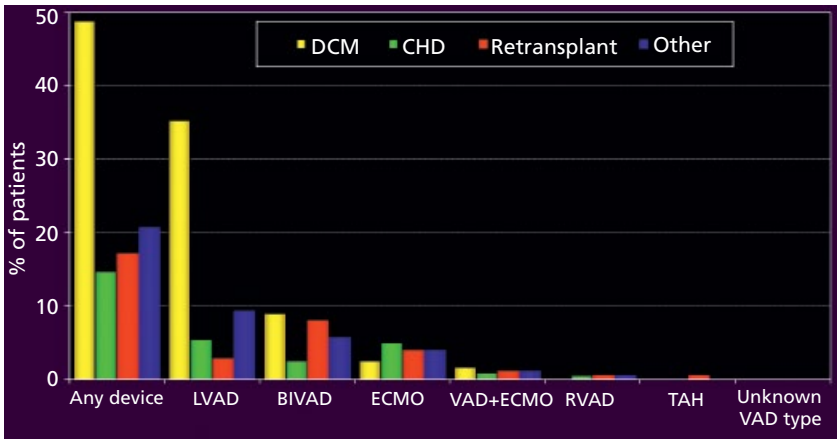


Figure 30.15 Pediatric heart transplant recipients bridged with mechanical circulatory support by diagnosis, 2009–2016. BIVAD, biventricular assist device; CHD, congenital heart disease; DCM, dilated cardiomyopathy; ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device; RVAD, right ventricular assist device; TAH, total artificial heart; VAD, ventricular assist device. *Source*: Reproduced from Rossano et al [102] with permission of Elsevier.

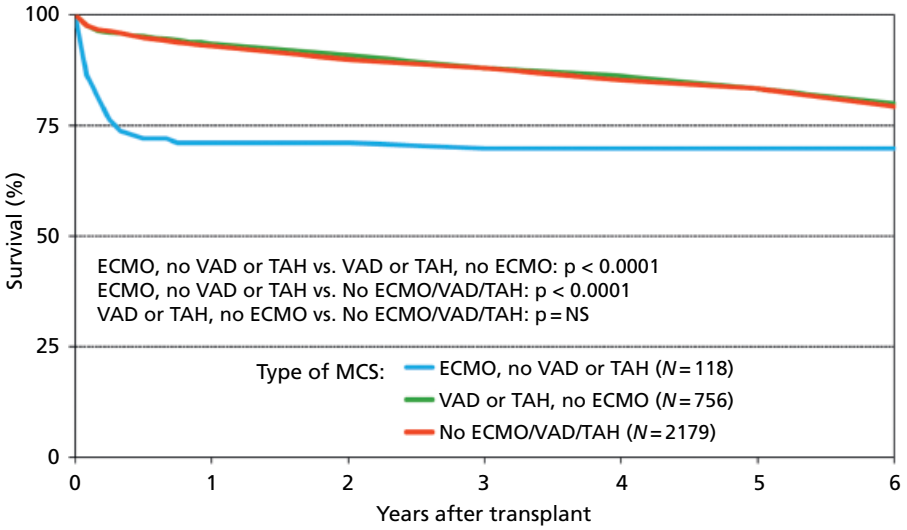


Figure 30.16 Survival of pediatric heart transplant recipients by mechanical circulatory support use, 2009–2015. ECMO, extracorporeal membrane oxygenation; TAH, total artificial heart; VAD, ventricular assist device. *Source*: Reproduced from Rossano et al [102] with permission of Elsevier.

required some form of MCS as a bridge to transplant, with the majority of cases being LVADs. ECMO as the primary support modality decreased from 42% of the MCS cases in 2005 to 9% in 2015 [102]. Perhaps, in the future, as technology advances and MCS survival and morbidity improves, implantable devices will be regarded as more of a long-term therapeutic option rather than just a bridge to transplant.

Lung transplantation

History

The first human lung transplant was performed on an adult in 1963 by James Hardy at the University of Mississippi [141]. This was followed by adult lobar (Shinoi, 1966) and pediatric heart–lung transplantation (Cooley, 1968) but outcomes were uniformly dismal. Advances over the next decade included the introduction of cyclosporine, better surgical techniques, and improved donor organ preservation, leading to the first long-term success with an adult heart–lung transplant by Reitz at Stanford in 1981 [142]. Cooper and colleagues in Toronto demonstrated that bronchial omentopexy enhanced the vascularity and integrity of the bronchial anastamosis and subsequently reported the first long-term successful adult (1983) and pediatric (1987) lung transplants [99]. Living donor lobar transplantation was first performed at Stanford by Starnes in 1990.

Data about lung and heart–lung transplantation from many centers around the globe are updated regularly by the ISHLT and can be viewed at their website (www.ishlt.org/registries; accessed April 2019). The ISHLT registry report in 2017 for the period 1988–2015 included 2326 pediatric lung transplant and 728 pediatric heart–lung transplant procedures [143]. Of note, heart–lung transplant procedures peaked in the late 1980s to early 1990s, at 50–60/year in the ISHLT registry. Over the last 10 years, only 5–10 heart–lung transplants are performed annually due to historically poor survival, especially in infants.

Forty to 50 centers have reported pediatric lung transplant procedures to the ISHLT over the last 10 years. Of these, only 1–3 centers report between 10 and 19 transplants per year over the past 10 years, 3–5 centers report 5–9 transplants per year, and the vast majority (35–40) of centers report <5 transplants per year (Fig. 30.17) [143]. Annually, an average of 100–120 children received lung transplant surgery over the past 10 years. Most patients were adolescents; the number of infant transplants has remained low at about 5–10 annually over the past 10 years (Fig. 30.18) [143].

In addition to the specific challenges inherent in caring for children, pediatric lung transplantation has many unique aspects, including a diverse spectrum of pulmonary and non-pulmonary diseases, donor–recipient matching, and growth of the transplanted organs. Children receiving transplantation undergo many surgical and diagnostic interventions and frequently require sedation or general anesthesia. Provision of safe perioperative care requires familiarity with the relevant issues, including pulmonary pathophysiology and the conduct and consequences of lung transplantation.

Indications

Generally, lung transplant surgery is considered for children with any end-stage lung disease for whom there is no medical treatment [144]. For all children less than 18 years of age, the common primary diagnoses leading to lung transplantation are cystic fibrosis (56%) and pulmonary hypertension, either idiopathic (10%) or related to CHD (5%) [143], whereas the common primary diagnoses in adults are chronic obstructive pulmonary disease or interstitial lung diseases. Indications for transplantation differ by age with cystic fibrosis the predominant indication for children aged 6 years or older (Table 30.17).

Cystic fibrosis

Respiratory failure is the commonest cause of death in these children. Many variables, like rate of decline in forced expiratory volume in 1 s (FEV_1), elevated pCO_2 (>50 mmHg), falling pO_2 (<55 mmHg), deteriorating nutritional status, frequency of hospitalizations, and the 6 min walk test are considered before listing the patient for lung transplant [145]. Perioperative management should address non-pulmonary

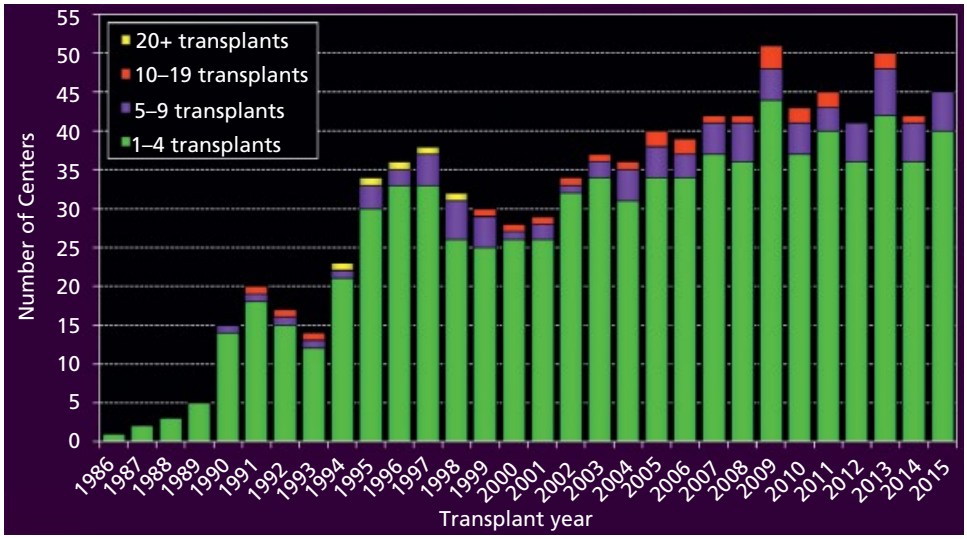


Figure 30.17 Pediatric lung transplants by center volume. *Source*: Reproduced from Rossano et al [102] with permission of Elsevier.

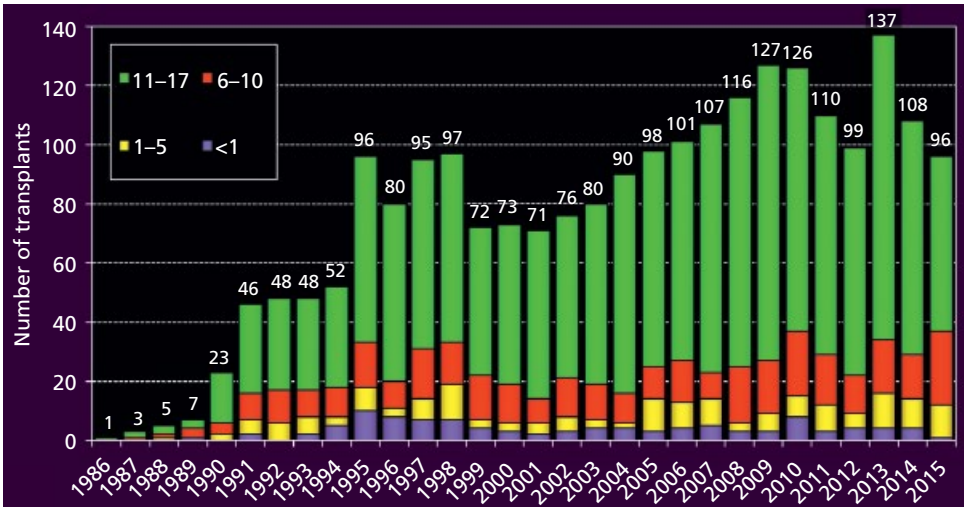


Figure 30.18 Pediatric lung transplant recipient age distribution by year of transplant. *Source*: Reproduced from Rossano et al [102] with permission of Elsevier.

Table 30.17 Pediatric lung transplant indications by age group, 2000–2016

Diagnosis	<1 years		1–5 years		6–10 years		11–17 years	
	n	%	*n*	%	*n*	%	*n*	%
Cystic fibrosis	0		4	3.7%	116	50.0%	814	66.7%
Non CF-bronchiectasis	0		0		2	0.9%	23	1.9%
ILD	5	8.3%	9	8.3%	6	2.6%	37	3.0%
ILD, other specify cause	6	10.0%	10	9.3%	21	9.1%	46	3.8%
Pulmonary hypertension/pulmonary arterial hypertension	7	11.7%	28	25.9%	24	10.3%	100	8.2%
PHT, Eisenmenger syndrome	0		1	0.9%	2	0.9%	6	0.5%
PHT, other	15	25.0%	21	19.4%	8	3.4%	20	1.6%
Obliterative bronchiolitis (non-retransplant)	0		10	9.3%	26	11.2%	58	4.8%
Bronchopulmonary dysplasia	4	6.7%	4	3.7%	3	1.3%	3	0.2%
ABCA3 transporter mutation	5	8.3%	4	3.7%	1	0.4%	1	0.1%
Surfactant protein B deficiency	13	21.7%	4	3.7%	1	0.4%	0	
Surfactant protein C deficiency	0		1	0.9%	0		1	0.1%
Retransplant (obliterative bronchiolitis)	0		4	3.7%	8	3.4%	41	3.4%
Retransplant (not obliterative bronchiolitis)	0		4	3.7%	6	2.6%	41	3.4%
COPD, with or without α1-ATD	2	3.3%	1	0.9%	3	1.3%	10	0.8%
Other	3	5.0%	3	2.8%	5	2.2%	20	1.6%

α1-ATD, α1-antitrypsin deficiency; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; PHT, pulmonary hypertension.
Source: Reproduced from International Society for Heart and Lung Transplantation [143] with permission of ISHLT, 2017.

manifestations of cystic fibrosis such as severe malnourishment, chronic infection, pancreatic insufficiency, diabetes mellitus, cholelithiasis, hepatic cirrhosis, distal intestinal obstruction syndrome, sinusitis, nasal polyps, osteoporosis, and genitourinary problems [146,147]. Pretransplant mechanical ventilation was predictive of poor 1-year survival after lung transplantation [148]. There are reasonably compelling data documenting the beneficial impact of lung transplantation on functional status, hemodynamics, and quality of life but demonstration of a survival benefit for children remains controversial [149,150]. Newer treatments for cystic fibrosis such as dornase alpha and ivacaftor (an oral cystic fibrosis transmembrane conductance regulator (CFTR) potentiator that improves chloride transport in cells expressing certain CFTR gating mutations), have contributed to sustained improvements in pulmonary function, weight gain, life expectancy, and delay in age of lung transplantation [151,152].

Pulmonary hypertension

During the Fourth World Symposium on Pulmonary Hypertension held in Dana Point, California in 2008, a reclassification of pulmonary hypertension based on clinical evolution, histopathology, and response to therapy was proposed. A diagnosis of primary (or idiopathic) pulmonary arterial hypertension is made when no known risk factor is identified. Familial pulmonary arterial hypertension has been linked to mutations in receptors in the transforming growth factor β superfamily, such as BMPR2 (bone morphogenetic protein receptor 2) and ALK-1 (activin-like kinase 1) which affect vascular intimal proliferation. Pulmonary arterial hypertension associated with CHD constitutes a heterogenous group of conditions and has been classified based on circulatory pathophysiology [153].

Transplantation options for pulmonary hypertension include lung transplantation, heart–lung transplantation, or lung transplantation in combination with repair of the underlying cardiac defect. Survival rates for these strategies have been reviewed [154]. In Eisenmenger syndrome secondary to ventricular septal defect, there was a survival benefit of heart–lung over lung transplantation [155]. Transplantation may improve the quality of life of patients with Eisenmenger syndrome but may not improve survival because most unrepaired Eisenmenger patients will survive beyond their 40th birthday [156]. Many children with pulmonary hypertension will be receiving agents such as endothelin receptor antagonists, phosphodiesterase inhibitors, prostacyclin analogs and nitric oxide. For idiopathic pulmonary hypertension, contemporary guidelines recommend referral to lung transplantation centers for evaluation of patients who are in World Health Organization (WHO) functional class III or IV on optimized medical therapy or who have rapidly progressive disease [157].

Disorders of surfactant metabolism

Pediatric interstitial lung disease syndrome is an uncommon indication for lung transplantation and includes diseases of surfactant metabolism [158]. Surfactant proteins B, C, and ABCA3 transporter are necessary for surfactant homeostasis, and mutations in the genes encoding these proteins lead to surfactant dysfunction, giving rise to both lethal and chronic respiratory disease in infants. Patients may require lung transplantation in early infancy because of severe respiratory failure.

Miscellaneous disorders

Lung transplant surgery has also been performed in children for a variety of other indications like bronchopulmonary dysplasia, congenital diaphragmatic hernia, hemosiderosis, bronchiolitis obliterans, and emphysema.

Criteria for listing and contraindications

The criteria for listing children for lung transplant surgery are based on the natural history of the disease, functional status, and expected improvement in quality of life. Generally, a clear diagnosis with a life expectancy of less than 2 years is necessary for listing the child for the lung transplant. However, it is hard to develop survival models for relatively rare diseases.

Contraindications to lung transplantation are listed in Table 30.18 [144]. Mechanical ventilation is a risk factor for morbidity and mortality in older children but not infants. Children with cystic fibrosis who are colonized with multidrug-resistant organisms like *Burkholderia cenocepacia* and *B. gladioli* do poorly and most centers consider this a strong contraindication. Children with liver disease secondary to cystic fibrosis may be candidates for combined liver–lung transplant surgery and have good survival rates. Patient and parental psychosocial issues can be particularly challenging and may become a significant contraindication if child and family consistently fail to meet agreed-upon expectations for care and follow-up [13].

Perhaps the most difficult decision for pediatric lung transplant physicians is determining the appropriate time to accept organs because there is wide variation in the natural history of the primary diseases (Table 30.19) and the 5-year survival rate after lung transplantation is only about 50% [13]. Most pediatric centers consider multiple factors, including waiting list survival estimates (when available), growth and nutrition status, frequency of hospitalizations, and potential for improvement in overall quality of life before committing a child to lung transplant.

Table 30.18 Contraindications to pediatric lung transplantation

Absolute	Relative
Active malignancy	Pleurodesis
Sepsis	Renal insufficiency
Active tuberculosis	Markedly abnormal body mass index
Severe neuromuscular disease	Mechanical ventilation
Documented, refractory non-adherence	Scoliosis
Multiple organ dysfunction	Poorly controlled diabetes mellitus
Acquired immunodeficiency syndrome	Osteoporosis
Hepatitis C with histological liver disease	Hepatitis B surface antigen positive
	Fungal infection/colonization
	Chronic airway infection with multiply resistant organisms

Source: Reproduced from Faro et al [144] with permission of John Wiley and Sons.

Table 30.19 Recommendations regarding timing of referral to lung transplant center

Specific disease	Timing of referral
Surfactant deficiencies	Patients with SP-B deficiency and ABCA3 deficiency with refractory respiratory failure should be referred immediately Patients with SP-C deficiency and less severe forms of ABCA3 deficiency may respond to medical therapy and should be referred when unrelenting progression of disease develops
Primary pulmonary hypertension	Patients who present in NYHA class III or IV or have evidence of right heart failure should be referred immediately Patients who fail to respond adequately to vasodilator therapy should also be referred
Eisenmenger syndrome	When the trajectory of pulmonary hypertension appears to be worsening with impaired exercise tolerance and worsening quality of life
Other pulmonary vascular disorders (pulmonary vein stenosis, alveolar capillary dysplasia)	These patients should be referred immediately since they typically do not respond to medical management and are at risk for sudden death
Cystic fibrosis	Patients with percent predicted FEV_1 values less than 30%, frequent hospitalizations, refractory hypoxemia or hypercapnia should be referred for transplant
Bronchopulmonary dysplasia	Patients with recurrent or severe episodes of respiratory failure or evidence for progressive pulmonary hypertension
Diffuse parenchymal lung disease	Patients without evidence for systemic disease that could affect outcome should be referred early

FEV_1, forced expiratory volume in 1 s; NYHA, New York Heart Association; SP, surfactant protein.
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Donor selection, availability, and the lungs allocation system

Like other organ transplant surgeries, donor availability has been a limiting factor. Only about 15% of cadaveric donors have lungs that are considered acceptable for transplantation [159]. The OPTN implemented a new lungs allocation system in 2005 that used medical urgency as the primary determinant of organ allocation and discouraged the use of waiting time [160]. Under this system, a lung allocation score is calculated for every patient >12 years of age using multiple variables like age, functional status, forced vital capacity, and oxygen requirement. The new policy also mandated that the donor lungs from pediatric donors be preferentially given to pediatric patients. Recent data from adult and pediatric patients suggest that implementation of the lung allocation score system has decreased waiting times and increased the annual number of lung transplant surgeries performed [160].

However, children younger than 12 years of age still received organs based on the waiting time accrued on the transplant list. Recognizing that infants carry the highest waiting list mortality rate among all transplant candidates, the OPTN recently approved proposals to preferentially direct organs from donors under 11 years old to younger children [161].

Donor lungs are selected after thorough medical screening and multiple laboratory tests. In younger children, comparable age and height (<20% discrepancy) are considered acceptable for matching lung volume. Selection criteria are relatively subjective. An ideal donor is younger than 55 years, a nonsmoker, and has no history of cardiopulmonary or significant neurological disease. The donor lungs should produce good gaseous exchange (PaO_2 >350 mmHg with FiO_2 of 1.0) on a moderate amount of ventilatory support. The chest radiography and bronchoscopy should rule out any significant infection, consolidation, and tumor. An expected ischemic time of <6 h is preferred. Optimal donor lung management has been reviewed [162]. To increase the number of potential donors, some centers have advocated acceptance of longer ischemic times and "marginal" donors with reversible mild lung pathology [163]. Biochemical markers in the bronchoalveolar lavage fluid from the donor lungs (e.g. interleukin (IL)-8, IL-6, and IL-1b), are being evaluated as predictors of early and late graft dysfunction [164]. Additionally, using lung donation after cardiac death is another option that has been being considered to alleviate organ shortage [165].

The process of harvest includes systemic heparinization of the donor and infusion of prostaglandin E1 into the main pulmonary artery. A number of preservation solutions have been tried but currently Euro-Collins solution is used by most centers. Lungs are inflated with an FiO_2 of less than 0.4 to an airway pressure less than 20 cmH_2O. Lungs are removed en bloc with the thoracic aorta, left atrial cuff, and main pulmonary artery [162].

KEY POINTS: INDICATIONS, CONTRAINDICATIONS, AND LISTING FOR LUNG TRANSPLANTATION

- Cystic fibrosis and pulmonary hypertension are the leading indications for lung transplantation
- Contraindications include active malignancy, sepsis, colonization with multidrug resistant bacteria or fungus, and severe neuromuscular disease
- Life expectancy of less than 2 years is generally necessary before listing for lung transplant

Preoperative assessment and preparation

Candidates for lung transplantation undergo an extensive medical and psychosocial evaluation. Imaging studies of major thoracic systemic and pulmonary vessels may be required for patients with CHD because abnormal vasculature can alter the conduct of organ harvest and transplantation surgery. Children with pulmonary hypertension undergo a diagnostic cardiac catheterization to quantify hemodynamics and test for reactivity to pulmonary vasodilator therapy. After listing, the child's clinical progress is monitored regularly and an anesthetic consultation obtained. Many children can be living at home with minimal oxygen supplementation while others, especially infants, are on chronic ventilatory or

extracorporeal hemodynamic support. Recently, extracorporeal devices that facilitate respiratory exchange have been utilized as a bridge to lung transplant [166–168]. In addition, there are now a number of reports of "awake" venovenous ECMO in older pediatric patients awaiting lung transplant [169–171]. This strategy allows oral intake, physical therapy, and even ambulation and may improve preoperative transplant status.

Anesthetic management

Box 30.6 summarizes the intraoperative management of pediatric lung transplantation. Like other solid organ transplants, time of surgery is unpredictable. Most families are provided a hospital pager and have been anticipating the surgery for a long period of time. Patients are often excited and frightened. Anxiolytics such as midazolam can be safely given to most children but discretion and monitoring are advised because of the potential for compromise to upper airway control, respiratory effort, and hemodynamic stability.

When relevant, the patient and family should be informed preoperatively that surgery may possibly not proceed to transplantation if the donor lungs are deemed unsuitable. Good communication between the donor and recipient teams is vital, with all parties having a clear understanding of the expected time of anesthesia induction and donor organ arrival. Anesthesia preparations are similar to those for pediatric hypothermic open heart surgery. Anesthesiologists often work under considerable time pressure because of concerns about extending the donor organ ischemic time.

Standard NPO guidelines are followed to minimize the risk of aspiration and contamination of the new lungs. The method of anesthesia induction and choice of agents will depend on the patient's clinical and NPO status. The hemodynamic goal is to preserve stability without increasing PVR. Both volatile and intravenous anesthetic agents are acceptable. Propofol is safe for hemodynamically stable children (e.g. many cystic fibrosis patients) but ketamine or etomidate may be the preferred drug for patients who have poor cardiac reserve and/or pulmonary hypertension. Anesthetic depth can be maintained

Box 30.6: Summary of intraoperative considerations for pediatric lung transplantation

Pre-bypass period

- Consider pathophysiology of lung disease: CF, pulmonary hypertension, congenital heart disease, others
- Maintain all pulmonary vasodilator therapy on schedule
- Administer immunosuppressant induction agents and antibiotics according to preoperative plans
- Standard single-lumen endotracheal tube for most cases. Plan with surgeon for tracheostomy management
- Vascular access: arterial line (consider femoral if arms up for clamshell incision), CVP, large-bore peripheral intravenous catheters
- Discuss surgical approach: BSLT (clamshell incision, separate bronchial anastomoses), versus en bloc technique with bronchial revascularization (sternotomy, single tracheal anastomosis)
- Ventilate to baseline $PaCO_2$ values (e.g. hypercarbia common)
- ICU ventilator or HFOV may be required for infants
- Maintain pulmonary toilet pre-bypass: suction, bronchodilators
- Prepare for possibility that donor lungs are unsuitable after visualization (limit fixed agents, reverse muscle relaxant, awaken patient, remove lines)

Bypass period

- Normally mild to moderate hypothermic bypass
- Repair any congenital cardiac lesions, e.g. atrial septal defect
- Normally no aortic cross-clamp
- Instill antibiotics into trachea for CF patients
- Prepare bronchoscope to visualize bronchial/tracheal anastomoses, suction/irrigate blood, mucus, clot
- Ideally ischemic time goal is <6 h until lungs are reperfused (completed pulmonary artery anasotomoses)

Postbypass period

- Separate from bypass on ventilator settings that minimize volutrauma, barotrauma, oxygen toxicity: 6–7 mL/kg (donor weight), peak pressure <25 cmH_2O), PEEP 5 cmH_2O, FiO_2 0.4–0.5 or less
- Inhaled nitric oxide 20 ppm, epoprostenol frequently used
- Limit fluid administration (no lymphatic drainage): CVP 4–6
- Milrinone, vasopressors (vasopressin, phenylephrine) as needed
- Significant bleeding treated with platelets, cryoprecipitate/fibrinogen concentrate, and fresh frozen plasma/coagulation factor concentrate/activated factor VII
- Usually no TEE unless intracardiac repair
- Early graft dysfunction (hypoxemia, pulmonary edema) treated with increased FiO_2, PEEP, inhaled nitric oxide to maintain SpO_2 in low 90s; venovenous ECMO if needed
- Usually will not extubate in operating room; but stable patients can be extubated in 12–24 h
- Full hand-over report from anesthesia/surgical team to ICU team
- Pain management via opioid infusion, dexmedetomdine, and patient/nurse-controlled analgesia

CF, cystic fibrosis; BSLT, bilateral sequential lung transplantation; CVP, central venous pressure; ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; HFOV, high-frequency oscillatory ventilation; ICU, intensive care unit; $PaCO_2$, partial pressure of CO_2 in arterial blood; PEEP, positive end-expiratory pressure; SpO_2, peripheral capillary oxygen saturation; TEE, transesophageal echocardiogram.

with opioids and benzodiazepines, and supplemented with inhalational or intravenous agents [172]. Nitrous oxide is best avoided because of concerns about myocardial depression, pulmonary hypertension, air embolism, and the requirement for high concentrations of inspired oxygen. The combination of anesthesia, right ventricular diastolic dysfunction, and positive pressure ventilation may unmask a relative intravascular volume deficiency that can be corrected by IV fluid infusion.

Most often, pediatric lung transplants are performed with the assistance of CPB and the airway is secured with a single-lumen endotracheal tube because lung isolation is not required. Occasionally, patients have a tracheostomy, and airway management needs to be planned with the surgeon; i.e. intubate the trachea from above and temporarily seal the stoma, endotracheal tube in the stoma for improved airway access, or utilize the existing tracheostomy (see Chapter 16). Frequent toilet of the airway is advised, particularly in patients who have cystic fibrosis. Bronchodilator therapy should be available. Effective oxygenation and carbon dioxide elimination may be difficult during the pre-CPB period, and permissive hypercapnia is acceptable. Ventilation should be adjusted to minimize air trapping because lung hyperinflation can impede venous return to the heart. Strategies to limit airway pressure are advised for patients at increased risk of barotrauma, such as those with restrictive lung disease or chronic obstructive pulmonary disease. Occasionally, especially in infants, a sophisticated pediatric intensive care ventilator may be required in the OR. Many patients who have end-stage lung disease have a chronic compensatory metabolic alkalosis. Enthusiastic hyperventilation to normal $PaCO_2$ values induces an iatrogenic alkalotic blood pH level that increases cerebral vasoconstriction and leads to relative cerebral ischemia.

Invasive monitoring appropriate for surgery with CPB is established. At many institutions, continuous monitoring of pulmonary pressure with pulmonary artery catheter is limited to adolescents with the pretransplant diagnosis of pulmonary hypertension [173]. The pulmonary artery catheter is introduced through a sheath in the internal jugular vein and advanced to the pulmonary artery after the patient has been weaned from CPB. For smaller children, a transthoracic catheter can be placed directly into the pulmonary artery by the surgeon. Intraoperative TEE is useful for assessing cardiac anatomy and function, pulmonary hypertension, and to rule out pulmonary venous obstruction [174,175].

Anesthesiologists must ensure that the non-anesthetic drugs like immunosuppressants and preoperative antibiotics are administered at appropriate times. For children with pulmonary hypertension, selective vasodilators like nitric oxide and prostacyclins must be maintained throughout the pre-bypass period to avoid rebound pulmonary hypertension.

Children undergoing lung transplantation are at increased risk for perioperative bleeding because of coagulopathies associated with CPB and cyanosis, and bleeding from chest wall adhesions (infections, previous surgery) or abnormal vessels (venovenous or arteriovenous collaterals). Antifibrinolytic prophylaxis with the lysine analogs may help reduce blood loss but there is insufficient information about their efficacy and safety in young children.

The function of the implanted lungs could be adversely affected by donor pathology, ischemia-reperfusion injury, CPB, blood product transfusions, denervation, lymphatic stasis, positive pressure ventilation, oxygen toxicity, and hyperacute rejection. Ischemia-reperfusion injury contributes to primary graft dysfunction (PGD) and can increase the risk of acute and perhaps chronic rejection. Oxygen is readily available to the metabolically active endothelium of lung allografts during the ischemic period and this allows production of free radicals, making lungs more susceptible to graft failure than other solid organs. Reperfusion injury appears to occur in two distinct phases. The first phase, seen immediately after the reperfusion, is initiated by donor macrophages and includes the release of superoxide anions and inflammatory cytokines, with mast cell degranulation and complement activation. These damage the vascular endothelium causing movement of fluid to the interstitial and alveolar space [176]. The delayed phase of PGD starts a few hours later when the recipient's neutrophils are recruited by cytokines to the injured endothelium. These neutrophils produce reactive superoxide anions and greatly amplify the initial injury. Strategies to minimize reperfusion injury include improvements to the lung preservation solution, gentler reperfusion techniques, protective ventilation strategies, and inhaled nitric oxide [177]. Ultrafiltration during and after CPB can ameliorate the inflammatory response. However, modified ultrafiltration increases right ventricular volume load and may precipitate right heart failure in the presence of pulmonary hypertension [178].

Before weaning from CPB, a bronchodilator may be administered by metered dose inhalation or nebulization, and the lungs are carefully re-expanded to check for bronchial air leaks and ventilation is then resumed. Ventilator parameters are guided by the donor weight. Tidal volume and airway pressures are adjusted so that all atelectatic areas are expanded but not over distended. Volutrauma caused by overdistension of the new lungs can increase endothelial permeability and potentiate primary graft dysfunction. Typically, flexible bronchoscopy is performed to assess the bronchial anastomosis, and to remove blood and secretions from each lung under direct visualization. If possible, inspired oxygen concentrations should be lowered because of concern about oxygen toxicity and free-radical damage [179]. Restriction of fluid infusions is advocated because the lung allograft is very sensitive to pulmonary edema but trials substantiating this practice are lacking.

Inhaled selective pulmonary vasodilator therapy (e.g. nitric oxide, epoprostenol) is initiated when pulmonary artery pressures are increased. Some centers routinely administer intravenous prostacyclin or prostaglandin E1 to reduce pulmonary artery pressures and preserve right heart function. Pulmonary hypertension must be anticipated and managed carefully [180,181]. Inhaled nitric oxide before and after transplantation may improve allograft function [182]. Right ventricular dysfunction can be supported by intravenous inotropes. Milrinone is a common choice because of its lusitropic and vasodilator effects.

Cardiopulmonary bypass

Although controversial, there is some evidence that CPB is an independent or contributing factor for PGD [183]. Therefore, most adult bilateral lung transplant centers perform lung transplantation using single-lung ventilation through dual-lumen

endotracheal tubes. However, most children are physically too small to accommodate a double-lumen tube. Additionally, some children are too tenuous clinically to tolerate a prolonged period of single-lung ventilation. CPB allows the resection of both diseased lungs simultaneously, thus minimizing the risk of cross-contamination of the new lungs. Also, it provides stable hemodynamics during the extensive surgical dissection, greatly simplifies the anesthetic and surgical management, and consequently reduces lung ischemic times. Therefore, most pediatric lung transplants are performed using CPB. A large single-center comparison of the incidence of PGD in pediatric and adult lung transplant found no difference suggesting that CPB did not carry additional risk in children [184].

Surgical technique

Most children undergo bilateral sequential lung transplantation through a trans-sternal, clamshell incision (Fig. 30.19) [185]. Very few pediatric single-lung transplants are performed because the primary disease usually affects both lungs. Beating heart CPB with moderate hypothermia (28–32°C) is employed. Aortic cross-clamping and cardioplegia may be necessary if co-existing intracardiac defects require repair. Once CPB is established, both lungs are removed and the recipient's tracheal stump is irrigated with an antibiotic solution. Meanwhile, a second surgical team prepares the donor lungs that are then implanted using end-to-end bronchial anastomoses. Since the surgery compromises the bronchial vasculature, peribronchial tissue is sutured loosely around the anastomoses to provide blood flow by new vessel ingrowth. The donor pulmonary artery is attached to the native main pulmonary artery. The pulmonary veins are reconnected to the recipient's left atrium en bloc, using the donor's atrial cuff. This method not only reduces the surgical time but also minimizes the risk of developing pulmonary vein stenosis.

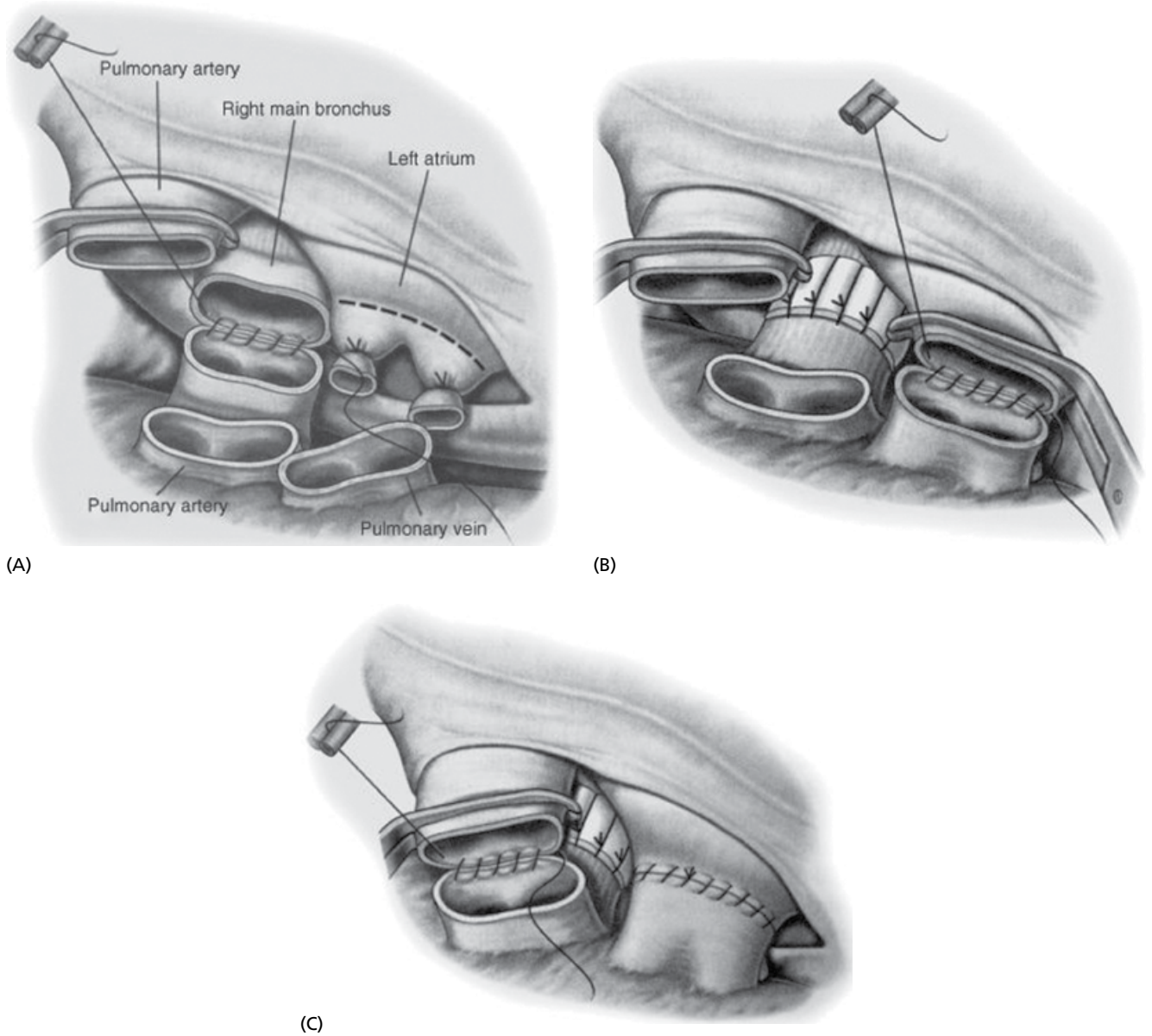

Figure 30.19 (A) End-to-end right bronchial anastomosis. (B) End-to-end right pulmonary vein anastomosis. (C) End-to-end right pulmonary artery anastomosis. *Source*: Reproduced from Ren et al [185] with permission of John Wiley and Sons.

Another surgical approach is the en bloc technique with a single tracheal anastomosis, and bronchial artery revascularization using a using a cuff of donor aorta [186]. The theoretical advantage of this technique is much improved perfusion to the graft because the bronchial artery circulation normally provides 50% of the airway's dual blood supply. This in turn may reduce airway and infectious complications, and delay the onset of bronchiolitis obliterans syndrome, which can have an ischemic etiology. The descending aorta is clamped with a partial occlusion clamp, and the bronchial artery button is anastomosed to this area (Fig. 30.20). After reperfusion of the bronchial arteries, bleeding will be observed from the cut edge of the trachea, and blood return is often identified in the pulmonary arteries and veins. This theoretically limits further graft ischemia. A single end-to-end tracheal anastomosis is completed, followed by flexible bronchoscopy by the anesthesiologist for removal of bloody secretions. During aortic cross-clamp, a single left atrial anastomosis is performed, and other intracardiac anomalies may be addressed. After removal of the aortic cross-clamp, an end-to-end main pulmonary artery anastomosis is performed. Another advantage of this technique is that it can be done through a median sternotomy, reducing pain and facilitating early tracheal extubation. In a single institution comparison study of 88 bilateral sequential lung transplants and 31 en bloc transplants with bronchial artery revascularization, there was no difference in ischemic or bypass times, early or longer term survival, graft dysfunction, or cellular rejection scores. Bilateral sequential lung transplant was associated with higher ischemic injury and non-airway complications.

Living donor lobar transplant (LDLT) involves two living donors, each providing a lower lobe to the recipient. LDLT has often been used to provide organs rapidly to children with cystic fibrosis who have undergone an unexpected rapid progression of their disease. Although outcomes can be comparable to deceased donor transplant [187] and there is some evidence to suggest that the incidence of bronchiolitis obliterans is lower in LDLT recipients [188], the procedure is resource intensive and has ethical implications because 10–20% of donor lobectomy surgeries have serious complications [189,190]. The 2017 ISHLT report noted the number of LDLT surgeries in pediatric recipients peaked in 1998–1999

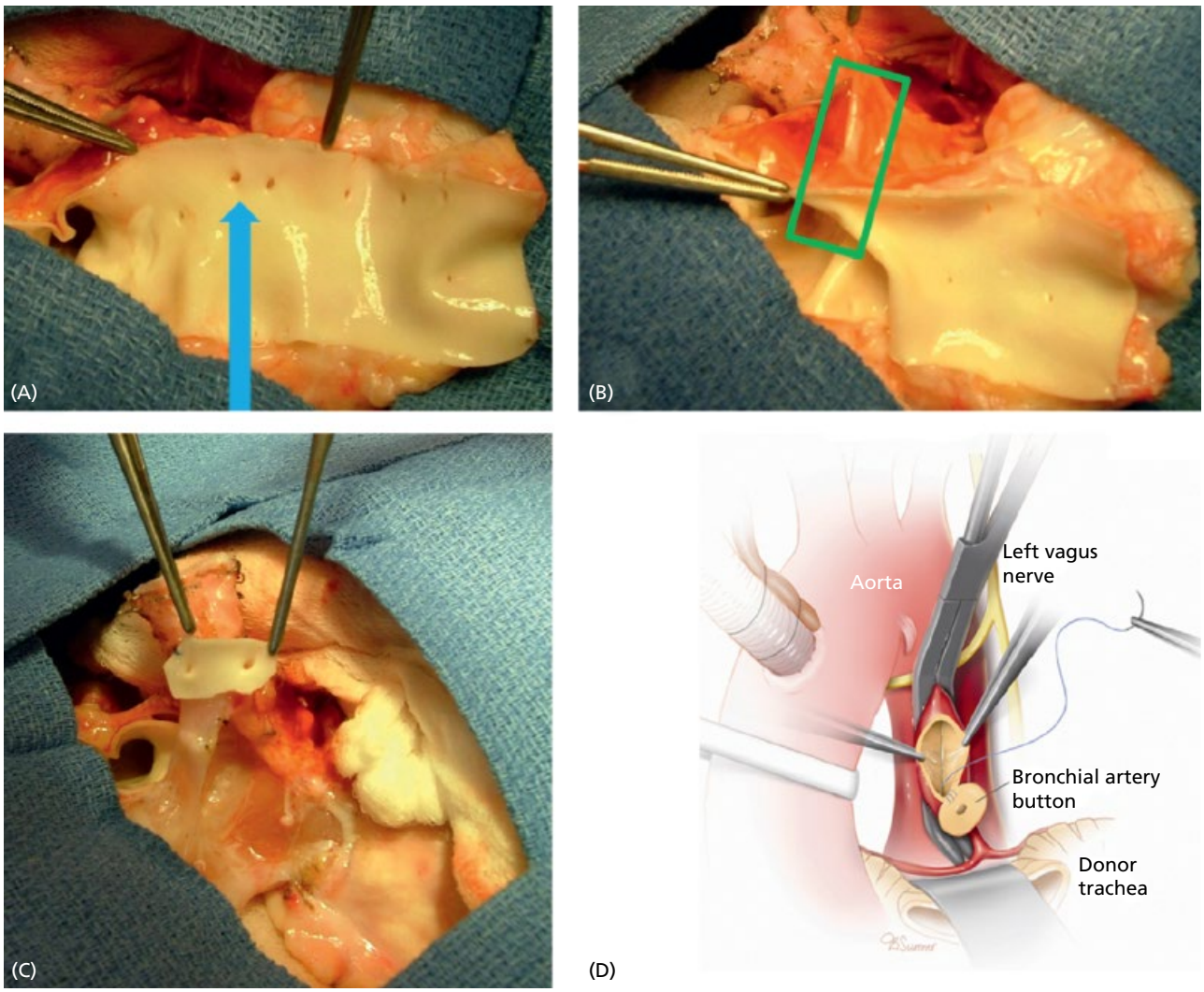

Figure 30.20 Key operative aspects involving bronchial artery revascularization technique. (A) The descending donor thoracic aorta is opened longitudinally. (B) The bronchial artery is identified arising from the aorta. (C) The aortic button containing the origin of two bronchial arteries is identified; the esophagus has been previously removed. (D) Suturing the bronchial arteries to the aorta. *Source*: Reproduced from Guzman-Pruneda et al [186] with permission of Elsevier. (D) © Texas Children's Hospital.

and since then has decreased substantially, and none were reported in 2013–2015 [143].

When the recipient's chest is too small to accommodate the donor lungs, the donor lungs can be reduced in size. Options include lobectomy (typically, the right middle lobe or lingula), wedge resection using a linear stapler, single lobe transplant, or split lung "bipartitioned" transplant (in which two smaller "lungs" are created from a single deceased donor lung). Reports suggest that outcomes in pediatric recipients of reduced-size organs can be comparable to recipients of full-sized grafts [191].

KEY POINTS: PREOPERATIVE CONSIDERATIONS AND ANESTHETIC MANAGEMENT FOR LUNG TRANSPLANT

- Extensive pretransplant evaluation and preparation is necessary; preoperative condition ranges from stable outpatients, to ventilated inpatients, and even ambulatory ECMO
- Most pediatric transplants are bilateral sequential lung transplant on CPB via a clamshell incision
- Careful attention to volutrauma and barotrauma, oxygen toxicity, fluid overload, and acute graft dysfunction are necessary for anesthetic care

Early postoperative management

Patients are sedated and on ventilator support when admitted postoperatively for intensive care. The duration of mechanical ventilation has to be individualized for each child but many can be extubated within 12 h of the surgery. Infants often have complex clinical problems and are critically ill before surgery; they required ventilation for longer (average 24 days) than older patients with cystic fibrosis (average 3 days) [192].

Some programs elicit the help of pediatric pain service specialists for postoperative pain management. Many centers provide patient-controlled anesthesia and opioid infusions. There are no pediatric studies of postoperative analgesia after lung transplantation comparing epidural and intravenous techniques. Regional anesthesia via an epidural catheter has been frequently used in adults and some older children when transplantation was performed without CPB. A report of 58 pediatric patients who underwent epidural insertion before surgery and CPB, showed no apparent complications from this technique and a median time to extubation of 19 h [193]. Epidural analgesia was less effective in adult patients undergoing unilateral and bilateral lung transplantation than in patients undergoing a thoracotomy for other indications, perhaps due to the extensive clamshell incision [194]. A survey of adults found the occurrence of moderate to severe persistent pain after lung transplantation was low (5–10%) [195].

Physiological changes and growth of the transplanted lungs

The allograft lungs are denervated but this produces few clinically significant effects on airway reflexes, mucociliary movement, and bronchial hyper-reactivity [196]. Lack of afferent stimuli to the respiratory center in transplanted patients results in poor coordination between the thoracic and abdominal muscles, and a subnormal increase in the minute ventilation with carbon dioxide challenge was noted in adult patients [197]. Loss of lymphatic drainage makes the transplanted lungs more susceptible to interstitial edema, increased water content, and lower compliance [198].

It is uncertain whether transplanted lungs grow. Although spirometry measurements (i.e. FEV_1 and forced vital capacity) after lung transplant may be in the normal range in infants [197] and older children [199], these measurements may indicate increased volume of each alveolar unit rather than alveolar tissue growth or increased surface area for gas exchange. Animal studies demonstrated lung tissue growth, and serial imaging studies in humans showed airway growth [200]. The measurement of diffusing capacity for carbon monoxide (DLCO) provides an estimate of gas exchange surface area. A single-center study of the DLCO in pediatric recipients of cadaveric and living donor transplants did not show an appreciable increase in DLCO, thereby suggesting the increase in lung volume seen in mature lobes is secondary to hyperinflation [201].

Complications of lung transplantation

Common complications are summarized in Table 30.20 [143]. Hypertension is diagnosed in as many as 70% of lung transplant survivors at 5 years.

Airway complications

A single-center study involving 470 bronchial anastomoses at risk reported 42 (9%) airway complications (stenosis, $n = 36$; dehiscence, $n = 4$; malacia, $n = 2$) requiring interventions. Most (90%) complications were diagnosed within the first 3 months after transplantation. Associated risk factors were preoperative infection with *Pseudomonas cepacia*, postoperative fungal lung infection, and prolonged mechanical ventilation [202]. Infants are prone to developing tracheobronchomalacia and dynamic airway obstruction. Often the problem resolves without surgical intervention but patients may need prolonged ventilatory support [203]. Airway stenosis is usually treated successfully with repeated mechanical balloon dilation through a rigid bronchoscope. Stents are generally avoided in children with potential for airway growth; the devices are difficult to remove and can cause problems with exuberant granulation tissue growing through the wire mesh.

Vascular complications

A perfusion scan is typically performed early after surgery to quantify the distribution of pulmonary blood flow. Vascular complications are infrequent, with pulmonary vein obstruction being the commonest problem. Cardiac catheterization is indicated if a vascular abnormality is suspected. Any significant obstruction to pulmonary blood flow requires urgent treatment either by surgery or interventional cardiac catheterization [204].

Nerve injuries

Early re-exploration of the chest was performed in 11% of cases in one series, most commonly for bleeding [204]. Phrenic

Table 30.20 Cumulative morbidity rates in pediatric lung transplant survivors, 1994–2015

Outcome	Within 1 year	Total *N* with known response	Within 5 years	Total *N* with known response	Within 7 years	Total *N* with known response
Renal dysfunction:	9.7%	(*N* = 815)	29.6%	(*N* = 291)	42.0%	(*N* = 169)
Abnormal creatinine ≤2.5 mg/dL	6.4%		22.7%		30.8%	
Creatinine >2.5 mg/dL	2.2%		4.5%		7.1%	
Chronic dialysis	0.9%		1.7%		1.8%	
Renal transplant	0.2%		0.7%		2.4%	
Diabetes*	20.3%	(*N* = 865)	30.1%	(*N* = 336)	-	
Bronchiolitis obliterans syndrome	10.8%	(*N* = 805)	38.2%	(*N* = 259)	44.9%	(*N* = 147)

* Data are not available 7 years post-transplant.
Source: Reproduced from International Society for Heart and Lung Transplantation [143] with permission of ISHLT, 2017.

nerve injury (typically the right) occurred in 22% of cases and previous thoracotomy was a risk factor. Hoarseness from left recurrent laryngeal nerve injury was noted in 10% of patients. Most of these nerve injuries resolved in the first several months after transplantation, but some patients required diaphragm plication because of poor respiratory function [204,205].

Injury to the vagus nerve frequently leads to gastropharyngeal reflux and gastric paresis. Gastroesophageal reflux disease and resulting recurrent silent aspiration has been implicated in deteriorating graft function and bronchiolitis obliterans syndrome [206]. The incidence of severe gastroesophageal reflux is high (50%), particularly in the young [207]. Patients with deteriorating pulmonary function have been shown to benefit from surgical treatment of gastroesophageal reflux [208].

Arrhythmias

Arrhythmias encountered that require therapy include atrial flutter (11% of pediatric transplants), atrial fibrillation, and supraventricular tachycardia [209]. Most can be controlled with drug therapy. The left atrial suture line is the presumed source.

Primary graft dysfunction

Primary graft dysfunction represents a severe form of acute injury to the allograft and is characterized by patchy pulmonary infiltrates, a low ratio of arterial oxygen to the fraction of inspired oxygen, diminished lung compliance, and pathological findings of diffuse alveolar damage [210,211]. There are many opportunities for lung damage during the processes of donor death, organ harvesting, allograft preservation, and transplantation. PGD is the net product of these insults, with ischemia-reperfusion injury being a major contributor [212]. Interestingly, primary pulmonary hypertension is a recipient risk factor independently associated with the development of PGD [213], presumably from right ventricle dysfunction. PGD may contribute to nearly half of the short-term mortality after lung transplantation [214]. Survivors of PGD even have increased risk of death extending beyond the first post-transplant year and PGD is associated with the subsequent development of bronchiolitis obliterans syndrome [214,215].

Once PGD develops, patients are managed with aggressive cardiopulmonary support involving mechanical ventilation or non-invasive ventilation in the prone position [216], inotropes, and occasionally with the use of venovenous ECMO. Early use of nitric oxide reduces the early mortality [217]. In most patients PGD resolves over several days. Children who need extracorporeal support have significantly higher mortality.

The preventive strategies to reduce the incidence of PGD include minimizing reperfusion injury, reducing ischemic time, improving donor management, and avoiding volu- and barotrauma. Surgeons routinely allow the ejection of small amounts of blood into the pulmonary artery immediately after establishing vascular supply to the first lung. Prostaglandin E1 and prostacyclin may reduce the incidence and severity of the reperfusion injury [218]. The value of prophylactic nitric oxide is questionable [219].

Rejection

Hyperacute rejection

This rare complication may lead to early graft failure and results from circulating, preformed, recipient serum antibodies binding to donor tissue antigens and causing complement-mediated graft injury. Endothelial cells lining the blood vessels of the new organ are the principal targets. Preformed antibodies directed at HLA or endothelial antigens are generally attributed to prior blood transfusions, a previous transplant, or pregnancy. To evaluate the risk for this complication, testing for PRAs is performed during the assessment process. PRAs include a mix of 60–100 different samples that express a wide range of antigens tested with the recipient serum. Sensitized patients with high PRA scores may qualify for specialized therapies such as intra- and postoperative plasmapheresis, thymoglobulin, and intravenous immunoglobulins [177].

Acute rejection

Acute cellular rejection is T-cell mediated and is common in the first year after lung transplantation, especially during the first 3 months. Clinically, it may be difficult to differentiate from an acute respiratory infection and the histopathological findings are not always helpful. Often the diagnosis of acute rejection is made on clinical suspicion and confirmed by the

response to therapy. Some patients are asymptomatic and the acute rejection is detected by airflow limitation (a 10% decrease from baseline in FEV_1 is considered significant). Others present with dyspnea and hypoxia and have infiltrates on chest radiograph. Infants and toddlers have immature immune systems and a lower incidence of acute rejection compared with older children [220]. Also, patients who receive lung–liver transplants have lower rates of acute rejection and bronchiolitis obliterans [221]. A pathological diagnosis of acute cellular rejection is based on the presence of perivascular and interstitial mononuclear cell infiltrates in the lung biopsy samples. Histology is classified as follows: acute rejection (A0–A4); lymphocytic bronchitis (B0–B2R, Bx); and obliterative bronchitis (C0–C1) [222]. Lymphocytic bronchiolitis represents airway-directed rejection. In adults, acute rejection and lymphocytic bronchitis have consistently been identified as strong risk factors for chronic rejection [223] but the evidence is less convincing for pediatric lung transplant recipients [224]. It is unclear to what extent humoral rejection, which is antibody mediated, occurs among lung transplant recipients [222].

Methylprednisolone pulse at 10 mg/kg/dose daily for 3 days followed by augmented oral prednisone is the treatment of acute cellular rejection. Overall, the response to this treatment is improvement of symptoms and pulmonary function test results within several days. Management of steroid-resistant acute rejection is currently controversial. Treatment options for humoral rejection include plasmapheresis for antibody removal and immunoglobulin infusion.

Chronic rejection

Chronic rejection is the primary obstacle to better long-term outcomes after lung transplantation (Fig. 30.21) [143]. It manifests as obliterative bronchiolitis, which is characterized histologically by fibroproliferative tissue remodeling with extracellular matrix deposition and results in small airway occlusion with sparing of the alveoli. Because the pathology has a patchy distribution, diagnosis by transbronchial biopsy has low sensitivity and specificity. Therefore, a clinical surrogate – the bronchiolitis obliterans syndrome – was created and is defined as a progressive deterioration in pulmonary function tests (Table 30.21) [222,225]. Measurement of lung function in young children can be challenging. Changes in lung function tests are likely late manifestations of obliterative bronchiolitis but other diagnostic modalities, including imaging and exhaled biomarkers, have not proven useful.

The etiology of bronchiolitis obliterans syndrome is unclear. Identified risk factors include late or recurrent refractory acute rejection, lymphocytic bronchiolitis, cytomegalovirus (CMV) infection, ischemia-reperfusion injury (longer ischemia times), HLA mismatches, infection, and gastroesophageal reflux with aspiration. Young children, LDLT recipients, and liver–lung recipients have a lower risk of bronchiolitis obliterans syndrome.

To date, there is no effective treatment of bronchiolitis obliterans syndrome. Therapies attempted include pulse steroids, methotrexate, cyclophosphamide, cytolytic therapy, inhaled cyclosporine, total lymphoid irradiation, photophoresis and switching to a different immunosuppression protocol [226]. Azithromycin and other macrolides may be useful [227]. Antireflux surgery may reverse the decline in pulmonary function in some patients and statins have beneficial potential because they induce apoptosis in fibroblasts. Retransplantation is considered in relatively few patients; the risk of post-surgical death within 1 year is nearly 50% [143].

Table 30.21 Classification of bronchiolitis obliterans syndrome

Stage	Definition
BOS 0	FEV_1 >90% of baseline and FEF25–75% >75% of baseline
BOS 0-p	FEV_1 = 81–90% of baseline or FEF25–75% ≤75% of baseline
BOS 1	FEV_1 = 66–80% of baseline
BOS 2	FEV_1 = 51–65% of baseline
BOS 3	FEV_1 ≤50% of baseline

BOS, bronchiolitis obliterans syndrome; FEF25–75%, forced expiratory flow between 25% and 75% of vital capacity; FEV_1, forced expiratory volume in 1 se. Baseline: the average of the two highest measurements at least 3 weeks apart after transplantation.
Source: Reproduced from Estenne et al [225] with permission of Elsevier.

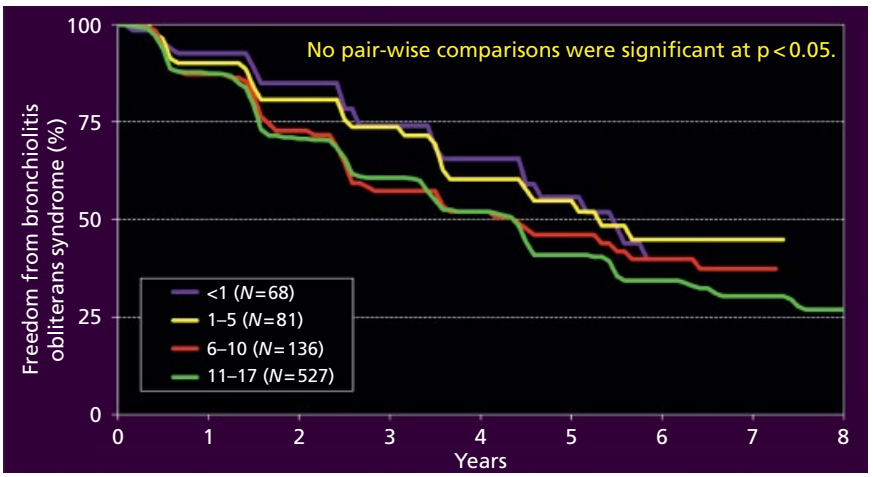

Figure 30.21 Freedom from bronchiolitis obliterans syndrome in pediatric lung transplant recipients by age, 1994–2015. *Source*: Reproduced from Rossano et al [102] with permission of Elsevier.

Immunosuppression

Higher doses of immunosuppressant agents are administered for pediatric lung transplantation than for other solid organ transplantation. Induction immunosuppression is currently used in approximately half of recipients, with about 10% receiving polyclonal antilymphocyte globulin and 40% receiving IL-2 receptor antagonists [143]. Most patients are given triple drug therapy for maintenance immunosuppression. This consists of a calcineurin inhibitor (tacrolimus more commonly than cyclosporine), cell cycle inhibitors like azathioprine or mycophenolate mofetil, and prednisone. Sirolimus (target of rapamycin inhibitor) is seldom administered during the first year post-transplant, but is more common at 5-year follow-up. Virtually all patients receive long-term maintenance corticosteroids [143].

Infection

Infections occur in 60–90% of recipients. The risk of infection is largely determined by the interaction of three factors: (1) technical/anatomical factors that involve the transplant procedure itself, and the perioperative aspects of care such as the management of vascular access, drains, and the endotracheal tube; (2) environmental exposure to pathogens; and (3) the patient's net state of immunosuppression [228]. Bacterial infections are most common but fungal and viral infections result in higher mortality. Hypogammaglobulinemia post-transplant was associated with increased infections [229].

Respiratory viral infections are associated with decreased 1-year survival after transplantation [230]. Common pathogens included adenovirus, rhinovirus, respiratory syncytial virus, and parainfluenza virus. Fungal infections were independently associated with a decreased 1-year post-transplant survival [231,232] and most centers routinely administer antifungal prophylaxis. Lung transplant patients are also at increased risk for invasive mold infections [233].

CMV after lung transplantation is a serious infectious complication, especially in CMV-negative recipients receiving CMV-positive donor lungs (i.e. mismatch). Pediatric patients are at increased risk for mismatch because they are more likely to be CMV negative and their incidence of CMV disease was 30% [234]. CMV disease was associated with increased mortality after pediatric lung transplantation. Usually it presents as pneumonitis but can also involve the liver, small bowel, and retina. Antiviral prophylaxis (e.g. ganciclovir) is beneficial although the optimal duration of prophylaxis is uncertain. Surveillance blood testing to measure the viral load is recommended.

KEY POINTS: COMPLICATIONS OF LUNG TRANSPLANTATION

- Early postoperative graft dysfunction is managed with mechanical ventilation, nitric oxide, and possibly veno-venous ECMO
- Acute rejection is usually treated with increased doses of corticosteroids
- Chronic rejection includes bronchiolitis obliterans syndrome; onset of this syndrome carries a high mortality within 1–2 years

Surveillance

Lung transplant recipients are closely monitored for rejection and other complications. Routine monitoring for rejection includes daily home spirometry, regular pulmonary function testing, chest radiographs, bronchopulmonary lavages, and transbronchial lung biopsies (a typical biopsy schedule would be at 2 and 6 weeks, and 3, 6, 9, and 12 months after transplant) [177]. Transbronchial biopsies are the mainstay of rejection surveillance in young children because spirometry is not feasible [235]. Infant pulmonary tests (peak expiratory flow rate) using thoracoabdominal compressions can be done but require anesthesia and are not part of the bronchiolitis obliterans syndrome criteria. Sometimes it is difficult to obtain sufficient tissue via transbronchial biopsy in small children and an open lung biopsy may be necessary [13,199,236].

Outcome

Lung transplant

Survival after lung transplantation is similar in children and adult recipients and has improved in recent years. Children transplanted between 2008 and 2015 had a 1-year survival of 84.1% and a 5-year survival of 56.7% [143]. These outcomes are

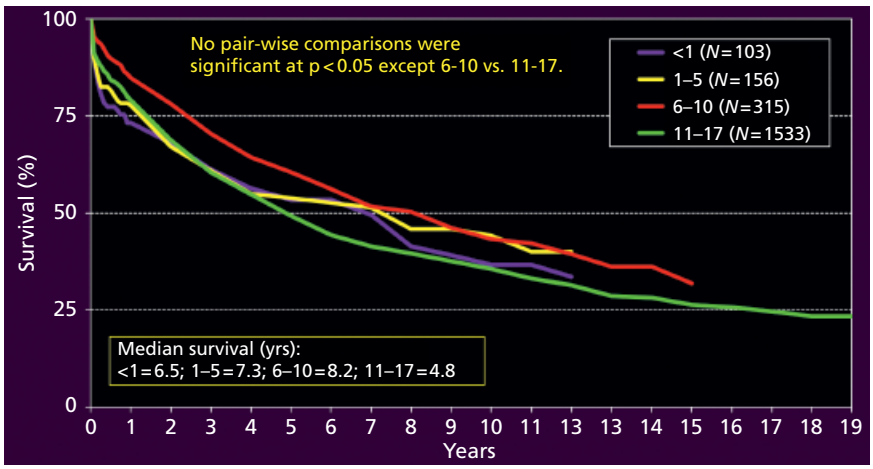

Figure 30.22 Pediatric lung transplant survival by recipient age group, 1990–2015. *Source*: Reproduced from Rossano et al [102] with permission of Elsevier.

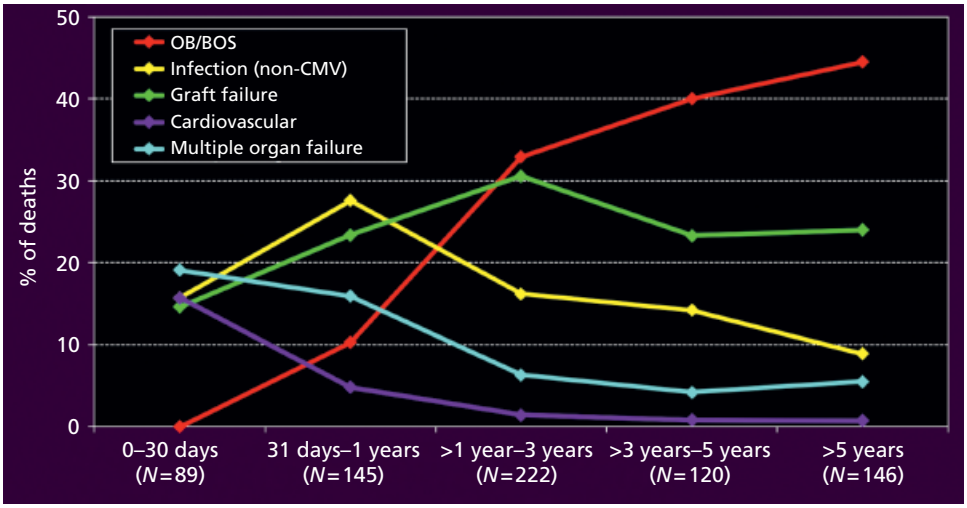

Figure 30.23 Relative incidence of leading causes of death in pediatric lung transplantation, 2000–2016. BOS, bronchiolitis obliterans syndrome; CMV, cytomegalovirus; OB, obliterative bronchiolitis. *Source*: Reproduced from Rossano et al [102] with permission of Elsevier.

inferior to those for other pediatric solid organ transplantation. Children in the 6–10-year age group have better long-term outcomes than adolescents (Fig. 30.22). Significant risk factors for mortality include preoperative ventilatory support, earlier era of transplant, center volume of <5 pediatric lung transplants per year, and adolescent age group. The poor long-term outcome of adolescents is ascribed to the propensity for poor adherence to medical therapies [237]. Children with tetralogy of Fallot and pulmonary atresia had a worse outcome after lung transplantation than patients with Eisenmenger syndrome or pulmonary vein stenosis [238]. Graft failure, technical issues, cardiovascular failure, and infection are common causes of death in the early post-transplant period, whereas infection, graft failure, and bronchiolitis obliterans syndrome are common causes of late death (Fig. 30.23) [143]. Children undergoing repeat lung transplant have a worse outcome (42% 5-year survival).

Heart–lung transplant

Fewer than 15 heart–lung transplants are reported per year to the ISHLT [143]. About 90% of procedures are for congenital heart disease with pulmonary hypertension, primary pulmonary hypertension, or cystic fibrosis. A higher proportion of younger children undergo heart–lung transplantation compared with lung transplantation but the majority of procedures are performed in adolescents. Survival after heart–lung transplantation is slowly improving, with a 5-year survival of 50% in the 193 transplants from 2000 to 2015. Infants <1 year in age have worse survival than older children; there have been no heart–lung transplants in this age group reported to the ISHLT since 2007.

Intestinal, multivisceral, and pancreatic transplantation

Indications

Successful transplantation of liver, kidneys, hearts, and lungs has led transplant surgeons to attempt to treat other illnesses affecting infants and children. The etiology of intestinal failure in children is most often the short-gut syndrome, which results from necrotizing enterocolitis, intestinal malrotation, and volvulus, or congenital defects (intestinal atresia, abdominal wall defects), and leads to dependence on total parenteral nutrition (TPN) (Table 30.22) [239]. The long-term sequelae of TPN include steatotic liver disease and eventual hepatic failure and the complications of long-term venous access. Isolated small bowel transplants, combined small bowel–liver transplants, and extensive multivisceral transplants (liver, pancreas, gastrointestinal tract from stomach to colon) have been performed in an attempt to manage short-gut syndrome (Fig. 30.24) [239]. The results of intestinal transplantation have improved over the past decade. Transplantation of the intestine before liver failure improves early outcomes [240]. In 2016, the results of 2887 intestinal transplant procedures (from 82 centers in 19 countries) were summarized in the report of the International Intestinal Transplant Registry [239]. The most recent cohort (transplanted after 2009) demonstrated 76% overall 1-year patient survival and over 80% 1-year

Table 30.22 Causes of intestinal failure in children

Short bowel syndrome	Congenital
	Surgical
	Necrotizing enterocolitis
	Malrotation with midgut volvulus
	Gastroschisis
	Intestinal atresia
	Inflammatory bowel disease
	Trauma
Motility disorders	Long segment Hirschsprung disease
	Intestinal pseudo-obstruction
Enteropathies	Neonatal diarrheas
	Microvillous inclusion disease
	Tufting enteropathy
	Sodium channel diarrhea
	Autoimmune enteropathy
Other	Tumors
	Familial polyposis
	Inflammatory pseudotumor
	Ischemia

Source: Reproduced from Martinez Rivera and Wales [239] with permission of Springer Nature.

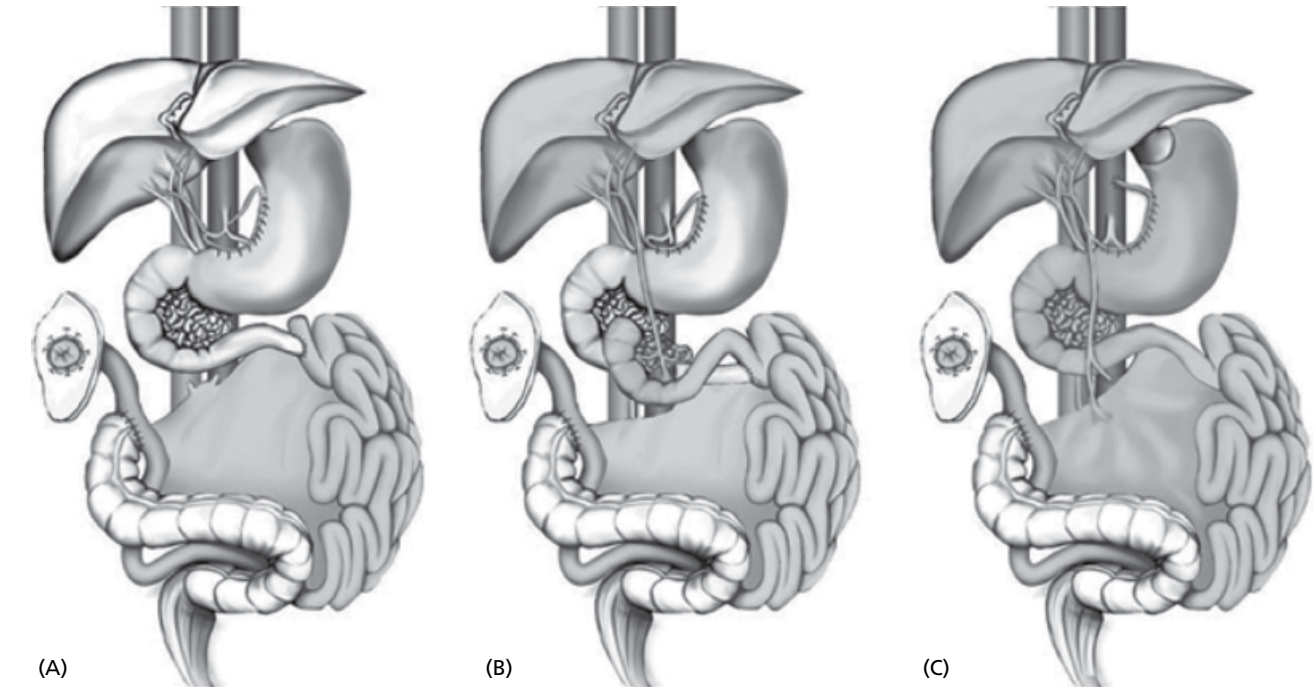

Figure 30.24 Types of intestinal transplantation. (A) Isolated intestinal transplant. (B) Combined liver–intestinal graft, which also contains, in continuity, the donor duodenum and pancreas. (C) Multivisceral transplant, where the donor organs include liver, stomach, duodenum, pancreas, and small bowel. *Source*: Reproduced from Martinez Rivera and Wales [239] with permission of Springer Nature.

survival in those recipients who received induction therapy combined with tacrolimus. Recently a single-center series reported 1- and 5-year patient and graft survival to be 78–85% and 56–61%, respectively, despite divergent immunosuppression protocols [241]. More than 80% of transplant recipients who survive attain freedom from parenteral nutrition and resume normal daily activities. Intestinal transplant procedures peaked in 2008 with130 children reported to the International Intestinal Transplant Registry. There has been a significant decline in recent years to 50–60 annually; the reason is likely from improved long-term intestinal rehabilitation protocols reducing the need for transplantation [239].

Pancreas transplantation has been utilized most commonly as combined renal and pancreas transplantation for the treatment of ESRD in diabetics with other end-organ dysfunction (retinopathy, neuropathy). Because of the interval between the development of insulin-dependent diabetes in children and end-organ complications, few reports of pancreas transplantation have been reported in children, apart from the multivisceral procedures described above. The number of pancreas transplants peaked in 2004, and steadily declined through 2008. Even though pancreas transplantation of diabetic patients has stabilized or improved their nephropathy, retinopathy, and neuropathy, immunological failures of the transplant has led to the abandonment of isolated pancreas transplants and only combined kidney and pancreas transplants are now performed in children [242].

Anesthetic management

The exact form of intestinal transplantation (i.e. isolated, combined liver–small bowel, or multivisceral transplantation) depends upon the cause of intestinal failure and associated extraintestinal organ involvement. Following identification of an appropriate donor, the recipient undergoes a regimen designed to purge and decontaminate the intestinal tract. Routine premedication is avoided, but may be required and administered under appropriate monitoring situations. Rapid-sequence induction of general anesthesia and tracheal intubation is planned. Despite normal or slightly impaired hepatic function, there is a potential for extensive blood loss and hemorrhage in most of these cases. Previous abdominal surgery and extensive dissection and evisceration of the native organs prolong the dissection period and increase blood loss. Venous access sites, particularly around the central circulation, may be limited because of previous TPN catheters. However, central venous access is essential for management. Arterial blood pressure and CVP should be monitored directly. Intraoperative management is similar to liver transplantation: hemodynamic stability may require rapid infusion of crystalloid, colloids, or blood products; and maintaining metabolic homeostasis requires frequent arterial blood gases and electrolyte concentration determinations.

In multivisceral transplantation and combined pancreatic renal transplantation, particular attention is required to maintain normoglycemia. Tight intraoperative control of the glucose concentration may result in improved pancreatic allograft function. To achieve glucose concentrations of 80–150 mg/dL requires frequent intraoperative determinations of glucose concentration, and titration of a regular insulin infusion. A period of hyperglycemia is common following reperfusion of the pancreatic graft and requires additional insulin administration.

Complications following transplant

Rejection

A common complication associated with all forms of allograft transplantation is the occurrence of rejection of the

transplanted tissue by the recipient. Rejection in the early post-transplant period may be a subtle process and difficult to assess by routine physical and laboratory examination. Clinical signs of rejection will vary by the transplanted organ, and are not likely to be specific. Therefore, there is need for early histological evaluation of the organ to diagnose acute rejection. Many transplant centers routinely biopsy the organ at weekly to monthly intervals to search for evidence of acute rejection. This generally requires an invasive procedure requiring anesthesia or sedation in children. Routine immunosuppression is altered in the face of acute rejection. Steroid administration is increased first, and then maintenance immunosuppressive therapy may be increased. See earlier specific discussions of heart and lung rejection and surveillance.

Infection

Immunosuppression leads to an increased risk of infection. Various forms of infection are more common at different time periods [228,243,244]. In the *1st month*, there are three major causes of infection: (1) infection that was present in the recipient before transplant; (2) infection conveyed with a contaminated allograft; and (3) typical postoperative infections also observed in immunocompetent patients, such as surgical wound infections, pneumonia, and infected lines or drains.

One to 6 months after transplantation is when more intense immunosuppression produces the greatest effect on the risk of infection. During this period, two major classes of infection predominate: chronic viral infections and opportunistic infections. Viral pathogens such as CMV, Epstein–Barr virus (EBV), human herpesvirus 6, and the hepatitis viruses B and C may be acquired from the donor, reactivated in the host, or the patient may become infected with a new strain of these viruses. During this 1–6-month post-transplant period opportunistic infections are also observed and include organisms such as *Listeria monocytogenes*, *Aspergillus fumigatus*, and *Pneumocystis jiroveci*.

Once patients are *more than 6 months* post-transplant, their infectious risk can be broken down into two categories of patients: those with a good result from transplant and a smaller group with a poor graft function. The majority of patients have good graft function, are on maintenance immunosuppression therapy, and are at greatest risk from typical community-acquired infections such as influenza, parainfluenza, and respiratory syncytial virus. The smaller group of patients with acute and chronic immunosuppression, poor allograft function, and, often, chronic viral infection remain at high risk for recurrent infections related to mechanical problems from surgery as well as opportunistic infections attributable to organisms like *Pneumocystis jiroveci*, *Listeria monocytogenes*, *Cryptococcus neoformans*, and *Nocardia asteroides*. Infectious risk and outcomes related to lung transplant are discussed earlier in the chapter.

Malignancy

The risk of developing cancer after solid organ transplantation is about 5–10-fold more than that of the general population. Children receiving transplants are at high risk of developing a malignancy during their lifetime. The cumulative risk of cancer increases with age and is >50% at 20 years after transplantation.

Post-transplant lymphoproliferative disease (PTLD) is the most common cancer observed in children following solid organ transplantation, accounting for half of all such malignancies [245]. The incidence is about 5–10%. PTLD results from the uncontrolled proliferation of lymphocytes in the immunosuppressed transplant recipient and is a major contributor to long-term morbidity and mortality in this population. Among children, most cases are associated with EBV infection. PTLD is an early event (i.e. within the first 2 years after transplant) in most cases, likely because of more intense immunosuppression used for induction therapy or the exposure of the EBV-naive host to the virus, often from EBV-infected passenger lymphocytes in the allograft. PTLD commonly affects the lung allograft, lymphoid tissues, gastrointestinal tract, and liver. Gastrointestinal involvement is associated with increased mortality [246]. Therapy for PTLD includes empirical reduction in immunosuppression antiviral drugs, monoclonal antibodies specifically targeting the B-lymphocyte antigen CD20 (e.g. rituximab), or chemotherapy, when appropriate [247]. Skin cancers and atypical solid tumors are also seen with significantly higher incidence than in the general population. Outcomes of treatment of these secondary malignancies are generally worse than in the general population.

Renal dysfunction

Renal dysfunction is one of the most common complications following solid organ transplantation. Ojo and colleagues found that the cumulative 5-year risk of chronic renal failure, defined as the need for either chronic dialysis or kidney transplantation, was 6.9–21.3% depending on type of organ transplanted. This study included more than 69,000 non-renal solid organ transplant recipients who were predominately adults. The risk of death increased more than fourfold with the onset of chronic renal failure, and the cost of care was dramatically increased [248]. Table 30.23 shows the risk of renal failure related to the type of organ transplant.

There are multiple factors that produce renal dysfunction following solid organ transplantation; however, the CNIs cyclosporine and tacrolimus are the major contributing factors. The CNIs produce both acute and chronic nephrotoxicity. Acute nephrotoxicity involves afferent arteriolar vasoconstriction and reduced renal plasma flow, and is associated with high trough levels. In contrast, chronic CNI-induced nephrotoxicity is not predicted by individual trough levels, and is characterized by potentially irreversible structural changes including arteriolopathy, tubulointerstitial fibrosis, and, eventually, glomerulosclerosis [249]. Strategies for management of post-transplant renal dysfunction have largely focused on CNI minimization, replacement, or avoidance.

Growth and developmental delay

Organ failure frequently leads to a poor nutritional state and growth failure. After organ transplant, most patients demonstrate catch-up growth, yet a large percentage of patients do not reach their predicted adult height and weight. Immunosuppression regimens that limit the use of steroids seem to be well tolerated and allow for better growth; however, the long-term effect of CNIs on growth is not well studied, and may also contribute to growth failure [250]. Growth

Table 30.23 Cumulative incidence of chronic renal failure according to type of transplanted organ

Type of organ	Cumulative incidence of chronic renal failure after transplantation (% ± SE)			Relative risk of chronic renal failure (95% CI)
	12 months	36 months	60 months	
Heart	1.9 ± 0.1	6.8 ± 0.2	10.9 ± 0.2	0.63 (0.61–0.66)
Heart–lung	1.7 ± 0.5	4.2 ± 0.9	6.9 ± 1.1	0.48 (0.36–0.65)
Intestine	9.6 ± 2.0	14.2 ± 2.4	21.3 ± 3.4	1.36 (1.00–1.86)
Liver	8.0 ± 0.1	13.9 ± 0.2	18.1 ± 0.2	1.00 (reference group)
Lung	2.9 ±0.2	10.0 ± 0.4	15.8 ± 0.5	0.99 (0.93–1.06)

Source: Reproduced from Ojo et al [248] with permission of Massachusetts Medical Society.

Table 30.24 Incidence of hypertension in pediatric solid organ transplantation

Organ	Prevalence			References
	2 years	5 years	7 years	
Kidney	75%	70%		North American Pediatric Renal Transplant Cooperative Study
Lung	14.5%/15.7%			Studies in Pediatric Liver Transplantation
Heart–lung		71.6%	64.7%	International Society for Heart and Lung Transplantation

Source: Reproduced from Dharnidharka et al [251] with permission of Wiley-Blackwell.

hormone can be used but there are theoretical concerns about the risk of triggering rejection [13].

Solid organ transplant recipients display a wide range of developmental outcomes, from normal development to significant delays. Factors that lead to poor developmental outcome likely include long-term hospitalization, chronic malnutrition in the pretransplant period, and surgical complications. Children who receive heart transplantation may have better cognitive outcomes than expected considering the results of older studies of children with cyanotic CHD. The cognitive outcomes of liver and kidney transplant recipients may also be improving, but many still require special educational resources. Infants requiring intestine or liver and intestine transplant are probably at the highest risk for cognitive delay, but there is a lack of longitudinal studies that affirm these delays [250]. In all cases neurological co-morbidities increase the risk of delay. Despite recent advances, a significant proportion of liver and heart recipients have serious developmental delay or neurological injury.

Cardiovascular side-effects

Immunosuppressive agents produce cardiovascular toxicity, causing an increased likelihood of hypertension, hyperlipidemia, hypercholesterolemia, and diabetes mellitus. Hypertension is found in 62–75% of pediatric patients (Table 30.24) [251]. Although both tacrolimus and cyclosporine can cause hypertension, cyclosporine appears to have a greater impact on blood pressure [252].

These side-effects are treated via an alteration of immunosuppressive regimen, or the addition of specific medications to address each risk factor or complication. Since steroids and CNIs provide the mainstay of immunosuppressive treatments, they generally cannot be eliminated. Steroid withdrawal or reduction as well as the use of tacrolimus over cyclosporine may decrease the risk of hypertension, dyslipidemia, or diabetes mellitus [249]. All classes of antihypertensive medications have been used and are ideally chosen based on the therapeutic profile. In addition to surveillance of tacrolimus levels, long-term monitoring of cardiac function may also be warranted in high-risk populations.

KEY POINTS: GENERAL COMPLICATIONS FOLLOWING TRANSPLANTATION

- Infection is a constant threat for transplant recipients; chronic viral infections such as CMV, EBV, and hepatitis B and C, and opportunistic infections such as *Aspergillus*, *Pneumocystis*, and *Listeria* are seen
- Secondary malignancy is seen in 5–10% of organ transplants; post-transplant lymphoproliferative disorder is most common
- Renal dysfunction, growth, and developmental delay, and hypertension are common in transplant recipients

Post-transplant surgery

Regardless of the transplant procedure, as transplant recipients age, they are likely to acquire diseases or conditions that require additional surgery. Prior to such procedures, the anesthesiologist must assess the function of the transplanted organ, review the status of the patient's immunosuppression, and perform a careful assessment of the other organ systems. Hypertension and chronic renal insufficiency are common findings in patients. Most patients will demonstrate evidence and findings of chronic steroid administration.

Quality of life

The functional status of most long-term survivors of solid organ transplantation is good, with more than 80–90% of 5-year survivors from kidney, liver, heart, and lung transplantation reporting no limitations in activity. Despite excellent function, children may experience psychological difficulties and an impaired quality of life [253]. Pediatric studies focusing on quality of life after transplantation remain scarce [253,254]. Research thus far shows improved overall quality of life after kidney, liver, heart, and lung transplantation; although the debate continues for patients with cystic fibrosis [150]. The quality of life after small bowel transplantation is probably equal to or better than quality of life on parenteral nutrition, and children report a quality of life similar to normal school children. A study that used qualitative interviews to examine psychosocial issues after lung transplantation in adolescents with cystic fibrosis reported that patients were able to develop long-term goals, and a wish to reclaim control over their lives as much as possible and adjust to a new lifestyle; yet common emotional responses included fear and anxiety over rejection, uncertainty over the future, and frustration with parental overprotectiveness [255]. It has been proposed that quality of life should be included in the assessment of transplantation benefit [256]. Presently, timing of transplantation relies primarily on estimates of survival benefit because comprehensive objective measures of quality of life for pediatric lung transplantation are not available.

CASE STUDY

History

A 14-year-old, 67 kg boy listed status 1A was scheduled for orthotopic heart transplant with an "in room" time of 0200. He was born with hypoplastic left heart syndrome and received a three-stage palliation to a Fontan circulation, which subsequently started failing 2 years ago. He was initially managed as an outpatient on oral heart failure medication (enalapril, furosemide, digoxin, and aspirin) but his clinical condition declined significantly over the past 6 months and despite modification to his oral heart failure regimen he was admitted to hospital 2 months ago for increasing fatigue, poor appetite, nausea, and ascites. He has been an inpatient for the past 1 month in the cardiovascular ICU (CVICU) dependent on milrinone and dopamine infusions.

Preoperative assessment

The patient was malnourished with moderate abdominal distention. His heart rate was 116 beats/min and blood pressure 80/42 mm Hg; SpO_2 was 86% on room air; respiratory rate was 28 breaths/min. He was alert and could speak but was short of breath with minimal exertion. His peripheries were cool to touch.

The most recent echocardiogram 5 days preoperatively revealed severely depressed right ventricular (RV) systolic function with moderate to severe tricuspid valve regurgitation. The Fontan pathway appeared unobstructed. Cardiac catheterization data from 1 month preoperatively (prior to starting inotropes) showed a Fontan pressure 23 mmHg, left pulmonary capillary wedge pressure of 16 mmHg, RV end-diastolic pressure of 16 mmHg, pulmonary vascular resistance index of 2.3 Wu, and a cardiac index of 1.9 L/min/m^2. Preoperative lab results included: Hgb 14 g/dL, Na 122 mEq/L, K 5.1 mEq/L, Cr 1.9 mEq/L, and INR 1.6.

He had a double-lumen percutaneously inserted central catheter (PICC) line in place with milrinone at 0.75 μg/kg/min and dopamine 5 μg/kg/mn. He also had an epicardial pacemaker implanted 5 years preoperatively for sick sinus syndrome. His last pacemaker interrogation 2 months prior to surgery showed 80% atrial-paced, ventricular-sensed rhythm and was set with a lower rate of 80 beats/min and an upper rate 120 beats/min. A CT scan performed for vascular mapping 2 months prior to transplant showed that all major vessels are patent but both femoral arteries appeared small from previous access.

Preoperative huddle

A multidisciplinary huddle occurred at 8 pm the evening prior to transplant and was attended by the attending cardiothoracic surgeon and fellow, cardiac anesthesia attending and fellow, CVICU attending, heart failure attending and fellow, and the perfusionist. Given the recipient's tenuous cardiovascular status and high risk of cardiovascular collapse during anesthesia induction it was decided that the patient would have a preinduction radial arterial line placed in the operating room and would be started on low-dose epinephrine at 0.02 μg/kg/min prior to anesthesia induction. It was also decided that because of small femoral arteries the neck would be the preferred site for emergency CPB cannulation should the patient decompensate during anesthesia induction or surgical dissection. The surgeon's preference was for the anesthesia team to place the right internal jugular central venous line using a high approach to allow him room lower down on the neck to perform a cut down if needed. A plan was also made to place a pigtail catheter in the abdomen to allow for controlled drainage of ascites soon after anesthesia induction.

The huddle discussions revealed that the donor was a good match for size with good cardiac function. The donor mode of death was status epilepticus and the organ was coming from a location with a 2.5 h total travel time and therefore an anticipated short ischemic cross-clamp time. The recipient was highly sensitized to blood cell antigens with a high panel reactive antibody titer, and would follow an immunosuppression protocol involving plasmapheresis on CPB with a 1.5 volume exchange in the OR just after CPB was initiated, followed by methylprednisolone post separation from CPB, IV immunoglobulin in the OR, and then thymoglobulin and tacrolimus post-op in the CVICU.

Because of the pre-existing renal dysfunction it was decided to follow the high-risk renal protective protocol that

had recently been instituted at the hospital, which involves perioperative aminophylline infusion in addition to maintaining a higher mean arterial pressure (60 mmHg) on CPB.

Intraoperative course

The patient was brought into the operating room at 2 am and standard ASA monitoring was instituted. Epinephrine infusion 0.02 μg/kg/min had been added to the inotropic regimen prior to transporting the patient. The patient received 2 mg of IV midazolam in divided doses for anxiolysis prior to placing a radial arterial line with ultrasound guidance. After placement of the arterial line the invasive blood pressure was 85/45 mmHg. A slow induction of general anesthesia was then started, carefully titrating fentanyl and etomidate bolus to effect, ensuring adequate time for the drugs to circulate (given the patient's low cardiac index) prior to giving subsequent doses. In total, 4 mg of midazolam, 250 μg of fentanyl, and 10 mg of etomidate was administered before the patient lost verbal communication and an eyelash response and required assisted ventilation. Then, 70 mg of rocuronium was given and positive pressure ventilation instituted taking care not to use high intrathoracic pressures or large tidal volumes that may impede Fontan flow and RV function, and also avoiding hypoxia, hypercarbia, and atelectasis. The patient was intubated easily with a 7.0 mm cuffed endotracheal tube and the hemodynamics remained stable throughout with a heart rate hovering between 115 and 120 beats/min and systolic blood pressure ranging between 80 and 85 mmHg. The surgeon then placed a pigtail catheter in the abdomen to allow for controlled drainage of the ascites prior to sternotomy and the anesthesia team inserted a 5 Fr triple-lumen 13 cm catheter in the right internal jugular vein using a high approach and ultrasound guidance. A 9 Fr 10 cm sheath was also placed in the left femoral vein using ultrasound and connected to a rapid infusing device (Belmont Rapid Infuser®; Belmont Instrument Company, Billerica, MA, USA). Two 14 G peripheral IV catheters were also placed in the upper extremities. Since the most recent pacemaker interrogation had revealed that the patient was pacemaker dependent with an 80% paced rhythm, the device was reprogrammed to an asynchronous (DOO) mode prior to incision to avoid any interference from surgical diathermy. Antibiotics and induction immunosuppressants were administered.

The chest, neck and right groin were prepped into the surgical field and the sternotomy was started. Dissection proved to be very difficult due to dense adhesions from prior cardiac surgeries and there was considerable microvascular oozing and bleeding from chest wall collaterals, which was managed by transfusing 2 units of FFP, 1 unit of platelets, and 1 unit of packed red cells in addition to a prophylactic aminocaproic acid infusion. After 2 h of careful surgical dissection the patient was ready to be cannulated for cardiopulmonary bypass. The ascending aorta, superior vena cava (SVC), and inferior vena cava (IVC) were cannulated and CPB instituted. Soon after institution of CPB the patient underwent plasmapheresis and cooled down to 32°C. A left atrial (LA) vent was inserted in the right upper pulmonary vein and after applying a cross-clamp on the ascending aorta, the recipient heart was removed while the donor heart was prepared on the back table. The recipient SVC was removed from the pulmonary arteries and patch augmentation of the pulmonary arteries performed. The donor heart was then implanted in the patient using LA anastomoses and then IVC, pulmonary artery, and aortic anastomoses. The donor heart was then de-aired, the cross-clamp removed after lidocaine and magnesium sulfate were administered, and rewarming commenced. While rewarming the SVC anastomoses was completed.

The donor ischemic time was 3 h and 10 min and the heart was reperfused for 1 h before separating from CPB – approximately one-third of the donor ischemic time, in accordance with the institution's standard practice. The patient subsequently separated from CPB on dopamine, epinephrine, calcium, and milrinone infusion and transesophageal echocardiography confirmed integrity of all the anastomoses without stenosis and adequate cardiac function of both ventricles. Heparin was reversed with protamine using a heparin-protamine titration system, and activated clotting time (ACT) to guide the dosage of protamine. There was significant bleeding post-CPB separation requiring 20 units of cryoprecipitate, 4 pheresis units of platelets, 3 units of red cell concentrate, and three 10 IU/kg doses of prothrombin complex concentrate. Once adequate hemostasis was achieved the sternum was closed and the patient transported to ICU where a comprehensive multidisciplinary sign-out occurred including cardiothoracic surgery, anesthesia, CVICU, heart failure, bedside nurses, and the respiratory therapist. The patient was successfully extubated the next day.

Conclusion

This case illustrates that, despite the increasing complexity of pediatric patients presenting for orthotopic heart transplant, involving complex congenital heart disease and multiorgan dysfunction, with careful multidisciplinary planning and communication, these cases can be managed successfully with good outcomes. Significant concerns include perioperative cardiovascular collapse with potentially limited rescue options, perioperative bleeding, and challenging pre-CPB dissection from previous multiple sternotomies and post-CPB RV dysfunction, pulmonary hypertension, and renal impairment.

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A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 31
Anesthesia for Abdominal Surgery

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Introduction

Anesthetics for abdominal surgical conditions are among the most common cases in the pediatric age group. They range from simple outpatient surgeries such as inguinal herniorrhaphy to extensive surgery, such as radical excision of neuroblastoma or hepatic tumors. The extensive adoption of laparoscopic surgery for many abdominal procedures has significantly changed the anesthetic approach for abdominal surgery, including postoperative analgesia. This chapter begins with a presentation of common abdominal surgical conditions, including intussusception, biliary atresia, malrotation and intestinal atresia, inflammatory bowel disease, abdominal tumors, inguinal hernia, pyloric stenosis, and appendicitis. Then, specific procedures such as gastrointestinal endoscopy, gastrostomy, Nissen fundoplication are discussed. Finally, laparoscopy, including physiological changes in response to gas insufflation and positioning are reviewed.

ABDOMINAL SURGICAL CONDITIONS

Intussusception

Intussusception is the most common cause of bowel obstruction in children less than 5 years of age [1]. The incidence is one in 2000 infants and children and it is always considered as a true pediatric emergency. Intussusceptions occur when a segment of bowel (the intussusceptum) invaginates into the distal bowel (the intussuscipiens), usually in an antegrade direction, resulting in venous congestion and bowel wall edema (Fig. 31.1) [2]. If not recognized and treated it could cause bowel necrosis and perforation. Overall mortality is less than 1% and the outcome is excellent if the condition is diagnosed early and treatment is instituted within the first 24 h.

Epidemiology

Intussusception occurs primarily in infants and toddlers. Males are affected twice as often as females. Peak incidence occurs between 5 and 9 months of age, with only 10–25% of cases occurring after 2 years of age [3]. Ninety percent of intussusception is idiopathic. Lymphoid hyperplasia has been suggested as the "lead point" in the pathogenesis of intussusceptions [4]. Incidence is higher during the fall and spring suggesting the possibility this might be a sequela following a preceding viral infection; adenovirus, rotavirus, and human herpesvirus 6 have all been associated with intussusceptions [5–7]. Other common lead points are Meckel diverticulum, intestinal polyps, lymphoma, and an inverted appendiceal stump. Patients with systemic conditions like Henoch–Schönlein purpura, Peutz–Jeghers syndrome, familial polyposis, nephrotic syndrome, and mesenteric nodes are predisposed to developing intussusceptions [7–9]. In 1999 the oral rotavirus vaccine was introduced in the US childhood immunization schedule, and was linked with intussusception among vaccine recipients. It was found to be greatest in the first 3–14 days after the first dose of rotavirus vaccine in infants older than 3 months [10]. Subsequently the vaccine was withdrawn from the market in 1999 [11].

Recurrent intussusceptions is uncommon but has been reported to occur in 1–3% after operative repair and 10–15% after hydrostatic reductions [12].

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

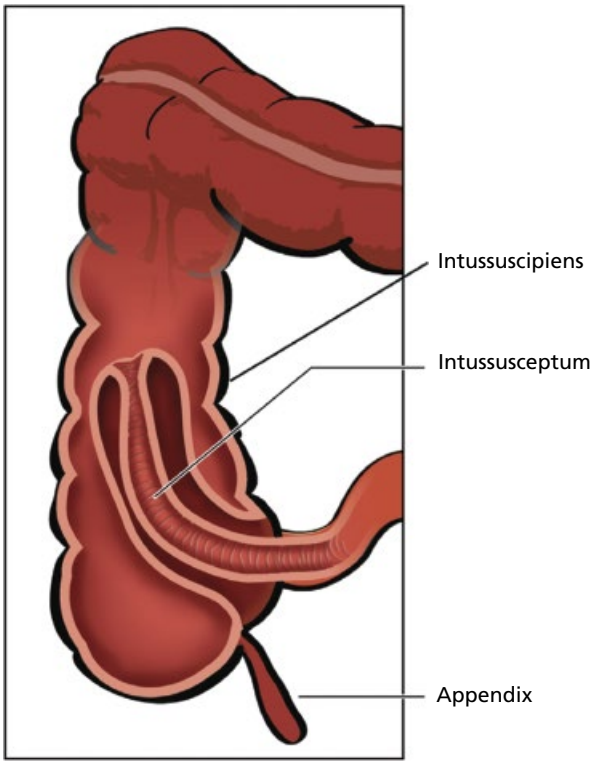

Figure 31.1 Ileocolic intussusception. *Source*: Reproduced from and Moses [2] with permission of Elsevier. Illustration by Colin Fahrion.

Pathophysiology

Ileocolic intussusception account for over 90% of cases. During the process the intussusceptum is propagated distally along the intestine and draws its blood supply with it. Initially the compression of the blood vessels causes venous congestion and bowel wall edema. As the obstruction progresses, the arterial supply may be compromised resulting in intestinal ischemia and infarction [3].

Clinical presentation

Intussusception has both typical and atypical presentations, but many present with non-specific sign and symptoms. The classic presentation is a young child with history of recent viral illness with vomiting and/or diarrhea. The classic clinical triad of intermittent abdominal pain, red currant jelly stool, and a palpable mass is found in 7.5–40% of children; 20% are pain free at their initial presentation, and 30% present with diarrhea leading to misdiagnosis of gastroenteritis [13,14]. On physical examination a palpable mass in the right upper quadrant is present, usually sausage shaped and ill defined, which may enlarge during episodes of pain. Some patients may present with syncope, sepsis, or hypovolemic shock. Recognition of hypovolemia and shock is an important priority for the surgical and anesthetic team.

Diagnosis

There is no reliable clinical model to accurately diagnose all patients presenting with intussusception. Imaging studies are essential in confirming the diagnosis. Plain abdominal films, ultrasound, or computed tomography (CT) scans have all been used to confirm the diagnosis, but in recent years ultrasound has become the preferred modality [2]. The classic finding is called the target sign, where concentric, alternating rings of low and high echogenicity are seen, corresponding to the layers of intestine and mesenteric fat (Fig. 31.2).

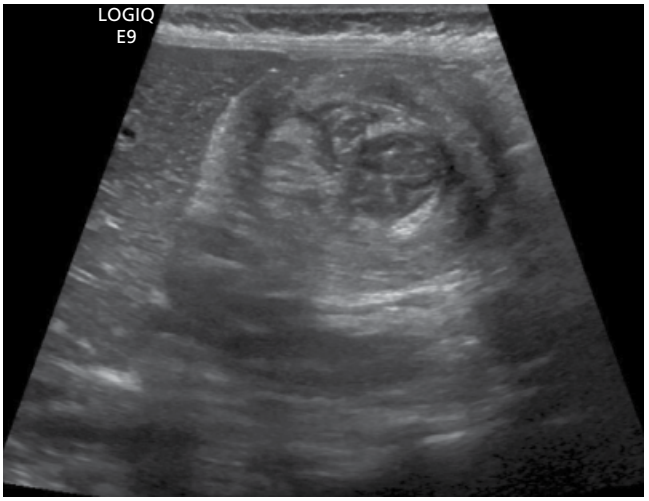

Figure 31.2 Ultrasound image of ileocolic intussusception demonstrating the target sign. *Source*: Reproduced from Padilla and Moses [2] with permission of Elsevier.

Management

In recent years, management of intussusception has changed significantly. Barium, aqueous, or air enemas have been used to reduce intussusception. Reduction rates with air range from 60% to 90%, and for barium/aqueous contrast from 60% to 80%. If non-operative reduction is not successful or is contraindicated, patients may require operative reduction. Sedation or anesthesia is rarely required for radiological reduction; but if non-operative reduction has failed, these patients may be significantly dehydrated. Aggressive fluid resuscitation is often necessary in the preoperative period; and antibiotic administration is essential [15,16].

The standard operative approach to intussusception reduction has been open laparotomy; although in recent years more surgeons are employing a laparoscopic approach. A recent retrospective review found a 71% success rate of laparoscopic intussusception reduction in 276 cases, with a very low complication rate [1].

Preoxygenation and rapid sequence intravenous induction using propofol and muscle relaxant using succinylcholine or rocuronium with endotracheal intubation is recommended to minimize the risk of regurgitation and aspiration. Maintenance of anesthesia is accomplished with isoflurane, sevoflurane, or an opioid-based anesthetic in critically ill patients. Careful attention to isotonic fluid replacement to compensate for often significant third-space losses from bowel manipulation and possible bowel resection is essential.

KEY POINTS: INTUSSUSCEPTION

- Intussusception is a common cause of bowel obstruction, with an incidence of one in 2000
- The classic clinical triad is of intermittent abdominal pain, red currant jelly stool, and a palpable mass
- On physical examination a palpable sausage-shaped mass is often present in the right upper quadrant

- Barium, aqueous, and air enemas are used for non-operative reduction; if this is not successful or is contraindicated patients may require operative reduction
- Aggressive fluid resuscitation in the preoperative period is often necessary

Biliary atresia

Biliary atresia is defined as the absence of patent extrahepatic bile ducts. It is the most common cause of jaundice in neonates and infants. If untreated it causes cirrhosis and liver failure within the first 2 years of life. The incidence ranges from one in 10,000 to one in 16,700 live births with a slight female preponderance [17,18]. There are three main types of biliary atresia: type I, atresia at the site of the common bile duct (11.9%); type II, atresia at the site of the hepatic duct, which is relatively less common (2.5%); and type III, atresia at the porta hepatis, which is the most common type (84.1%) [19]. Ten to 20% of patients with biliary atresia have associated congenital malformation, e.g. polysplenia, asplenia, inferior vena cava anomalies, bowel atresia, annular pancreas, and genitourinary anomalies [19,20].

Etiology

The exact cause of biliary atresia remains elusive, but there is some association between perinatal viral infections (reovirus type 3, rotavirus, cytomegalovirus, human papillomavirus, respiratory syncytial virus, and Epstein–Barr virus) and biliary atresia [21–25]. There may also be a genetic predisposition to its development. Defects in immune response, autoimmune disorders, and morphogenesis are other possible causes of biliary atresia. Evidence exists that these inciting factors, including viruses, toxins, and gene sequence variations in the etiology of biliary atresia, trigger a proinflammatory response that injures the biliary duct epithelium and results in a rapidly progressive cholangiopathy. This immune response also activates the expression of type 2 cytokines that promote epithelial cell proliferation and extracellular matrix proliferation by non-parenchymal cells [26]. This new information could lead to innovative medical therapies to lessen the severity of the liver disease.

Pathophysiology

Whatever the cause, the end result is complete obstruction of the lumen of the extrahepatic bile ducts and progressive cellular inflammation of the intrahepatic ducts. The degree of intrahepatic bile duct involvement is responsible for much of the morbidity encountered after hepatic portoenterostomy (Kasai procedure).

Clinical presentation

Most patients present with jaundice, acholic stools, dark urine, and an enlarged, firm liver within several weeks after birth – eventually leading to cirrhosis and splenomegaly. Coagulopathy and portal hypertension are often present. Malabsorption of fat-soluble vitamins often leads to anemia, malnutrition, and failure to thrive. Karrer et al reported a less than 10% 3-year survival in children who do not undergo a definitive biliary drainage procedure [17].

Diagnosis

No single test reliably diagnoses biliary atresia. However, a combination of physical examination, liver function tests, ultrasonography, and percutaneous liver biopsy is suggested in the diagnosis of the infant with suspected biliary atresia. Of these, percutaneous liver biopsy has an overall accuracy of more than 90%, and if the the patient is less than 60 days of age accuracy increases to over 95% [27]. Absolute definitive diagnosis requires surgical exploration.

Management

Currently, biliary atresia is managed in two phases [28].

- *Phase 1*: attempts are made to preserve the infant's own liver by performing a Kasai procedure, which involves excising all of the extrahepatic biliary structures at the liver hilus, which is then anastomosed to a Roux-en-Y jejunal limb. The microscopic biliary structures contained within the transected fibrous tissue drain into the intestinal conduit. Over time autoanastomosis occurs between the intestinal and ductal epithelial elements and provides biliary drainage.
- *Phase 2*: if the bile flow is not restored by the Kasai procedure or the cirrhosis worsens, the infant is considered for liver transplant (see Chapter 30).

Anesthetic management for infants with biliary atresia can be challenging since these patients are frequently malnourished. Preoperatively it is important to review all the laboratory and other diagnostic studies. Blood products should be available, especially packed red blood cells and fresh frozen plasma, since these patients may have a coagulopathy. There is also a potential for intraoperative blood loss due to surgery around the major intra-abdominal vascular structures, e.g. the inferior vena cava (IVC) and the hepatic artery. Depending on the infant's condition and the type of surgery, the procedure may be scheduled as same-day surgery or after admission to hospital prior to surgery.

Intravenous access can be difficult. Arterial and central venous access may be considered for ill patients, for close monitoring of arterial pressure, frequent blood draws, and secure venous access.

Anesthesia is usually induced with IV propofol and fentanyl; muscle relaxation is provided with rocuronium, vecuronium, or cisatracurium. Anesthesia is often maintained with either isoflurane or sevoflurane. It is preferable to have IV access in the upper extremity in case there is massive bleeding. Having a functioning arterial line during surgery is very helpful. Intraoperative hypotension is common with IVC compression by surgical instruments or with sudden blood loss. All replacement IV and irrigation fluids should be warmed. Plans are made before surgery for postoperative respiratory and pain management. Some children develop cholangitis after a Kasai procedure and are very ill.

KEY POINTS: BILIARY ATRESIA

- Biliary atresia is a common cause of cirrhosis and liver failure during the first 2 years of life
- Complete obstruction of the lumen of the extrahepatic bile ducts and progressive cellular inflammation of the intrahepatic ducts are common
- These patients present with jaundice, acholic stools, dark urine, and an enlarged, firm liver within weeks after birth
- Biliary atresia is managed in two phases: phase 1, the Kasai procedure; and phase 2, liver transplantation.

Malrotation of the bowel and intestinal atresia

Intestinal obstruction can occur at any age, but the etiology of obstruction varies according to the age of the patient. It is often embryological in origin, especially in children less than 1 year of age. The common congenital causes of bowel obstruction include bowel atresia/stenosis, malrotation of the bowel, Hirschsprung disease, imperforate anus, and meconium ileus. Congenital or acquired small bowel obstructions are more common in children than are large bowel obstructions. Hernias, intramural and extramural intestinal lesions, tumors, inflammatory bowel disease, intestinal volvulus, and adhesions are some of the common causes of pediatric bowel obstruction. Adhesions account for about 60% of all small bowel obstructions [29]. Early diagnosis of intestinal obstruction depends on early recognition of the symptoms, e.g. bilious vomiting, abdominal distension and tenderness, and radiographic findings.

Intestinal atresia

Jejunoileal atresia and stenosis are common causes of neonatal intestinal obstruction. Atresia is a congenital anomaly that completely occludes the intestinal lumen; this accounts for 95% of the cases of obstruction. Stenosis is defined as a partial intraluminal occlusion that incompletely obstructs the intestine. It is responsible for 5% of jejunoileal obstructions. Jejunoileal obstruction occurs in 0.7 per 10,000 livebirths. Intrauterine mesenteric vascular compromise is thought to be the etiology of jejunoileal atresia. On the other hand, mucosal atresia is thought to cause duodenal atresia.

Prenatal ultrasound is useful for diagnosing intestinal atresia in babies whose mothers have polyhydramnios. A history of maternal polyhydramnios, neonatal bilious vomiting, abdominal distension, and failure to defecate meconium on the first day of life is the usual clinical presentation [30]. The diagnosis is confirmed by radiographic examination. Thumb-sized intestinal loops and air–fluid levels are highly suggestive of neonatal intestinal obstruction.

Management of intestinal atresia consists of surgical resection of the atretic/stenotic section of bowel with reanastomosis. Common postoperative complications include obstruction at the anastomotic site and anastomotic leaks. Factors contributing to the morbidity and mortality of these patients include associated anomalies, respiratory distress, prematurity, and short bowel syndrome.

Malrotation of the bowel

Intestinal malrotation refers to abnormal rotation of the midgut around the superior mesenteric artery and abnormal fixation of the gut within the peritoneal cavity. Several types of malrotation occur and are caused by errors in growth, rotation, and position of the duodenum and the ligament of Treitz. These abnormalities in rotation range from non-rotation to reversed rotation (Fig. 31.3) [31,32]. The most common form of gut malrotation in children is due to incomplete rotation and narrow attachment of the mesentery of the midgut to the posterior abdominal wall, which predisposes to midgut rotation and volvulus. Rotational abnormalities commonly occur with heterotaxy, which in this case refers to abnormal attachments of the body organs. Major, complex cardiac anomalies and other gastrointestinal anomalies (e.g. malposition of the stomach, liver, and pancreas, asplenia, or polysplenia) are associated with heterotaxy [31].

Epidemiology

The exact incidence of malrotation of the gut is unknown, but it is thought to be about one in 500 livebirths [32]. The incidence is high in patients with heterotaxy (40–90%). There is no gender-specific preponderance for this lesion. Malrotation is also associated with other congenital or acquired lesions of the gastrointestinal tract (e.g. Hirschsprung disease, intussusceptions, and atresia of the jejunum, duodenum, and esophagus) [33]. These abnormal gut rotations and fixations can obstruct and strangulate the gut at any time between 10 weeks of intrauterine life and adulthood. Malrotation of the gut also occurs in patients with abdominal wall defects, e.g. omphalocele, gastroschisis, and diaphragmatic hernias.

Clinical presentation

Sixty percent of patients presenting with malrotation of the gut do so during the first month of life. Twenty percent present between 1 month and 1 year of age and the remainder present later. Some patients are asymptomatic and their lesion is found accidentally. The usual presenting symptoms of neonates are bilious vomiting or signs of midgut volvulus [34]. Beyond the neonatal period, the presenting symptoms vary from vomiting, intermittent colicky abdominal pain, failure to thrive, diarrhea, constipation, gastrointestinal hemorrhage (i.e. hematemesis or bloody stools), and acute intestinal obstruction [35]. Signs of abdominal distension and peritonitis are often found on physical examination.

Diagnosis

Diagnosis of malrotation is radiological. Making the diagnosis may be difficult if there is heterotaxy because the location of the liver, spleen, and stomach is often ambiguous. Plain radiographs of the abdomen are frequently non-diagnostic. Occasionally, however, there is a "double bubble" sign (i.e. two air-filled structures in the upper abdomen – the stomach on the left and the duodenum on the right – with little or no air seen distally). This finding is usually indicative of acute duodenal obstruction. On an upper gastrointestinal series, if the duodenojejunal flexure and loops of jejunum are on the right side of the abdomen and the cecum is above its normal position on a delayed film, this is diagnostic of malrotation. Abdominal ultrasound and CT scans can fail to rule out the diagnosis of malrotation.

Management

Preoperative management of malrotation requires fluid resuscitation with a balanced salt solution to correct vomiting-induced hypovolemia and dehydration. Attaching a nasogastric tube to suction can increase volume loss. Antibiotics should be administered early. Symptomatic patients with midgut volvulus must be managed urgently or emergently; delays can lead to irreversible intestinal ischemia, worsening sepsis, and

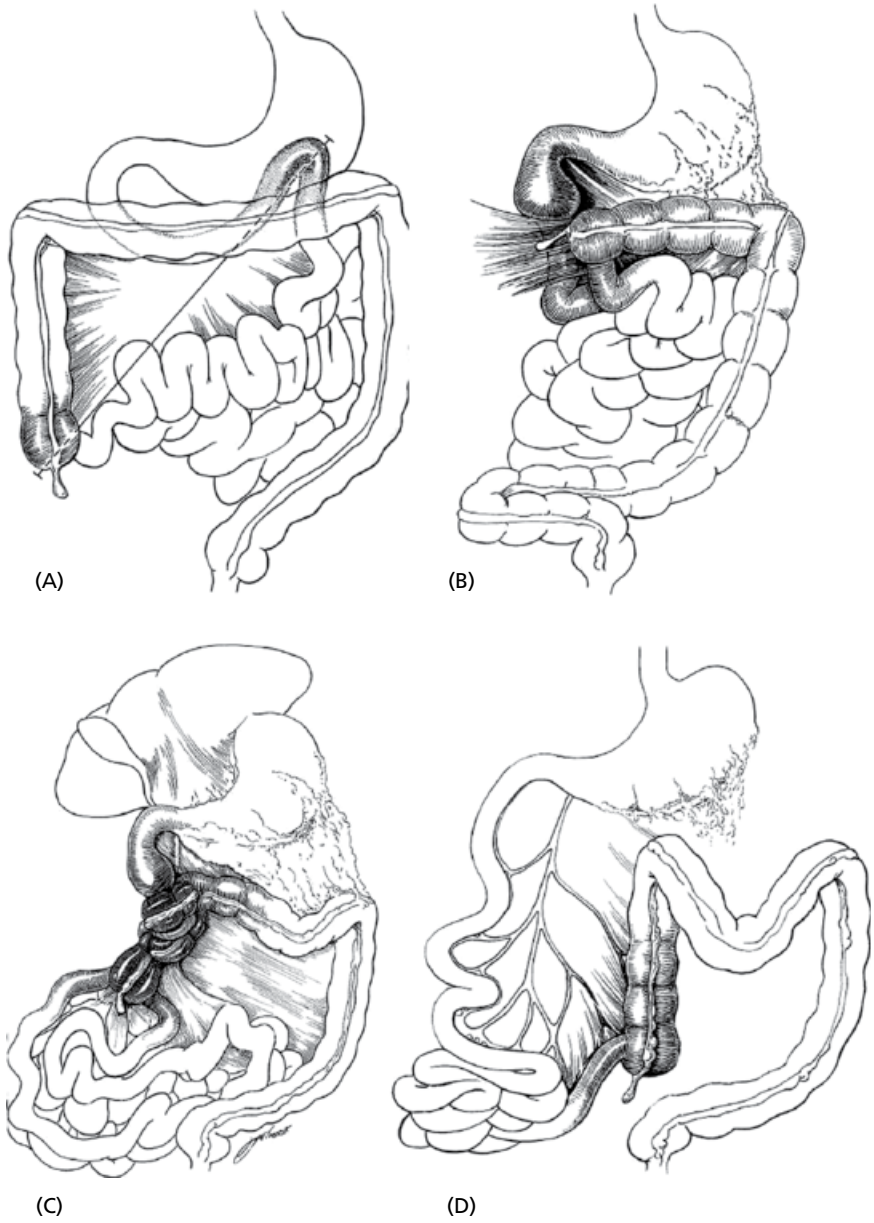

Figure 31.3 (A) Normal intestinal rotation. (B) Malrotation without volvulus. (C) Malrotation with volvulus. (D) Non-rotation. *Source*: Reproduced from Langer [32] with permission of Elsevier.

death. Some patients are severely acidotic from both hypovolemia and poor gut blood flow. If the acidosis is not corrected by fluid replacement, partial correction of pH with bicarbonate or tromethamine should be considered. Once the patient is normovolemic, a Ladd procedure is done, which includes derotation of the midgut volvulus, division of bands and adhesions when present, and an appendectomy. The small bowel is then placed in the right side of the abdomen and the colon on the left side (Fig. 31.4) [32].

These patients must be considered to have a full stomach. Before inducing anesthesia, all laboratory and other diagnostic studies should be reviewed and the degree of acid–base imbalance and electrolyte abnormalities corrected. Adequate venous and intra-arterial access is required. Just before the induction of anesthesia, the stomach is decompressed through an orogastric or nasogastric tube, and the lungs are preoxygenated. Rapid sequence induction of anesthesia is accomplished with intravenous propofol 2–3 mg/kg or etomidate 0.2–0.3 mg/kg and a non-depolarizing muscle relaxant, e.g. rocuronium 1–1.2 mg/kg or vecuronium 0.1–0.2 mg/kg, to facilitate rapid intubation. Intraoperatively, the patient's lungs are ventilated with a mixture of air and oxygen and low concentrations of sevoflurane or isoflurane. Intravenous opioids, e.g. fentanyl, are titrated to effect. The key to a good outcome is fluid resuscitation and replacement of extracellular fluid losses in the perioperative period. Occasionally, large volumes of colloids and blood are required. Circulatory support with vasopressors may be required, especially after derotation of the bowel. These infants frequently require intensive care after

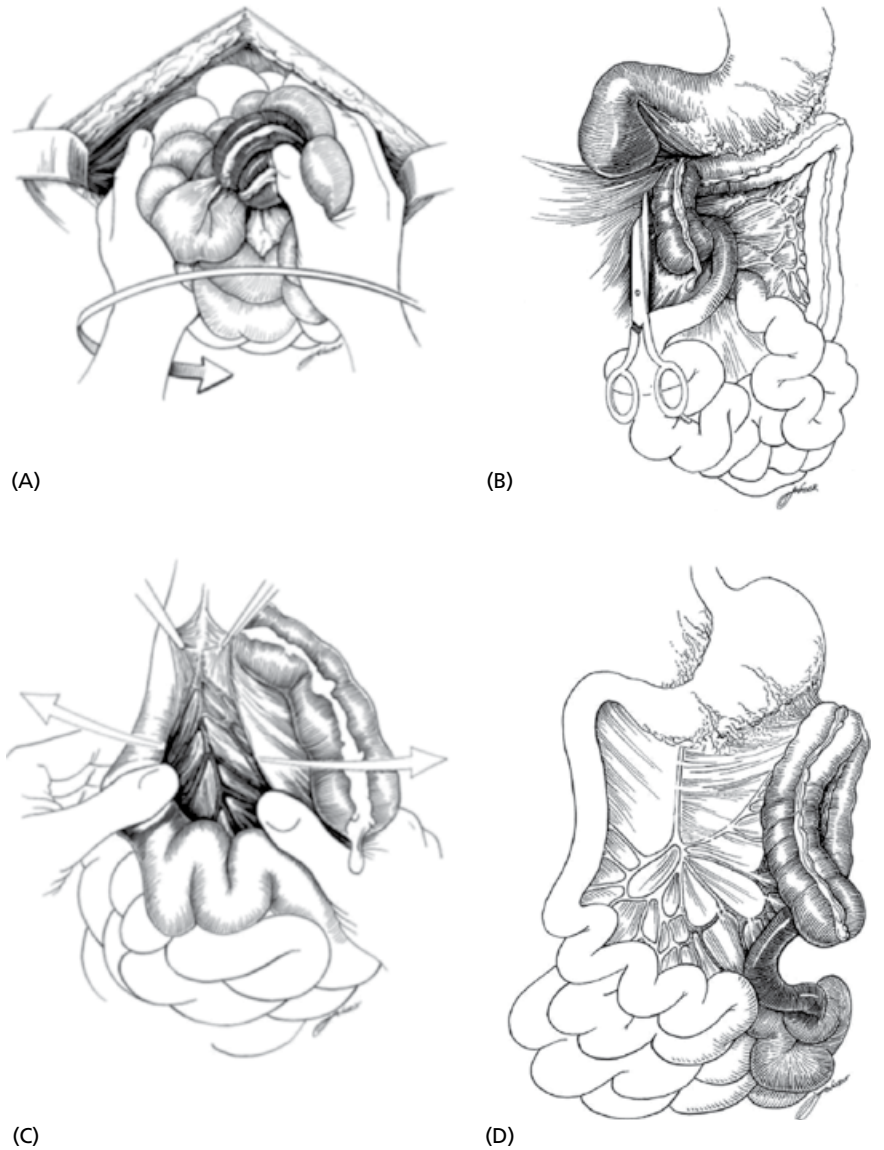

Figure 31.4 Operative steps of Ladd procedure. (A) The bowel is assessed and, if volvulus is present, gently detorsed in a counterclockwise direction (arrow). (B) Ladd bands attaching the colon to the liver, gallbladder, or retroperitoneum are divided sharply or with electrocautery. (C) Adhesions to the mesentery are divided (arrows) and the mesenteric pedicle widened, allowing the colon to be placed on the left side of the patient and the small bowel with a straightened duodenum on the right. (D) Final position of the bowel contents at the completion of the Ladd procedure. An appendectomy has been performed to avoid future confusion with the presentation of atypical appendicitis in the left abdomen. *Source*: Reproduced from Langer [32] with permission of Elsevier.

surgery. Depending on the stability of the patient, the magnitude of the surgery, and associated co-morbid conditions, some patients require postoperative mechanical ventilation. Delayed return of intestinal function often makes parenteral nutrition necessary for a period of time.

Management of asymptomatic patients with malrotation is controversial, with some authorities arguing for an elective Ladd procedure when diagnosed, and others preferring to observe for development of symptoms [36–38]. Laparoscopy may aid in determining the risk for volvulus, i.e. true malrotation with narrow mesenteric stalk, which confers high risk; repair can often be completed laparoscopically. Patients with complex, congenital, single-ventricle cardiac disease and heterotaxy with malrotation can be observed until after their initial cardiac surgery. Additional multicenter data addressing this issue are needed for more definitive recommendations.

Intestinal pseudo-obstruction

If the surgeons find no cause for the bowel obstruction, the patient may have intestinal pseudo-obstruction, a condition in which the signs and symptoms of intestinal obstruction are present but no mechanical lesion is found. Pseudo-obstruction is myopathical or neuropathical in etiology and is not limited to the small intestine. Box 31.1 lists the causes of intestinal pseudo-obstruction. These patients have recurrent attacks of variable duration and frequency that include nausea, vomiting, abdominal distension, diarrhea, and constipation. Treatment of intestinal pseudo-obstruction is difficult and is mainly medical. Erythromycin and octreotide have been used with some success to stimulate intestinal motility and contraction. New treatments that target intestinal serotonin receptors (e.g. alosetron) are in clinical trials. Surgery is only helpful for patients who have a short segment of intestinal dysmotility.

KEY POINTS: MALROTATION OF THE BOWEL AND INTESTINAL ATRESIA

- Jejunoileal atresia and stenosis are major causes of neonatal intestinal obstruction
- Abnormal intestinal rotation commonly occurs with heterotaxy, i.e. there is abnormal sidedness of the liver, spleen, and vascular structures
- Neonates with intestinal malrotation present with bilious vomiting or with signs of midgut volvulus
- Large volumes of crystalloids, colloids, and blood, as well as circulatory support with vasopressors, may be required. Acidosis is common and may necessitate blood volume expansion and alkali to correct it

Box 31.1: Causes of intestinal pseudo-obstruction

Disorders of the nervous system
- Familial autonomic dysfunction
- Neurofibromatosis
- Autoimmune disease
- Paraneoplastic syndrome
- Hirschsprung disease
- Chagas disease

Disease affecting muscles and nerves
- Muscular dystrophy
- Systemic lupus erythematosus
- Amyloidosis
- Ehlers–Danlos syndrome
- Electrolyte disturbances
- Hypokalemia

Disorders of the endocrine system
- Diabetes mellitus
- Hypothyroidism
- Hyperparathyroidism

Medications
- Narcotics
- Laxatives
- Tricyclic antidepressants
- Phenothiazines

Inflammatory bowel disease

Inflammatory bowel disease (IBD) includes two major forms of chronic intestinal inflammation: Crohn disease and ulcerative colitis. Both are associated with significant morbidity. Prompt and accurate diagnosis and appropriate treatment of IBD minimizes its short-term and long-term physical and psychological effects.

Epidemiology

The incidence of IBD is steadily increasing. Over 1 million Americans are afflicted with the disease, and 10–25% of them are children [39–41]. In pediatric patients, the incidence of Crohn disease ranges from two to seven per 100,000 per year compared with 1–4 per 100,000 per year for ulcerative colitis [42]. Males and females are equally afflicted. North America and northern Europe have the largest number of patients with IBD. Caucasians, especially in the Ashkenazi Jewish population, have the highest risk for the disease. However, the increased disease prevalence is occurring in diverse rural and urban populations alike and in people of different ethnic backgrounds.

Etiology

The etiology of IBD is unknown, but a number of risk factors appear to play a role in its development. There appears to be a genetic predisposition because pediatric IBD is familial in 19–41% of cases [42]. Monozygotic twins are more likely to have IBD than dizygotic twins. Environmental factors, infections, immune system disorders, and psychological stress play a role in the development of IBD. The gut microbiome has increasingly been studied and Crohn disease is associated with increased load of enteroinvasive *Escherichia coli* strains [42].

Pathophysiology

Ulcerative colitis is usually limited to the colon and rectum. However, the extent of the disease differs between children and adults. It is usually more extensive in children and may present as pancolitis. Microscopic changes of ulcerative colitis are limited to the mucosa and are continuous from the rectum upward [43]. Crohn disease, on the other hand, can affect any part of the gastrointestinal tract from the mouth to the anus. Children with Crohn disease usually have extensive lesions of the ileum and colon when first evaluated. The inflammatory lesions are focal, asymmetrical, and patchy in location and severity. In the colon, Crohn disease may be difficult to distinguish from ulcerative colitis. Patients with IBD also have extraintestinal manifestations and a higher than predicted risk of developing colorectal cancer.

Clinical presentation

The classic presentation of Crohn disease is abdominal pain, diarrhea, and weight loss. Bloody, mucoid diarrhea is classic for ulcerative colitis. Extraintestinal manifestations of IBD include anorexia, lethargy, pyrexia, arthralgia, arthritis, erythema nodosum, uveitis/iritis, and growth failure.

Diagnosis

The gold standard for diagnosing IBD is upper endoscopy, colonoscopy, and tissue histology. However, there is no substitute for a complete history and physical examination.

Laboratory screening tests include erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) [44], and examination of the stool for bacteria and parasites. Fecal inflammatory markers are also helpful for screening and monitoring patients with IBD. Fecal markers include proteins released from activated neutrophils in the bowel mucosa (e.g. lactoferrin, calprotectin, polymorphonuclear-elastase, and lysozyme) [45].

Serological biomarkers include anti-*Saccharomyces cerevisiae* (ASCA) immunoglobulin A (IgA) and IgG, anti-*E. coli* outer membrane porin C, antiperinuclear antineutrophil IgG, anti-*Pseudomonas fluorescens* CD-related protein IgA, and anti-flagellin. It has been postulated that patients who have immune reactivity to antimicrobial antigens have a more severe form of disease [46]. Higher ASCA levels are associated with younger age at disease onset, structuring of the bowel, penetrating disease, and a need for surgery in both adults and

children with Crohn disease. Radiographic studies, CT scans, ultrasound, magnetic resonance imaging (MRI), and barium enemas are also used to detect disease and complications of the disease (e.g. abscess); however, use of these modalities is limited.

Management

Inflammatory bowel disease is quite debilitating. Therefore, the goals of management include induction and maintenance of disease remission to facilitate normal growth and development and improve the child's quality of life. Medical management consists of a combination of pharmacological agents, including administering corticosteroids for their anti-inflammatory properties to children who have moderate to severe active IBD. Sulfasalazine and 5-aminosalicylate are locally active medications that are useful for the induction and maintenance of disease remission [47]. Immunomodulators, such as 6-mercaptopurine (6-MP) and azathioprine, are the most commonly prescribed agents for these children. These drugs act by incorporating 6-thioguanine nucleotide metabolites of 6-MP in leukocyte DNA [48]. Methotrexate is a second-line immunomodulator that has significant corticosteroid-sparing effects when injected weekly in children with IBD [48]. Cyclosporin and tacrolimus effectively control severe fulminant ulcerative colitis and fistula formation in Crohn disease by blocking production of the potent proinflammatory cytokine interleukin-2 [49,50].

Biological therapy with infliximab, a chimeric monoclonal antibody (IgG1), is directed against tumor necrosis factor α (TNF-α) and is widely used in children with IBD [51]. More recently, adalimumab has been used to treat pediatric patients with IBD. [42]. Antibiotics/probiotics, especially ciprofloxacin (Cipro) and metronidazole (Flagyl), are used to prevent and treat infection, e.g. pouchitis [52]. Nutritional therapy with an elemental diet or total parenteral nutrition helps maintain nutrition and improve growth, which is important because poor nutrition is a major cause of growth failure in patients with IBD. Finally, fecal microbial transplant has been utilized in recent years for pediatric IBD and initial results have been promising [53].

Psychological problems are common in children with IBD due to demanding treatment regimens, frequent relapses of their disease, pain, diarrhea, fecal incontinence, and altered physical appearance. These children frequently do not discuss their problem with peers. Multidisciplinary help is often needed for both the children and their families to help them cope with the practical and psychological implications of IBD [54].

Patients with IBD have an increased risk of developing cancer. It is estimated that the risk of cancer in patients with ulcerative colitis increases 1% per year after the first 10 years of the disease [55]. Patients with total colonic disease have the highest risk. After having the disease for 8–10 years, yearly surveillance of the bowel should be done in all patients, regardless of whether they are symptomatic or asymptomatic. The incidence of surgery in these patients is declining due to better medical and nutritional management. Since surgery does not cure the disease, it is reserved for failures of medical management or for complications of the disease. Emergency surgery is indicated for fulminant disease that is refractory to medical management, including extensive rectal bleeding or toxic megacolon. In the past, proctocolectomy with ileostomy was standard treatment for ulcerative colitis. Since the 1970s restorative proctocolectomy with ileal–anal anastomosis has been practiced. Some patients develop strictures and require surgery to relieve them.

Anesthetic management of patients with IBD begins with a thorough history and physical examination. Particular attention is paid to the patient's fluid and electrolyte status. Optimizing the fluid and electrolyte status before elective surgery is crucial to a good outcome. Prophylactic steroid administration is recommended for patients who have been on long-term steroid therapy. Patients on total parenteral nutrition (TPN) require monitoring of their blood glucose and metabolic states during the perioperative period. Sudden discontinuation of a TPN solution that contains high glucose concentrations may lead to severe hypoglycemia. No one particular anesthetic technique is preferred. Combined general and epidural anesthesia should be considered for abdominal surgery, since the epidural will provide significant postoperative pain relief. The extent of the surgery determines how much intraoperative monitoring is necessary. If the patient requires extensive colonic resection, arterial and central venous lines are appropriate. Attention to intraoperative fluid replacement, blood loss, and correction of fluid, electrolyte, glucose, and hematological derangements is important.

Postoperative pain management can be challenging because many of these patients were receiving narcotics before surgery for their abdominal pain. Intravenous patient-controlled analgesia (PCA) and regional analgesia provide good pain relief and are used routinely. Anastomotic leaks and abscess formation are the most frequent complications encountered after surgery. Abscess drainage by an interventional radiologist often requires general anesthesia.

KEY POINTS: INFLAMMATORY BOWEL DISEASE

- Ulcerative colitis is usually limited to the colon and rectum
- Crohn disease can affect the entire gastrointestinal tract from the mouth to the anus
- Children with IBD and extraintestinal manifestations have a higher risk of developing colorectal cancer
- The gold standard for diagnosing IBD is upper endoscopy, colonoscopy, and tissue histology
- The goals of IBD management are induction and maintenance of disease remission
- Medical management combines pharmacological agents, corticosteroids, anti-inflammatory agents, and biologicals directed against TNF
- Emergency surgery is indicated for fulminant disease that is refractory to medical management or for extensive rectal bleeding or toxic megacolon

Abdominal masses: major abdominal/liver tumors and pheochromocytoma

Major abdominal tumors

Neuroblastomas, Wilms tumor, and hepatomas are the most common intra-abdominal tumors in children. Neonates and infants with these tumors often present with an abdominal

mass and abdominal distension. Box 31.2 lists the differential diagnosis of abdominal masses in children.

Laboratory, radiographic, and imaging studies are common diagnostic measures used to determine the cause of the child's problem. Box 31.3 lists useful studies for the initial evaluation of patients with an abdominal mass.

Neuroblastomas

Neuroblastomas arise from neural crest tissue. In the abdomen they arise from the adrenal glands and paraspinal sympathetic ganglia. Neuroblastoma is the most common neoplasm in infancy and the most common extracranial solid tumor during childhood. The behavior patterns of neuroblastomas are heterogeneous and range from complete regression to life-threatening progression despite treatment.

Epidemiology

Neuroblastomas account for more than 7% of malignancies in patients less than 15 years of age and around 15% of all pediatric oncology deaths [56]. Approximately 40% of cases are diagnosed by 1 year, 75% by 7 years, and 98% by 10 years of age [57]. More than half of the patients are younger than 2 years old when diagnosed. The incidence of neuroblastoma is slightly more common in boys than girls (ratio of 1.2:1.0) [57]. A familial history of neuroblastoma, with an autosomal dominant pattern of inheritance, has been reported in 1–2% of patients. The median age at diagnosis of familial neuroblastoma is 9 months, compared with 18 months for sporadic cases [56]. Maris et al found that 20% of patients with familial neuroblastomas have bilateral or multifocal tumors with evidence for a locus on chromosome 16p12-13 [58].

Approximately 75% of cases of abdominal neuroblastomas have metastasis at diagnosis, the most common sites being lymph nodes, bone marrow, liver, and skin. In the USA the overall incidence is one per 100,000, with approximately 700 new diagnoses annually. The overall survival is 65%, but most patients have high-risk metastatic disease at presentation, where survival rates are less than 50% despite intensified chemotherapy and invasive surgery [59]. In contrast to neuroblastoma diagnosed after the neonatal period, neonatal neuroblastoma, which accounts for less than 5% of cases, most often regresses spontaneously and may resolve completely without treatment. Many authorities advocate a watch and wait approach for low-risk neonates, and reduced therapy for some intermediate-risk patients to minimize exposure to toxic chemotherapy and to surgery [60].

Box 31.2: Differential diagnosis of abdominal masses in children

Neonates

Neoplastic
- Teratomas
- Liver hemangiomas

Gastrointestinal
- Intestinal duplication
- Mesentery cysts
- Choledochal cysts

Renal
- Polycystic kidney disease
- Hydronephrosis

Ovarian
- Ovarian cysts
- Ovarian teratomas

Infants and children

Neoplastic
- Hepatocellular carcinomas
- Hepatoblastomas
- Neuroblastoma
- Wilms tumor
- Teratomas
- Retroperitoneal paraganglioma
- Lymphomas
- Rhabdomyosarcoma

Infectious causes
- Hydatid cysts
- Toxic megacolon
- Retroperitoneal/intra-abdominal abscess

Other
- Impacted feces
- Mesenteric cysts
- Intussusception
- Volvulus

Box 31.3: Studies for the evaluation of abdominal masses

Laboratory studies
- Complete blood count with differential
- Serum chemistry
- Serum electrolyte levels
- Liver function tests
- Plasma catecholamine levels
- Serum β-chorionic gonadotropin
- Serum α-fetoprotein levels
- Urinalysis
- Uric acid and lactate dehydrogenase levels
- Urine for vanillylmandelic acid and catecholamine levels

Radiographic imaging studies
- Plain abdominal x-ray
- Abdominal sonogram
- CT scan or MRI of the abdomen
- MIBG (metaiodobenzyl guanidine) scan

Clinical presentation

The clinical presentation of neuroblastomas varies, depending on the site of the primary disease, the extent of metastasis, the size of the tumor, and any associated paraneoplastic syndromes. Patients in the early stage of the disease may have non-specific symptoms, such as pain and generalized malaise. Between 50% and 75% of patients present with an abdominal mass and may have abdominal pain and abdominal distension, weight loss, failure to thrive, fever, and anemia [57]. Tumors producing catecholamine cause hypertension in 25% of patients. Thoracic tumors may be discovered accidentally on a chest radiograph or when the patient shows signs of Horner syndrome (ptosis, miosis, enophthalmos, anhydrosis, and heterochromia of the iris) on the affected side. Patients with metastatic neuroblastomas can present with proptosis and periorbital ecchymosis, often referred to as "raccoon eyes." Infants with neuroblastomas can have hypokalemia and intractable diarrhea with watery, explosive stools. The diarrhea is thought to be the result of tumor-produced vasoactive intestinal polypeptide.

Diagnosis

Neuroblastomas are diagnosed by serological and urine examinations and by radiological and isotope studies. While there are no specific serum markers for neuroblastoma, high levels of ferritin, neuron-specific enolase, and lactate dehydrogenase are often present [61]; patients occasionally have high levels of serum and urinary catecholamines. Immunological analysis of serum and bone marrow is sensitive for detection of tumor cells. Radiographic examinations include plain x-rays of the abdomen, CT scan, helical (spiral) CT, MRI, and isotope bone scans. Once the diagnosis is made, the disease is staged according to the International Neuroblastoma Staging System (INSS). The INSS score is one

of the main clinical variables used to predict outcomes of patients with neuroblastomas. Increasingly, histopathological characteristics are used to determine patient risk and treatment strategies. Finally, genomic and biological features such as DNA ploidy, chromosomal alterations, and amplification of specific genes are now used for staging and risk assessment, and to determine treatment.[59]

Management

Surgery, chemotherapy, radiotherapy, and immunotherapy are the main treatment modalities for neuroblastoma. Surgery is beneficial for patients who have localized tumors. However, more than half of children with neuroblastomas present with metastatic, unresectable tumors. When this occurs, they are initially treated with chemotherapy followed by tumor resection. Children with high-risk neuroblastomas undergo multimodal therapy, including induction of chemotherapy, surgical resection of the primary tumor, radiotherapy, and consolidation chemotherapy.

Surgical resection of the tumor

When children with neuroblastoma present for surgery, a complete history and physical examination and preoperative consultation with the patient's primary physician are important. Evaluation of the complete blood count, serum electrolyte concentrations, echocardiography, and radiological studies is also important. Knowledge of the chemotherapeutic drugs and steroids used is important as both therapies can cause complications. Intraoperative anesthetic management consists of general anesthesia, tracheal intubation, and standard monitoring plus intra-arterial and central venous monitoring. Occasionally neuroblastoma resection is accompanied by significant blood pressure fluctuations like that seen with pheochromocytomas (see next section).

Pheochromocytomas

Pheochromocytomas arise from catecholamine-producing chromaffin cells and are of neuroectodermal origin. These cells are found anywhere in the sympathoadrenal system but arise most commonly from the adrenal medulla. Tumors arising from extra-adrenal sympathetic and parasympathetic paraganglia are classified as extra-adrenal paragangliomas. Pheochromocytomas and sympathetic paragangliomas secrete catecholamines, but most parasympathetic paragangliomas are non-secretory. Pheochromocytomas secrete large amounts of adrenaline, noradrenaline, and dopamine, plus various peptides and ectopic hormones: enkephalin, somatostatin, calcitonin, oxytocin, vasopressin, insulin, and adrenocorticotropic hormones [62]. Data on the etiology, diagnosis, and management of pheochromocytoma in children are limited.

Epidemiology

Pheochromocytomas are one-tenth as common in children as in adults (one in 500,000 children compared to one in 50,000 in adults) [63]. Approximately 10% of tumors are bilateral, 10% are extra-adrenal, 10% are malignant, and 10% are familial. In children, 70% of the tumors are bilateral and extra-adrenal, the majority of them benign [64]. Advances in molecular genetics have allowed mutations in germline cells to be identified in 59% of patients presenting at 18 or fewer years of age and in 70% of patients presenting before age 10 years. The inherited predisposition is related to mutation(s) in the von Hippel–Lindau (VHL) gene, which encodes the subunits B and D of succinate dehydrogenase and also the RET proto-oncogene that predisposes patients to the development of multiple endocrine neoplasia type 2 (MEN2) or neurofibromatosis type 1 (NF1). The VHL gene is the most commonly mutated gene in children who present with pheochromocytoma [65].

Though rare, pheochromocytomas may present in the neonatal period. However, they present more commonly in older, male children. There is a female preponderance for the disease during the reproductive years, suggesting a hormonal influence.

Clinical presentation

Patients with pheochromocytomas are thin, anorexic, and hypermetabolic. The most common symptoms include headaches, flushing, palpitations, hypertension, and sweating. Central nervous system manifestations include tremors, nervousness, anxiety, visual disturbances, and psychosis. Cardiovascular symptoms include hypertension, ventricular arrhythmias, cardiomyopathy, and cardiac failure. Some patients have symptoms of gastrointestinal disturbances.

Diagnosis

Pheochromocytoma is diagnosed by biochemical testing and imaging studies. Measurement of 24 h urinary vanillylmandelic acid, total metanephrine, and catecholamine concentrations is valuable [66]. Urinary metanephrine levels are increased in 95% of cases, and vanillylmandelic acid and catecholamine levels are increased in approximately 90% of patients [67]. Plasma catecholamine concentrations that exceed 2000 pg/mL during a hypertensive episode are diagnostic of pheochromocytoma; normal levels are not. Plasma catecholamine levels between 500 and 1000 pg/mL are suggestive of pheochromocytoma, but further work-up is required [68]. CT or MRI scans and ^{123}I-labeled metaiodobenzyl guanidine (MIBG) scintigraphy are all also helpful in making the diagnosis [69]. Abnormal neuroectodermal tissue takes up the isotope, which produces a focal area of increased uptake on the scan. These scans help localize extra-adrenal tumors. Positron emission tomography with ^{18}F fluorodeoxyglucose or hydroxyephedrine is also useful for localizing tumors [70].

Management

Surgical excision of the tumor is the definitive treatment, but this requires optimization of the patient's condition medically before surgery. The goals of medical management include normalization of the arterial blood pressure and heart rate, restoration of blood volume, and prevention of a hypertensive crisis and its subsequent consequences.

Preoperative preparation of the patient should begin at least 10–14 days before surgery. Initial treatment includes α-adrenoreceptor blockade to reduce catecholamine-induced vasoconstriction and its sequelae [71]. Phenoxybenzamine is a non-selective α1 and α2 non-competitive blocker that is administered orally in doses of 0.5–1 mg/kg twice a day. The dose is adjusted according to the patient's response to the drug. Phentolamine, a competitive non-selective α-adrenergic blocker, is also used as an adjunct. Adequate α-blockade is

demonstrated by the presence of normotension or by the presence of side-effects to the drug, such as orthostatic hypotension tachycardia, nasal congestion, and dizziness [71]. The unopposed β-stimulation following α-blockade causes tachycardia and arrhythmias, which are controlled by β-adrenergic receptor-blocking agents, such as propranolol or labetalol. β-receptor blockade should never be initiated until α-blockade is fully accomplished because a severe hypertensive crisis can occur due to unopposed α-stimulation. Occasionally, α-methyl-para-tyrosine (metyrosine), which competitively inhibits tyrosine hydroxylase, the rate-limiting step in catecholamine biosynthesis, is added to reduce catecholamine stores in the tumor [72].

Patients with pheochromocytomas are generally intravascular volume depleted and have circulating plasma volumes of about 15% below normal. Once adequate pharmacological blockade is established, volume resuscitation is required.

Anesthetic management of patients with pheochromocytomas consists of providing stable anesthesia and avoiding surges in catecholamines. In spite of optimal medical management, patients can and do have sudden blood pressure fluctuations during induction of anesthesia and tracheal intubation, during surgical manipulation of the tumor, and after ligation of the tumor's venous drainage. Premedication with oral midazolam is often used to treat patient anxiety. General tracheal anesthesia or combined general and epidural anesthesia have been used successfully for intraoperative management of these patients. Anesthesia is usually induced by mask with sevoflurane or with intravenous propofol or etomidate. Following induction of anesthesia, large-bore intravenous catheters and an arterial line are inserted. Muscle relaxation is achieved with a non-depolarizing muscle relaxant, such as rocuronium, vecuronium, or *cis*-atracurium. A central venous catheter is inserted if one is not already in place. Fentanyl, sufentanil, or a continuous infusion of remifentanil can be used.

Intraoperative hypertension is managed by infusion of sodium nitroprusside, a potent arteriovenodilator. Esmolol is often used to control tachycardia and hypertension. Hypotension may occur once the adrenal vein is ligated and the tumor is removed. The hypotension usually responds to fluid administration and discontinuation of vasodilators. Occasionally vasopressors, such as phenylephrine or norepinephrine, are required.

After surgery the patients are admitted to the intensive care unit (ICU) to monitor for and control hypertension, hypotension, and hypoglycemia. Once the tumor is excised, pancreatic β-cell suppression is removed and insulin levels increase, which may cause hypoglycemia. Lipolysis and glycogenolysis cease after tumor removal and α-blockade. Residual adrenergic blockade may mask the signs and symptoms of hypoglycemia. Consequently, blood glucose concentrations should be closely monitored. If hypertension persists postoperatively, it is likely that there is a second pheochromocytoma. Normalization of catecholamine levels should be confirmed in all patients. Long-term follow-up is required to detect subsequent development of metachronous tumors and to detect tumors at other sites.

Wilms tumor

Wilms tumor (nephroblastoma) is the most common renal neoplasm affecting children. Diagnosis and treatment of Wilms tumor are discussed in Chapter 32.

Liver tumors

Liver tumors account for 1% of all pediatric tumors. Hepatoblastoma and hepatocellular carcinomas are responsible for most hepatic malignancies during childhood. Two-thirds of all liver tumors are hepatoblastomas. Benign liver tumors include vascular tumors, hamartomas, adenomas, and focal nodular hyperplasia. With advances in surgical technique, anesthesia, and chemotherapy, the 5-year survival of patients with hepatoblastoma has improved from 35% three decades ago to 75% at the present time [73]. However, the prognosis for patients with hepatocellular carcinoma remains poor.

Epidemiology

Hepatoblastoma and hepatocellular carcinomas occur more commonly in males and are more common in 0.5–3-year-old children, the median age at diagnosis being 18 months. Only 5% of new hepatoblastomas are diagnosed in children beyond 4 years of age. Other conditions associated with hepatoblastoma include Beckwith–Wiedemann syndrome, familial adenomatous polyposis, hemihypertrophy, and low birthweight. Hepatocellular carcinomas are diagnosed after 10 years of age and commonly occur in patients with underlying liver disease, such as cirrhosis, tyrosinemia, and other inherited metabolic disorders [74]. Genetic aberrations in several chromosomes have been identified that predispose patients to the development of malignant liver tumors.

Clinical presentation

Most children who have liver cancers present with a painless, palpable, abdominal mass. They may also have abdominal distension, anorexia, weight loss, and fatigue. Occasionally they present with abdominal pain, constipation, jaundice, or precocious puberty.

Diagnosis

Laboratory and imaging studies are key to the diagnosis of liver tumors. Laboratory studies include complete blood count, chemistry panel, liver function tests, coagulation profile, and serum α-fetoprotein (AFP) concentrations. AFP concentrations are the most sensitive laboratory test for hepatoblastoma and hepatocellular carcinomas, but this test is non-specific. On occasion, hepatoblastomas secrete β-human chorionic gonadotropin. Imaging studies, such as CT scan of the abdomen, ultrasonography, MRI, and magnetic resonance angiography, are also useful in diagnosing these tumors. The diagnosis is ultimately made, however, by liver biopsy.

Management

Treatment of hepatoblastoma has improved markedly during the past several decades. Primary resection of benign liver tumors and stage I hepatoblastoma is curative. Unresectable tumors are initially treated with vincristine, cisplatin, and fluorouracil before the tumors are resected. If the tumor remains unresectable despite chemotherapy and is not metastatic, orthotopic liver transplantation is considered. In recent years, international collaboration has resulted in a more precise staging and management system based on how many sectors of the liver are involved, and other features such as involvement of the IVC, hepatic, and portal veins. More

standardized approaches to intensive preoperative chemotherapy for high-risk tumors, and to extensive surgical resection, have increased survival to over 90% for patients with standard-risk hepatoblastoma, and 45–80% for patients with metastatic disease. Liver transplantation is now employed in as many as 27% of high-risk tumors in a recent series [75].

Preoperative assessment determines the extent of the tumor, whether it has metastasized, and if the patient has received chemotherapy. Careful attention should be paid to the patient's laboratory tests, liver function, blood count, coagulation status, and pulmonary, renal, and cardiac function, especially after chemotherapy. Echocardiography may be necessary after cardiotoxic chemotherapy. Patients should be typed and cross-matched for packed red blood cells and should have fresh frozen plasma and platelets available before and during surgery.

Anesthetic management of patients with liver tumors is challenging. Standard anesthesia induction agents are used. Tracheal intubation is facilitated with muscle relaxants, preferably *cis*-atracurium because its hepatic metabolism is minor. Standard monitors, plus intra-arterial and central venous pressure (CVP) monitoring, are usually used. Large-bore peripheral venous access is obtained, preferably in the upper extremities. In the event of major blood loss, perfusion, normothermia, and a normal pH should be aggressively maintained. It is occasionally necessary during surgery to quickly resuscitate patients who undergo acute, rapid hemorrhage. The main source of bleeding during liver resection is from the hepatic vein, which has no valves. High venous pressure increases bleeding. By keeping the CVP below 5 mmHg during the dissection phase, blood loss can be reduced. Vasopressors (e.g. norepinephrine or vasopressin) may be required to maintain arterial blood pressure during some phases of surgery. Whether the trachea is extubated in the operating room or the ICU depends on the extent of the liver resection, the amount of intraoperative blood loss, and the need for volume resuscitation. Postoperative pain is easily managed with patient- or nurse-controlled analgesia.

KEY POINTS: ABDOMINAL MASSES

- Neuroblastoma, Wilms tumor, and hepatomas are the most common intra-abdominal tumors in children
- Neuroblastomas account for about 7% of malignancies in patients younger than 15 years of age and 15% of all pediatric oncology deaths
- Diagnosis of neuroblastoma requires serological and urine examinations and both radiological and isotope studies
- Measuring 24 h urinary concentrations of vanillylmandelic acid, total metanephrine, and catecholamines makes the diagnosis of pheochromocytoma
- Preoperative preparation for pheochromocytoma surgery should begin with phenoxybenzamine-induced α-blockade prior to surgery
- Hepatoblastoma and hepatocellular carcinomas are the most frequent hepatic malignancies of childhood

Inguinal hernia

An inguinal hernia is a protrusion of intestine through an open processus vaginalis (Fig. 31.5). An incarcerated hernia is a hernia that is irreducible and does not slide back into the abdominal cavity. When bowel entrapment interferes with the vascular supply of the bowel, the hernia is said to be strangulated.

Epidemiology

Inguinal hernia repair is the most common elective procedure performed in pediatric patients. It occurs in 4.4% of all pediatric patients and is more common in males. Its incidence is 10–30% in premature infants versus 3–5% in full-term neonates [76,77]. Connective tissue disorders and cystic fibrosis also increase the incidence of inguinal hernia. Incarcerated hernias are more frequent in premature babies [78].

Clinical presentation and diagnosis

Inguinal hernias are diagnosed by physical examination when a bulge is felt at the internal or external inguinal ring. Most inguinal hernias are not painful, but large hernias may be. The bulge frequently disappears during sleep or rest. A Valsalva maneuver (e.g. crying) often provokes the bulge. The differential diagnosis of inguinal hernia includes hydrocele, retractable testis, lymphadenopathy, and a neoplastic process. Ultrasound helps diagnose a patent processus vaginalis. Patients with incarcerated hernias present with a tender, firm mass in the groin. These children are often inconsolable and may have anorexia. The "silk glove sign" (thickened peritoneum of the patent process vaginalis that can be felt during palpation of the cord) is suggestive of an inguinal hernia [79].

Management

Inguinal hernias do not heal spontaneously, but hydroceles often resolve during the first year of life. These hernias require surgical repair to reduce the risk of developing an incarcerated hernia. Incarcerated hernias can usually be manually reduced. Once reduced, the hernia should be repaired during

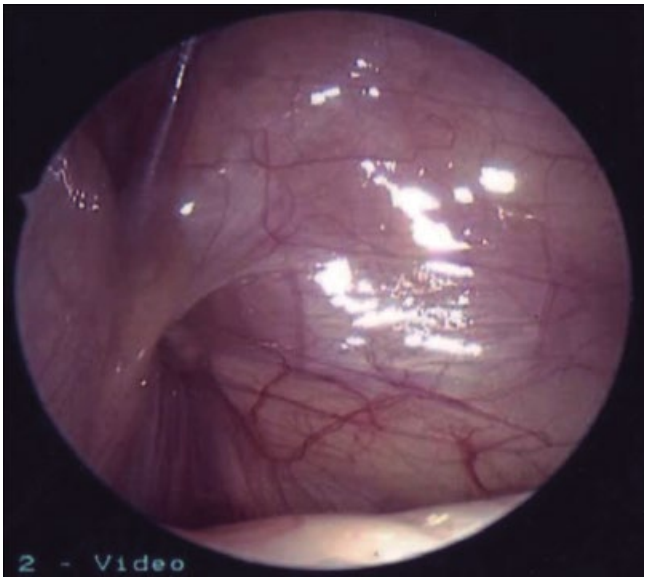

Figure 31.5 Laparoscopic view of a right inguinal hernia in a 2-month-old child.

the next 24–48 h to prevent recurrence of the incarceration [80]. If the hernia cannot be reduced, it may progress to strangulation, necrosis, and gangrene of the bowel. Strangulated hernias require immediate surgical correction. General anesthesia and muscle relaxation often make a non-reducible hernia reducible. Some patients with strangulated hernias have necrotic bowel and require bowel resection during herniorrhaphy. Table 31.1 details the characteristics of inguinal hernias. Children who are <6 months of age are at increased risk for developing strangulated or incarcerated hernias [81]. Consequently, their hernias are usually repaired soon after detection. Whether to operate on the contralateral side is debatable, but 28% of patients with a unilateral, clinically evident hernia early in life subsequently develop a symptomatic contralateral hernia [82]. Fifty percent of <2-year-old children have an open processus vaginalis, which should not be confused with an inguinal hernia. Laparoscopic visualization of the contralateral side is very helpful for determining if a second inguinal hernia exists on this side. This can be done even though the primary repair is done conventionally.

Premature babies often have bilateral inguinal hernias. Because of potential pulmonary complications and the fact that the surgical repair may be more difficult, there is controversy regarding when their hernias should be repaired. The reality is that most preterm neonates undergo hernia repair shortly before discharge home from the neonatal ICU for fear they will develop an incarcerated hernia.

Depending on co-morbidity and the surgical requirements, neuroaxial anesthesia or general tracheal, laryngeal mask, or facemask anesthesia is appropriate. Laryngeal mask airways (LMAs) should be used with caution in preterm infants. A no. 1 LMA increases the dead space by approximately 100% and may increase the $PaCO_2$ significantly. Unless the depth of anesthesia is adequate, laryngospasm may develop during surgical manipulation of the hernia sac. Despite these concerns, a new randomized controlled trial of LMA versus endotracheal tube in infants under 12 months of age demonstrated a much lower rate of perioperative respiratory adverse events, including laryngospasm and bronchospasm (18% versus 53%, n = 177 subjects, risk ratio 2.94, p <0.0001) [83]. Caudal blocks are often used as an adjunct to general anesthesia. In older patients, ileoinguinal or ileohypogastric nerve blocks can be helpful.

Postoperative apnea occurs in 20–30% of otherwise healthy former preterm infants who undergo inguinal hernia repair [84]. The risk for postoperative apnea decreases with increasing postconceptional age [85]. Spinal anesthesia is often used for these patients, although doing so does not decrease the incidence of apnea and bradycardia [86]. Ex-premature infants <60 weeks' post conception and full-term neonates <45 weeks postconception are usually admitted to hospital overnight for apnea monitoring. The recent GAS (*G*eneral *A*nesthesia compared to *S*pinal Anesthesia) Study had a primary aim of determining neurodevelopmental outcomes, but also assessed postanesthetic apnea. Early apnea at 0–30 min after surgery was less with spinal anesthesia (1% versus 3%, p = 0.04), but the overall rate at 0–12 h was similar at 3% with spinal and 4% with general anesthesia (p = 0.21). The strongest predictor of apnea was prematurity, with 96% of infants experiencing apnea being premature [87]. See Chapter 46 for further discussion of the GAS Study and anesthetic neurotoxicity.

Long-term outcome

In one study 28% of patients with a unilateral, clinically evident hernia had a symptomatic contralateral hernia later in life. The recurrence rate of an inguinal hernia repaired early in infancy is under 5% [88].

KEY POINTS: INGUINAL HERNIA

- Inguinal hernias are common in preterm infants
- It is important to determine whether the hernia is non-incarcerated, incarcerated, or strangulated
- Spinal anesthesia for premature infants does not reduce the incidence of postoperative apnea

Pyloric stenosis

Epidemiology

The incidence of idiopathic hypertrophic pyloric stenosis (IHPS) is 2–4 per 1000 livebirths, with a female to male preponderance of 1:3. Recently, the incidence of IHPS has decreased in some countries. Premature infants develop IHPS later than full-term infants [89].

Etiology

The mechanism for hypertrophy of the pyloric muscle is unknown, but the hypertrophy causes the gastroenteral obstruction (Fig. 31.6). The increased frequency of the condition in males and in first-born infants who have a positive family history for IHPS suggests that the lesion has a genetic predisposition. Feeding-related, environmental factors, duodenal feeding of premature infants, and erythromycin exposure have all been suggested as causes of IHPS. The pyloric muscle fibers are hypertrophic (not increased in number) and are markedly thickened and edematous. After a pyloromyotomy, the pyloric muscle becomes completely normal over time.

Clinical presentation and diagnosis

Between the 2nd and 12th (classically between the 3rd and 8th) weeks of life, most patients with IHPS present with

Table 31.1 Characteristics of inguinal hernias

	Simple	Incarcerated	Strangulated
Hernia sac	Herniates with Valsalva maneuver	Reducible	May or may not be reducible
Pain	No pain	Tender	Tender
Vascular supply	Intact	Intact	Compromised
Urgency	Elective	Within 24–72 h after reduction	Urgent

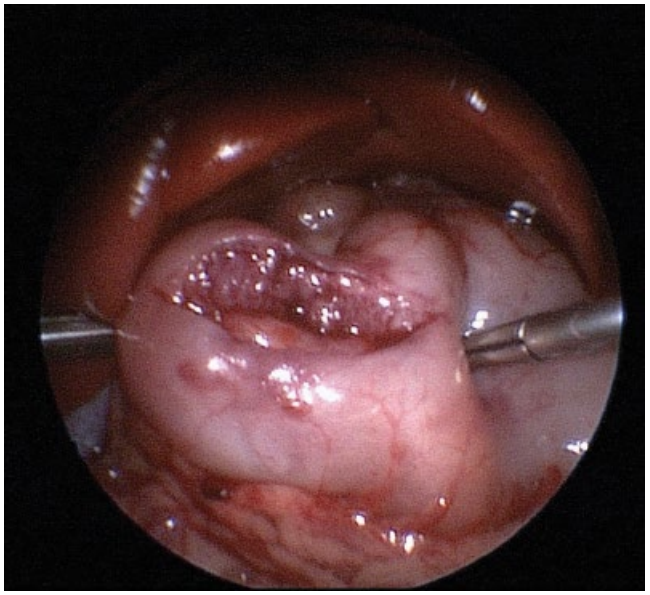

Figure 31.6 Pyloromyotomy. Note that the pyloric muscle has been partially transected and left open to heal. This increases the opening of the pylorus.

non-bilious, projectile vomiting. The differential diagnosis includes overfeeding, pylorospasm, gastroparesis, gastroesophageal reflux, and duodenal bands. Patients with pyloric stenosis are usually hungry and alert. When dehydration develops, they become lethargic.

The diagnosis of IPHS is usually confirmed by ultrasound. A barium swallow may be indicated if the ultrasound study is inconclusive. The hypertrophic pylorus can often be palpated through the abdominal wall. Careful observation of the child after feeding often reveals a characteristic peristaltic wave moving across the epigastrium. Historically, patients presented at an advanced stage of the disease. Now widespread use of ultrasound and much better understanding of the disease by pediatricians allow the diagnosis to be made earlier. Consequently, fewer patients have severe electrolyte disturbances and dehydration at presentation. If the diagnosis is made late, patients typically are dehydrated, hypochloremic, hypokalemic, and alkalotic at presentation. They may have lost weight and have gastritis with minor gastrointestinal bleeding. Initially these patients have an alkaline urine and loss of potassium and sodium as renal compensation for their vomiting. Later they secrete acidic urine, which further increases the metabolic alkalosis. This paradoxical aciduria occurs once potassium and sodium are depleted (Fig. 31.7).

Hypocalcemia often accompanies the hyponatremia. If this downward spiral is allowed to continue and additional fluid losses occur, prerenal azotemia, hypovolemic shock, and metabolic acidemia ensue.

Management

Idiopathic hypertrophic pyloric stenosis and concomitant hypovolemia represent a medical not a surgical emergency. The hypovolemia, acid–base abnormalities, and electrolyte abnormalities must be corrected prior to the induction of anesthesia. Surgery for IHPS is urgent but is not an emergency. Depending on the severity of these abnormalities, correction may require 12–48 h [90]. These patients should be made nil per os and their stomachs should be decompressed.

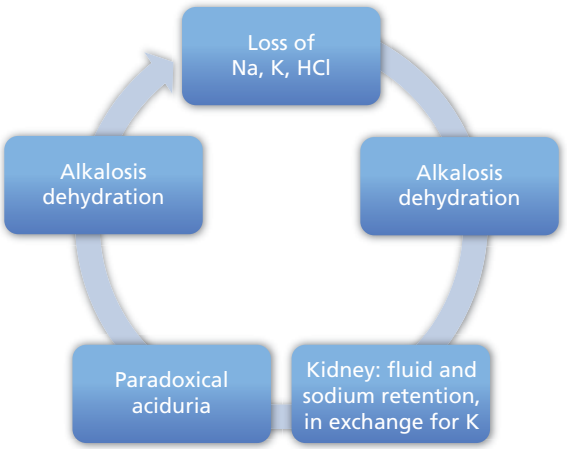

Figure 31.7 Pathophysiology of pyloric stenosis.

Intravenous fluid therapy usually includes normal saline (NS), dextrose 5% (D5) in 0.5 NS, or D5 in 0.25 NS at 1.5 times the maintenance fluid requirements. Care should be taken not to give excessive dilute solutions as they may cause seizures and death. Sufficient glucose should be provided to maintain normal blood glucose levels. Once satisfactory urine output is achieved, potassium can be added to the IV fluids. Homeostasis, as reflected by a serum chloride concentration >100 mEq/L and a serum bicarbonate concentration of <30 mEq/L, should be achieved before surgery commences. Urine chloride concentrations >20 mEq/L suggest adequate restoration of intravascular volume, since the kidney retains chloride during volume contraction. An underlying deficiency in glucuronyltransferase is responsible for jaundice in 2% of patients.

Before tracheal intubation, atropine is often given to prevent bradycardia, and the stomach is suctioned while tilting the patient in four different directions to empty the stomach as thoroughly as possible [91]. It is occasionally necessary to lavage the stomach to remove barium or milk curds. The high risk for aspiration of gastric contents warrants caution with airway management, but the prior practice of intubating the trachea whilst the patient is awake has decreased significantly in recent years because of the potential adverse effects of soft tissue injury, breath-holding, laryngospasm, aspiration, and the noxious and painful nature of the procedure.[90]. More commonly, a rapid sequence induction or modified rapid sequence induction of anesthesia with propofol and muscle paralysis with either succinylcholine or a non-depolarizing muscle relaxant is utilized. Intraoperatively, air is injected into the stomach through an orogastric catheter to verify the integrity of the duodenal mucosa. Preoperative cerebrospinal fluid alkalosis increases respiratory sensitivity to opioids. Consequently, these drugs are usually avoided because they can slow awakening from anesthesia and cause apnea. Acetaminophen per rectum or intravenously and infiltration of the wound with local anesthetics are often sufficient for postoperative pain management. Pyloromyotomy can be done open or laparoscopically. There are no clear advantages of one technique over the other, although recent meta-analyses demonstrate laparoscopy was associated with shorter time to full feeds and better cosmetic outcome, but also had a slightly higher rate of inadequate pyloromyotomy [92,93]. The hospital length of stay and postoperative complications are similar with

both techniques. Most patients have their trachea extubated at the conclusion of surgery. However, the presence of metabolic alkalosis increases their probability of postoperative apnea [94]. Other common complications of a pyloromyotomy include perforation of the duodenal mucosa (1–2%), wound infection, incisional hernia, incomplete myotomy, and bowel injury [95]. Oral feeds are usually instituted several hours after surgery. Some patients have persistent postoperative vomiting from gastroesophageal reflux or an incomplete myotomy.

Box 31.4 presents an evidence-based summary of perioperative management of pyloric stenosis [90].

KEY POINTS: PYLORIC STENOSIS

- Pyloric stenosis is a medical emergency, not a surgical emergency
- Allow time for adequate preoperative rehydration and correction of electrolytes
- Tracheal intubation is by rapid sequence induction or modified rapid sequence induction
- Opioids are avoided because they delay awakening from anesthesia and may increase apnea and the need for postoperative mechanical ventilation

Appendicitis

Epidemiology

Acute appendicitis is the most common abdominal lesion requiring surgical intervention. Four out of 1000 patients under 14 years of age will be diagnosed with appendicitis, and their lifetime risk for appendicitis is 7%. There is a male preponderance of appencititis (55–60%) [96]. No single test, examination, or symptom confirms the diagnosis in all cases. About 0.2–0.8% of patients with appendicitis die of complications of the disease. Preschool-aged children account for only about 5% of appendicitis, but the rate of appendiceal perforation in <4-year-old children is 80–100%, whereas it is 10–20% in children 10–17 years of age. The symptoms of appendicitis in younger children are often more diffuse [97], which makes the diagnosis more difficult to make. The atypical presentation increases the perforation rate in children [98].

Etiology and pathophysiology

Appendicitis is caused by luminal obstruction of the appendix by edema, inflammation, and overgrowth of fecal bacteria (Fig. 31.8). Lymphoid hyperplasia, a foreign body, or fecal

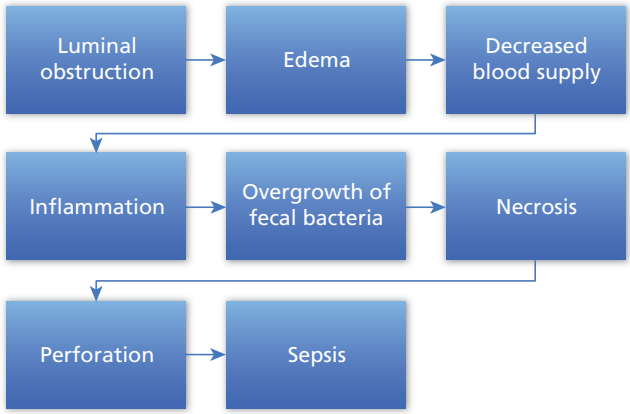

Figure 31.8 Pathophysiology of appendicitis.

Box 31.4: Summary of perioperative care for pyloric stenosis

Preoperative care

- Gastric fluid volumes are independent of a history of barium study, preoperative nasogastric suction, and fasting interval
- Preoperative decompression of the stomach by a nasogastric tube does not guarantee evacuation of gastric fluid
- Correction of electrolyte disturbances should target a serum chloride >100 mEq/L and serum HCO_3^- <30 mEq/L

Intraoperative care

- Aspiration of gastric contents by insertion of a large (e.g. 14 Fr), multiorifice orogastric catheter prior to the induction of anesthesia is warranted for avoiding aspiration of gastric fluid
- Atropine may be administered prior to endotracheal intubation in neonates to prevent reflex bradycardia during laryngoscopy
- Awake endotracheal intubation is not superior to rapid sequence intubation (RSI) or modified RSI
- Classic RSI including cricoid pressure is controversial and there is little to no evidence-based medicine supporting the role of that in preventing gastric aspiration
- Inhalation induction maybe safe in children undergoing pyloromytomy
- Succinylcholine continues to be employed because of its rapid onset and short duration of action
- A small dose of rocuronium (0.3–0.45 mg/kg) can achieve neuromuscular blockade and a shorter duration, but the onset of neuromuscular blockade may be delayed
- Desflurane has shorter recovery times (first movement, tracheal extubation, etc.) compared with sevoflurane or isoflurane
- Desflurane or sevoflurane is better in terms of the risk of postoperative apnea than isoflurane
- Nitrous oxide has the potential for the expansion of bowel gas. Its use should be limited especially during laparoscopic procedures
- Postoperative analgesia can generally be achieved with a combination of infiltration of the surgical site with a local anesthetic agent and the use of a non-opioid agent such as acetaminophen or a non-steroidal anti-inflammatory agent
- During laparoscopic procedures, the intra-abdominal pressure should be limited to ≤10 mmHg
- There is no strong evidence that shows that regional anesthesia is superior to general anesthesia for pyloromyotomy

Postoperative care

- The majority of patients can be managed with non-opioid analgesic agents and infiltration of the surgical site with a local anesthetic agent
- Regional anesthesia can be employed to provide postoperative analgesia
- Acetaminophen maybe a safer analgesic than ketorolac for postoperative pain control
- Preterm infants <44–60 weeks' postgestational age should receive appropriate monitoring for postoperative apnea
- The risk of postoperative apnea in preterm infants maybe increased by anemia (hemoglobin <10 g/dL)

Source: Reproduced from Kamata et al. [90] with permission of John Wiley and Sons.

matter causes the obstruction. If edema reduces the arterial blood supply, necrosis and perforation of the appendix may occur.

Clinical presentation and diagnosis

The diagnosis of appendicitis is often challenging because the position of the appendix within the abdomen varies. Only half of all patients have the classic symptoms of anorexia and periumbilical pain plus nausea, vomiting, and right lower quadrant pain. About one-third of patients present with atypical symptoms or are unable to describe their symptoms. In children, this leads to a false-negative appendectomy rate of 5–25%. Examinations by CT scan with contrast or ultrasound reduce the false-negative rate. The differential diagnoses include gastroenteritis, tubo-ovarian processes, mesenteric adenitis, cholecystitis, diverticulitis, pelvic inflammatory disease, ureterolithiasis, and more. Appendicitis rarely occurs in neonates, and when it does occur the symptoms are virtually indistinguishable from necrotizing enterocolitis [99].

Management

Fluid resuscitation and administration of intravenous broad-spectrum antibiotics that cover enteric organisms are required. Patients with a ruptured appendix require antibiotics until their clinical condition improves. The clinical goal is to perform an appendectomy before the appendix ruptures and to prevent peritonitis, sepsis, and abscess formation. Immediate surgery is not necessary if the appendix is unruptured and the patient has been appropriately treated with antibiotics [100]. This approach, combined with or without an interval appendectomy, is gaining popularity in acute, uncomplicated appendicitis in children. The presence of an appendicolith is a risk factor for failure of antibiotic treatment [101]. In one study 46% of non-operatively managed patients had an appendectomy in the first year after the initial appendicitis [102].

Most appendectomies are done laparoscopically because the incisions are smaller, there are fewer wound infections, and the incidence of ileus is lower. Initial experience with laparoscopic appendectomy suggested a higher incidence of intra-abdominal abscesses, but later studies have not confirmed this.

Anesthetic management

Anesthetic management of children undergoing appendectomy is usually straightforward and includes general endotracheal anesthesia. Rapid sequence induction of anesthesia is used to avoid aspiration of gastric contents. If patients are septic and have a ruptured appendix, aggressive fluid resuscitation is often required. Surgical manipulation of an infected abdomen may induce acute hemodynamic deterioration. Ketorolac plus opioids, along with infiltration of local anesthetic at the port sites, is usually sufficient for postoperative analgesia after endoscopic surgery [103]. Transversus abdominal plane block with ultrasound guidance has also been described as an effective pain management strategy, which may be associated with reduced opioid dosing, fasting time, antiemetic use, and duration of hospital stay [104]. Patient-controlled analgesia is seldom required if the appendix was not ruptured.

KEY POINTS: APPENDICITIS

- Rapid sequence induction of anesthesia is usually required to reduce the risk of aspiration of gastric contents
- Beware of contrast material given as part of the evaluation for appendicitis
- Patients with a ruptured appendix may require additional fluid resuscitation

SPECIFIC INERVENTIONAL AND SURGICAL PROCEDURES

Gastrointestinal/endoscopic retrograde cholangiopanceatography/endoscopy procedures

Sedation is adequate for most endoscopic procedures in adults, but children usually require general anesthesia. Since many of the procedures are done in non-operating room locations, it is important that operating room standards be applied when anesthetizing patients in these locations. This includes preoperative evaluation, monitoring, postoperative care, and having help readily available in case a problem arises. Anesthesiologists must understand the technical aspects of endoscopic procedures, some of which require multiple switching of endoscopes during the procedure or ultrasound examinations, banding varices, obtaining biopsies, and other interventions. Occasionally, the endoscope completely compresses the trachea and/or tracheal tube of an infant and obstructs the airway. Excessive insufflation of gas at high pressures and overdistension of the stomach and bowel may interfere with ventilation. Insufflation pressures should be kept at a minimum, usually 12 cmH_2O. At the end of the procedure, the stomach should be suctioned to remove as much gas and secretions as possible. Inserting a rectal tube may aid gas removal. Where multiple instruments are to be inserted through the esophagus or when contrast material or other fluids will be given into the esophagus or stomach during the procedure, it is advisable to intubate the trachea and secure the airway [105].

Esophago-gastro-duodenoscopy

Indications for esophago-gastro-duodenoscopies include gastroesophageal reflux and sclerotherapy for esophageal varices. Most anesthesiologists use inhalational induction of anesthesia if the patient has mild to moderate gastroesophageal reflux disease. It is usually safer and easier to secure the airway of younger children with an endotracheal tube, but some older children can be managed with intravenous anesthesia and a natural airway.

Insertion of the endoscope into the esophagus is the most stimulating part of the procedure and requires the deepest plane of anesthesia when procedures are done with a natural airway. Anteflexion of the neck makes insertion of the endoscope easier. The oropharynx can be anesthetized with topical local anesthetics, but doing so may leave the child without protective airway reflexes after the procedure and increase the likelihood of coughing spells and/or aspiration of fluids.

Most esophago-gastro-duodenoscopies take only a few minutes. If general anesthesia and tracheal intubation are used, it is helpful to avoid the use of muscle relaxants and to administer short-acting opioids, such as remifentanil, for the induction and maintenance of anesthesia. Tracheally

intubated patients are usually placed in the supine position for esophago-gastro-duodenoscopies. Patients with eosinophilic esophagitis must undergo repeated esophago-gastro-duodenoscopies. They frequently have multiple food allergies, including to soy and eggs, which contraindicate the use of propofol. They may also have asthma and atopic dermatitis so histamine-releasing drugs should be avoided [106].

Endoscopic retrograde cholangiopancreatography

Endoscopic retrograde cholangiopancreatography (ERCP) is used for patients with choledocholithiasis, for stent placement across malignant or benign strictures, and for tissue sampling [107]. Tracheal intubation is usually required when children undergo ERCP because the procedure can be long, patients are in the semi-prone position, and the use of multiple endoscopes may be required. These patients are often in acute distress from acute cholestasis and cholecystitis; they may also be dehydrated from prolonged anorexia, nausea, and vomiting. Injection of incremental doses of glucagon may be required during the procedure to increase bile duct motility.

Percutaneous endoscopic gastrostomy

A percutaneous endoscopic gastrostomy (PEG) allows placement of a gastrostomy tube without the need for a laparotomy. PEGs are usually indicated for prolonged nutritional support or decompression of the stomach, although they may not effectively do the latter. Surgical access to the stomach is identical to that used during an esophago-gastro-duodenoscopy; some surgeons verify placement of the gastrostomy by doing a mini-laparoscopy to rule out having produced a gastrocolic fistula. PEG placement in children has an increased risk of complications compared with laparoscopic gastrostomy tube placement, particularly perforation of intestines, infection, and mechanical complications such as excessive leakage [108].

The underlying disease (cerebral palsy, metabolic disease, congenital malformations) dictates the anesthetic management. Patients who already have a PEG in place should have their stomach decompressed prior to and during induction of inhalational anesthesia. Venting the stomach requires the use of a specific venting tube; the tubes used for feeding do not effectively allow air to escape from the stomach.

Colonoscopy

Colonoscopies are usually done in children who have inflammatory bowel disease or lower intestinal bleeding. Bowel preparation is required and may cause dehydration and electrolyte imbalances. In older children tracheal intubation is often not required for this procedure.

KEY POINTS: GASTROINTESTINAL/ERCP/ENDOSCOPY PROCEDURES

- Standards for monitoring and patient care in off-site areas should be the same as those used in the operating room
- Secure the airway with an endotracheal tube in smaller children when the esophagus is being instrumented
- Specific tubes (not feeding tubes) are required to vent gas through a PEG

Nissen fundoplication and gastrostomy

Gastroesophageal reflux is, to a certain extent, a physiological mechanism. The most common symptoms of this disorder in children are vomiting and regurgitation, pulmonary symptoms, dysphagia, abdominal pain, and hemorrhage [109]. In severe cases, life-threatening aspiration of gastric contents may have occurred.

Fundoplication is indicated for patients who have documented gastroesophageal reflux and who fail medical treatment, have recurrent aspiration of gastric contents, intermittent apnea, failure to thrive, and Barrett esophagitis. Infants who have had life-threatening events and gastroesophageal reflux frequently present for a fundoplication after other causes for these problems have been ruled out. In one case series, the life-threatening events resolved in most patients after surgery [110]. Neurologically impaired children who require a gastrostomy tube for feeding may also require fundoplication to prevent aspiration of gastric contents [111]. The former practice of performing a "prophylactic" Nissen fundoplication in neurologically impaired patients undergoing gastrostomy has largely been abandoned because of lack of any demonstrable difference in reflux symptomatology and complications [112]. In fact, many surgeons rarely perform this operation because of its lack of effectiveness and a significant failure rate of the procedure.

During a Nissen fundoplication, the fundus of the stomach is plicated 360° around the inferior esophagus to restore lower esophageal sphincter function. Once this is done, the patient cannot vomit. The anterior or Thal fundoplication, on the other hand, uses only a 270° wrap, which maintains the patient's ability to vomit. Intestinal obstruction is common after the open approach [113]. Inability to vomit can cause progressive intestinal distension, bowel ischemia, and death if the bowel obstruction is not quickly relieved. Typically, patients requiring a fundoplication have other underlying diseases, such as cerebral palsy, inborn errors of metabolism, trisomy 21, or other neurological impairments. The procedure is done either open or laparoscopically, and if needed, a gastrostomy is placed at same time. If a gastrostomy is placed without doing a fundoplication, the percutaneous approach is usually used.

Management

Symptoms of aspiration pneumonia or asthma may make it difficult to determine when to perform the procedure. One has to balance protecting the lungs from further aspirations with being able to improve the patient's pulmonary status. Rapid sequence induction of anesthesia is usually warranted. The trachea of most patients can be extubated at the end of the procedure, depending on their preoperative status.

Postoperative issues

The reoperation rate following Nissen fundoplication for recurrent gastroesophageal reflux is high (6–12%) [114].

KEY POINTS: NISSEN FUNDOPLICATION AND GASTROSTOMY

- The primary disease often dictates the anesthetic management
- There is a high risk for aspiration of gastric contents during the induction of anesthesia

- Patients may present with a suboptimal pulmonary status due to aspiration pneumonia
- Patients who require a gastrostomy frequently have a Nissen fundoplication to protect against aspiration of gastric contents

Laparoscopic surgery

Laparoscopic procedures are rapidly replacing many open pediatric surgical procedures (Box 31.5). Some advantages of the laparoscopic approach include minimizing the size of the incision and better visualization of the surgical area (Fig. 31.9). The pathophysiological changes associated with a pneumoperitoneum, the longer operating times, mechanical restrictions for the surgeon, and lack of haptic feedback and three-dimensional vision are the main drawbacks of laparoscopic surgery. A number of procedures are done laparoscopically without proof that the outcomes are better than those reported with open procedures.

Laparoscopic abdominal procedures require intraperitoneal access and insufflation of gas, often through the umbilicus.

Box 31.5: Common pediatric laparoscopic procedures

- Appendectomy
- Cholecystectomy
- Gastric banding
- Gastric bypass
- Colectomy
- Inguinal hernia repair
- Nephrectomy
- Pyloromyotomy
- Congenital diaphragmatic hernia
- Nissen fundoplication
- Orchidopexy
- Pyloplasty

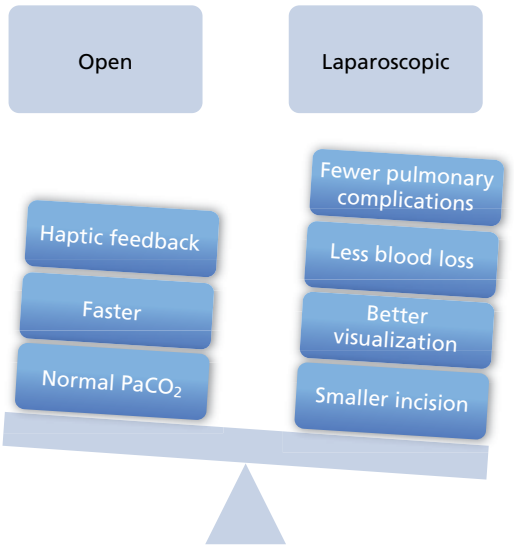

Figure 31.9 Advantages and disadvantages of open and laparoscopic procedures.

Usually, at least one additional incision is required for instrumentation, although single-port access through the umbilicus has been described for a variety of laparoscopic procedures, even in neonates and infants [115]. Various instruments are needed for ligation, stapling, suturing, and manipulation of viscera, but some are impractical for neonatal use because they are too large.

Pathophysiology

The effect of increased intra-abdominal pressure and absorption of the insufflated carbon dioxide are the two main pathophysiological changes associated with laparoscopic surgery.

Hemodynamic changes

Changes in cardiac output differ, depending on the patient's position during the procedure. Patients placed in the reverse Trendelenburg position, e.g. for laparoscopic cholecystectomy, often experience decreased arterial blood pressure, cardiac output, right atrial pressure, and wedge pressure. Pneumoperitoneum often raises the arterial, right atrial, and wedge pressures to their initial levels. Cardiac output also returns to baseline; systemic vascular resistance decreases mildly [116]. The reason why cardiac output normalizes is unclear, but it may be from reduced afterload or activation of the sympathetic nervous system by absorbed carbon dioxide. In the Trendelenburg position, cardiac output is unchanged or mildly increased from baseline during pneumoperitoneum. The increased intra-abdominal pressure and gravity synergistically reduce cardiac filling.

Changes in arterial blood pressure and pulmonary vascular resistance are independent of the patient's position during laparoscopy. Systemic vascular resistance (SVR) and arterial blood pressure increase. The combination of tachycardia and an elevated SVR raises myocardial oxygen consumption. Insufflation pressures below 10 cmH_2O have no significant effect on heart rate, arterial blood pressure, oxygen saturation, or base excess in children [117]. Absorbed carbon dioxide partially alleviates the effects of the increased intra-abdominal pressure. However, increased intra-abdominal pressure may also transiently reduce renal and splanchnic blood flow. Congestion and stasis of the lower extremities increase the risk for deep vein thrombosis. If there is a patent foramen ovale, the likelihood of paradoxical emboli and air embolism increases when the right atrial pressure rises. Peritoneal stretching may also produce vagally mediated hemodynamic changes.

Absorption of insufflated carbon dioxide

Carbon dioxide is absorbed from the abdominal cavity and causes respiratory acidosis and cardiac arrhythmias (in some patients). The rate of CO_2 absorption is higher when artificial cavities are created (e.g. nephrectomy) [118]. The rate of CO_2 absorption is very high when subcutaneous emphysema is present. Minute ventilation may need to increase as much as 400% to eliminate the insufflated CO_2 [119]. Occasionally, the increase in ventilation is insufficient to reduce the $PaCO_2$ to acceptable levels. When this occurs, the procedure must be halted and time allowed for return of the $PaCO_2$ to normal. It is rarely necessary to convert to an open procedure because of hypercarbia.

Pulmonary pathophysiology

The usual anesthesia-induced decrease in functional residual capacity and the mismatch of ventilation and perfusion are

aggravated by a further decrease in the functional residual capacity as the diaphragm is shifted more cephalad by the pneumoperitoneum. Due to the geometry of the infant's thorax (see Chapter 7), infants rely more on diaphragmatic excursion than on the intercostal muscles for ventilation. Positive end-expiratory pressure counteracts gas-induced pressure on the diaphragm and often improves ventilation and oxygenation. The tip of the tracheal tube can migrate towards the carina and enter a mainstem bronchus when a pneumoperitoneum is present [120].

Despite the negative intraoperative effects of the pneumoperitoneum, there are fewer postoperative pulmonary complications after laparoscopy than with conventional open procedures. On the other hand, the open approach for upper abdominal procedures decreases the vital capacity, forced expiratory volume in 1 s (FEV_1), and functional residual capacity. These decreases, plus the incisional pain, inhibit coughing and sighing. Laparoscopic cholecystectomy is less often associated with postoperative pneumonia [121,122].

Neuroendocrine effects

Surgical-induced inflammatory and immunosuppression responses are fewer with laparoscopic procedures. The concentrations of interleukin-1 and -6 and TNF-α are decreased compared with those found after open procedures. Dysfunction of mononuclear and polymorphonuclear cells, which are part of cell-mediated immunity, appears to be less deranged by laparoscopic procedures. The inflammatory effects are of concern with oncological procedures because tumor spread is a major concern.

Complications

Serious laparoscopy-related complications are rare. CO_2 is the gas used most often because it is more rapidly absorbed if it is inadvertently given intravascularly. Massive CO_2 embolism and venous air embolism produce the same sequelae [123]. Untreated pneumothoraces and pneumomediastina can be disastrous. Subcutaneous emphysema usually requires no treatment. CO_2-induced hypercarbia and acidosis occasionally cause cardiac dysrhythmias. Insertion of a trocar occasionally causes hemorrhage and injures internal organs, especially in thinner infants with more elastic abdominal walls [124]. Studies of three-dimensional laparoscopy (which allows the surgeon to have a three-dimensional view of the operative field) showed shorter operating times, but otherwise similar outcomes [125].

KEY POINTS: LAPAROSCOPIC SURGERY

- Intravenous access should be obtained above the diaphragm because a pneumoperitoneum can decrease blood flow through the inferior vena cava and delay drug and fluid administration
- Filling pressures are higher during a pneumoperitoneum because the increased intra-abdominal pressure is transmitted in the thorax. Effective transmural pressures are low to normal
- Changes in cardiac output are dependent on the patient's position
- Urine output decreases transiently
- Not all patients tolerate a pneumoperitoneum with high insufflation pressures

CASE STUDY

An 8-month-old, 10 kg child was brought to the emergency room with a history of loss of appetite, vomiting, irritability, and crying. His mother stated that he had diarrhea for the last 2 days and that his stools were initially watery but were now mucoid and blood tinged at the last diaper change. Only a minimal amount of urine had been noted during the last 8–12 h. The mother also stated that the child was no longer interactive and had become progressively lethargic during the last 2 days.

The emergency room physician saw the mother and child and obtained the following history. The boy was born at full term by normal vaginal delivery; there were no problems before or after birth. He went to the well baby nursery and was discharged home with the mother 24 h later. At home, the baby was feeding well and received his normal immunizations. He was well until 2 days before admission when he became increasingly irritable and had vomiting and diarrhea.

At admission he was found to be lethargic and had a sunken anterior fontanelle, sunken eyes, and dry oral mucous membranes. His heart rate was 160 beats/min, his arterial blood pressure was 80/40 mmHg, and his SaO_2 was 99% on room air. His abdomen was distended, and there was abdominal tenderness and guarding. An abdominal mass was palpated. A peripheral intravenous catheter was inserted and 5% dextrose with 0.45% normal saline was infused at 60 mL/h. Blood was sent for complete blood count and chemistry. Plain radiographs of the abdomen showed a paucity of bowel gas and air–fluid levels. The white cell count was 18,000 mm^3, the hematocrit 40%, and the platelet count 400,000 mm^3. The serum sodium was 138 mEq/L, serum potassium 4.5 mEq/L, serum chloride 100 mEq/L, serum bicarbonate 20 mmol/L, and the blood urea nitrogen and creatinine 20 and 0.5 mg/dL respectively. A surgery consult was obtained and a nasogastric tube was inserted. The surgeon entertained a differential diagnosis of bowel obstruction or intussusception and scheduled the child for an emergency exploratory laparotomy.

The anesthesiologist reviewed the patient's history with the mother and examined the child. The child was lethargic. Fluids were infusing through a peripheral intravenous line. After obtaining informed consent, the child was taken to the operating room. Rapid sequence induction of general anesthesia and tracheal intubation were planned. Standard monitors were placed, and suction was applied to the nasogastric tube. After preoxygenation, anesthesia was induced with

2 mg/kg of propofol and 1.2 mg/kg of rocuronium. Tracheal intubation was rapidly accomplished. A second peripheral intravenous line, an arterial line, and a Foley catheter were inserted. Anesthesia was maintained with sevoflurane and intravenous fentanyl. The patient was found to have an ileocolic intussusception, which was easily reduced; however, part of the bowel was ischemic and required resection. Intraoperatively, the patient required additional fluid resuscitation with a crystalloid solution. Blood loss was minimal and no blood transfusion was required.

At the end of the surgery, the trachea was extubated and the child was transferred to the intensive care unit. His postoperative pain was controlled with a continuous infusion of morphine and nurse-administered rescue boluses of the drug as needed.

This case illustrates the concepts that were explained in this chapter. Intussusception is a common cause of bowel obstruction in children less than 1 year of age, but the cause of intussusception is unknown in 90% of cases. Prompt diagnosis and treatment decrease the mortality and morbidity associated with intussusception. Preoperative assessment should include signs of dehydration, such as dry mucosal membranes, sunken fontanelles, sunken eyes, and minimal urine output, which together indicate significant dehydration. Fluid resuscitation should be initiated immediately to replete the intravascular volume. When the volume is repleted, surgery can proceed. Intraoperatively, the heart rate and arterial blood pressure may not truly reflect the patient's volume status. The urine output should exceed 0.5–1 mL/kg/h; urine output is a useful guide to circulating volume status. Careful fluid management is essential. The volume of fluid administered equals the sum of hourly maintenance fluid, pre-existing fluid deficits, plus an additional 6–10 mL/kg/h to compensate for the evaporative losses caused by the open abdominal wound.

Hourly fluid maintenance is calculated from the patient's bodyweight (see Chapter 9). For the first 10 kg, it is 4 mL/kg. For 10–20 kg it is 40 mL + 2 mL/kg for every kilogram over 10 kg. If the weight is >20 kg, the requirement is 60 mL + 1 mL/kg for every kilogram above 20 kg. Careful attention must be paid to blood loss. If significant blood loss is expected, the allowable blood loss should be calculated. Maximum allowable blood loss is:

$$\frac{\text{EBV} \times (\text{Starting hematocrit} - \text{Minimum acceptable hematocrit})}{\text{Starting hematocrit}}$$

Estimated blood volume (EBV) is 95 mL/kg for premature neonates, 85 mL/kg for term neonates, 70–75 mL/kg for infants and young children, and 65 mL/kg for older children and adults. The volume of packed red blood cells to be transfused can be determined by the following formula:

$$\frac{\text{EBV} \times (\text{Goal hematocrit} - \text{Current hematocrit})}{\text{Hematocrit of packed red blood cells}}$$

When blood products are used in neonates and infants, they must be filtered and irradiated to prevent emboli and graft-versus-host reactions. Normothermia is maintained by warming the operating room and the intravenous fluids, using warm irrigation fluids, and forced-air convention heating devices. Maintaining normothermia may be difficult during abdominal surgery because the bowels are exposed.

The postoperative decision to extubate the trachea depends on how awake the child is, whether he is breathing spontaneously after the reversal of muscle relaxants, and his core temperature. Intravenous fluids are continued until oral intake is re-established.

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 32
Anesthesia for Pediatric Urological Procedures

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Introduction

Pediatric urological procedures are among the most common encountered by the pediatric anesthesiologist. A thorough understanding of the developmental pathogenesis and surgical procedures on the genitourinary system are important for the anesthesiologist to provide optimized care for these patients. This chapter reviews the embryological development of the common urogenital anomalies. Then the surgical approach, anesthetic considerations, and anesthetic management of these anomalies, including pain management, will be reviewed. In addition, robotic approaches to urological surgery will be explored.

Development of urological anomalies

Anomalies of the genitourinary system that require surgical procedures under anesthesia often arise from abnormal development *in utero*. A full description of the development of the genitourinary system is beyond the scope of this chapter. See Chapter 9 for further discussion of the development of the genitourinatry system. It is helpful to have a brief overview recalling that the urinary and genital systems are closely associated. Normal development is influenced by genetic, hormonal, and anatomical influences.

Both the urinary and genital systems develop from intermediate mesoderm at the level of the 7th through the 28th somite [1]. The nephrogenic mass (cord) arises from the dorsal side from a bulge into the coelom called the urogenital ridge, from which the urinary and genital structures are formed. The nephrogenic tissue from the 7–14th somite levels breaks up into four segments: the cervical, thoracic, lumbar, and sacral. The cervical nephrotomes eventually give rise to glomeruli. The excretory tubules arise from the thoracic, lumbar, and sacral segments. Subsequent development leads to the primitive pronephros. By the 4th week of gestation, the mesonephros is present as an intermediate step in renal development. By around week 10, the mesoneprhos has receded in females, while evolving into the vas deferens in males. The permanent kidney or metanephros begins to develop early in the 5th week and is functional by the 11th week of development. The metanephric blastema gives rise to nephrons including the Bowman capsule, proximal convoluted tubules, loops of Henle, and distal tubules. The ureters are an outgrowth of the primitive mesonephric duct forming the major and minor calices and collecting ducts. The terminal end of each ureter becomes part of the bladder wall. Each eventually develops a distinct separate entrance into the bladder with time. Normal development of the ureteric bud and the mesonephric blastema is closely dependent on each other. As the fetus grows, the kidneys migrate from the pelvis to the abdomen. Fetal urine production is critical to normal amniotic fluid circulation. Amniotic fluid is aspirated by the fetus, and absorbed into the fetal bloodstream and subsequently excreted into the amniotic sac. Failure to produce adequate amounts of urine can lead to oligohydramnios and associated anomalies. One significant anomaly associated with oligohydramnios is pulmonary hypoplasia.

Development of the external genitourinary system occurs in parallel to internal development. The cloaca (Latin for sewer) forms from the caudal end of the hindgut. The allantois and mesonephric ducts open into the cloaca. During weeks 4 to 7 of development, the cloaca subdivides into the posterior portion, which becomes the anorectal canal, and the anterior portion, which gives rise to the primitive urogenital sinus. The bladder is formed from the upper part of the primitive urogenital sinus. Initially, the bladder is continuous with the allantois; subsequent obliteration of the allantois lumen forms the urachus, which connects the apex of the bladder with the umbilicus. The urachus eventually becomes the median umbilical ligament.

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

The reproductive system makes its appearance during the 5th and 6th weeks of development. The fetus goes through an indifferent stage in which sex cannot be determined. Eventually, gonads (testes and ovaries) develop from a thickening of the urogenital ridge to form the gonadal ridge and primordial germ cells. Primary sex cords form and grow into the underlying mesenchyme. If the *SRY* gene is present (normal genetic male), differentiation will proceed along the path leading to testes. Absence of *SRY* gene expression (normal genetic female) will lead to development of ovaries. Development of external genitalia is determined by both genetic and hormonal factors. In the presence of normal testes, androgen production by the adrenal glands is required to stimulate the development of the mesonephric ducts and produce normal external male genitalia. In the absence of normal androgens, paramesophric ducts develop and the fetus will develop female external genitalia. External genital development first goes through the indifferent stage with the genital tubercle forming at the upper end of the cloacal membrane. In the male, this tubercle then elongates to form the phallus. Labioscrotal swellings and urogenital folds appear around this time. The cloacal membrane divides to form urogenital and anal openings around the 7th week.

In the male, the phallus elongates to form the penis, pulling the urogenital folds together. When the folds start to fuse, they enclose the urethra and the urethral opening moves progressively towards the end of the penis. The labioscrotal swellings fuse to form the scrotum. In the female, the phallus becomes the clitoris. The urogenital folds do not fuse, and become the labia minora. The labioscrotal folds fuse only at the ends to form the labia majora.

Anomalies of gonadal development can be divided into anomalies of sex chromosomes, true hermaphrodites, and anomalies of receptors. Conditions that represent anomalies of sex chromosomes include Turner syndrome (45,X), Klinefelter syndrome (47,XXY), and other syndromes with multiple X polyploidy. True hermaphrodites are extremely rare and have both true testes and ovaries. Anomalies of receptors result in testicular feminization syndrome (XY females). Congenital anomalies of the reproductive system in females include ovarian dysgenesis, rudimentary uterus, bifid uterus, septate uterus, and imperforate hymen. Congenital anomalies in males include testicular agenesis, undescended testes, and hypospadias.

KEY POINTS: DEVELOPMENT OF UROLOGICAL ABNORMALITIES

- Anomalies of the genitourinary system often arise from abnormal development *in utero* and often require surgical repair
- The genitourinary system is determined by both genetic and hormonal factors

Bladder exstrophy

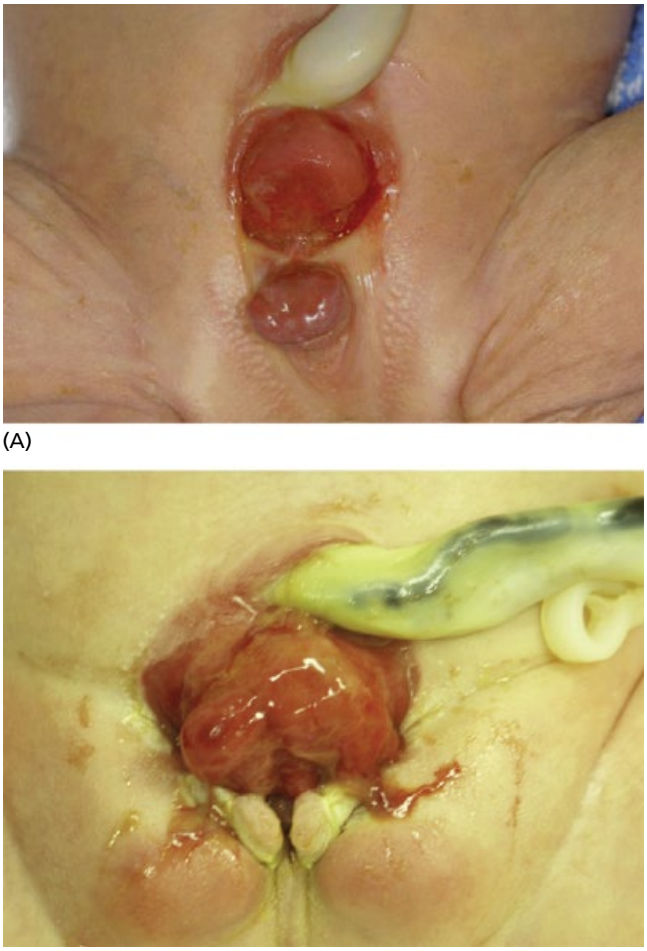
Bladder exstrophy remains one of the most challenging conditions managed by pediatric urologists. It can be likened to the challenges the cardiovascular surgeon faces with repair of the single ventricle. Although rare, this disorder imposes significant physical, functional, social, sexual, and psychological burdens on patients and families. For the healthcare system, the multiple, lengthy, and complex operative procedures for exstrophy consume resources disproportionate to the small number of affected individuals [2]. The rarity of this condition (2.5 in 100,000 livebirths in the United States) makes it imperative that communication between the anesthesiologist and urologist occurs well before the start of surgery. The correction choices and timing for surgery are continually being modified. While it was standard practice to perform surgery in the first several days of life, in some institutions surgeries are being delayed until the child is 4–6 weeks of age with no change in the success rate [3].

The goals of reconstructive surgery for bladder exstrophy are to achieve closure of the bladder, obtain urinary continence, preserve renal function, and produce satisfactory appearance and function of the external genitalia. Wound dehiscence, bladder prolapse, and multiple attempts at bladder closure have been identified as risk factors for lack of adequate bladder growth and inability to develop urine continence [4].

Classic bladder exstrophy can be conceptualized by visualizing one blade of a pair of scissors passing through the urethra into the bladder of a normal person; the other blade is used to cut the layers of the skin, abdominal wall, anterior wall of the bladder, urethra, and symphysis pubis, and the cut edges are unfolded laterally as if opening a book (Fig. 32.1) [5,6]. At birth, classic bladder exstrophy presents with an everted posterior bladder wall of varying size associated with separation of the symphysis pubis. This diastasis causes an outward rotation and eversion of the pubic rami at their junctions with the ischial and iliac bones [5,6]. Urine may be seen leaking from the inferior margin of the everted posterior bladder wall, but the ureteral orifices are not always obvious. The umbilicus is located on the immediate superior border of the bladder plate, and a small umbilical hernia or an omphalocele is ordinarily seen. The mucosa of the exposed bladder may look normal or thickened. In males, there is complete epispadias with dorsal chordee, and the overall penile length is approximately half of unaffected boys. The scrotum is typically separated from the penis and is wide and shallow. Undescended testes and inguinal hernias are common. Females also have epispadias, with separation of the two halves of the clitoris and wide separation of the labia. The anus is displaced anteriorly in both sexes, and there may be rectal prolapse [5–7].

In patients with classic exstrophy of the bladder, anomalous development in other systems is unusual. However, bladder exstrophy can be considered a spectrum of anatomical variants referred to as the exstrophy complex. These variants include bladder exstrophy with imperforate anus and cloacal exstrophy. With extreme cases of classic bladder exstrophy and cloacal exstrophy, omphaloceles are also encountered above the level of the exposed bladder. In cloacal exstrophy, some form of spinal dysraphism including tethered cord, myelomeningocele, or lipomyelomeningocele is present in nearly all patients, with recent reports ranging from 64% to 100% [8].

Two options have been described for surgical reconstruction: primary single-staged closure of the bladder or a planned staged repair [9–13]. Regardless of the strategy chosen, failure of the initial repair decreases the potential for the later



(A)

(B)

Figure 32.1 Features of classic bladder exstrophy (A, male; B, female): low umbilicus, exposed small bladder and bladder neck, pubis diastasis, rectus and pelvic floor divarication, anterior ectopia of the anus and/or vagina, and epispadias or bifid clitoris.

Figure 32.2 Modified Buck's traction. The child is positioned with weights maintaining the legs in an extended position parallel to the bed. *Source*: Reproduced from Kozlowski [14] with permission of Elsevier.

development of continence. Also, in each option, pelvic osteotomies are often used to allow approximation of the pubic symphysis. Modified Buck traction is often required after surgery for 4–8 weeks (Fig. 32.2) [14]. In a recently reported, large, single-center series, 67 infants with bladder exstrophy were treated; of 26 infants undergoing primary neonatal repair in the early years of the series, 21 were successful, and five had further operations for lack of healing or bladder dehiscence [6]. In the later years of the series, 41 had staged repair, with all achieving primary healing without would dehiscence. Because urinary tract infection (UTI) and renal scarring can result from the vesicoureteral reflux that is commonly present in these patients, this group now performs ureteral reimplantation at the time of the primary bladder closure, which has improved the rate of UTI.

Preoperative preparation involves an assessment of all organ systems to ensure that there are no associated anomalies of physiological significance. Preoperative complete blood count, and type and cross are recommended especially if pelvic osteotomies are necessary. Appropriate measures are taken to avoid trauma to the exposed bladder mucosa. Antibiotics are administered preoperatively and continued after surgery. The procedure involves a long operating time (5–7 h) and unpredictable bleeding and fluid shifts after intravenous induction of anesthesia and endotracheal intubation [15]. Therefore, two intravenous catheters should be placed in the upper extremities if possible, to avoid the sterile field. Central venous access may be necessary if peripheral venous access is difficult. An arterial line is also placed for both hemodynamic monitoring and measurement of blood gases, hemoglobin, coagulation studies, electrolytes, and glucose.

Preoperative placement of an epidural catheter is helpful for intraoperative and postoperative pain management (Fig. 32.3) [4]. The sacrococcygeal ligament is punctured, and an epidural catheter is threaded through the epidural insertion needle to reach a thoracic dermatome level of T10–12. The tunneling needle (a 17- or 18-gauge styletted Crawford or Tuohy needle) is inserted on the patient's side, near the posterior superior iliac crest. This is the final exit position and should be visible when the child is supine so that the site can be easily inspected in the postoperative period. The tunneling needle emerges at the epidural needle insertion. Note the epidural insertion needle is not removed and is left in place to protect the catheter. An 11 scalpel blade cuts the residual skin and subcutaneous tissue bridge between the two needles. The epidural insertion needle is removed leaving the catheter in place, depicted as a dashed line (Fig. 32.3D). The stylet from the tunneling needle is removed and the distal end of the epidural catheter is thread into the tunneling needle. The tunneling needle is then removed. The primary insertion site and the final catheter exit site are secured with Steri-strips and covered with transparent adhesive dressings. A loop is placed in the catheter to prevent accidental dislodgment [4].

At the time of surgery, the patient should have a wide surgical preparation, including the entire body anteriorly and posteriorly below the level of the nipples, so that turning the child for surgical orientation does not lead to wound contamination [5]. Timing of the removal of the endotracheal tube after surgery depends on the infant's age, the length and complexity of surgery, and the amount of fluid and blood the patient received during surgery.

In the postoperative period, it is imperative that the baby remain immobilized, sedated, and pain free to prevent movement that would cause distracting forces to compromise the repair. The tunneled epidural catheter is extremely useful in this situation. Epidural infusions through tunneled epidural catheters can provide safe analgesia for up to a month in

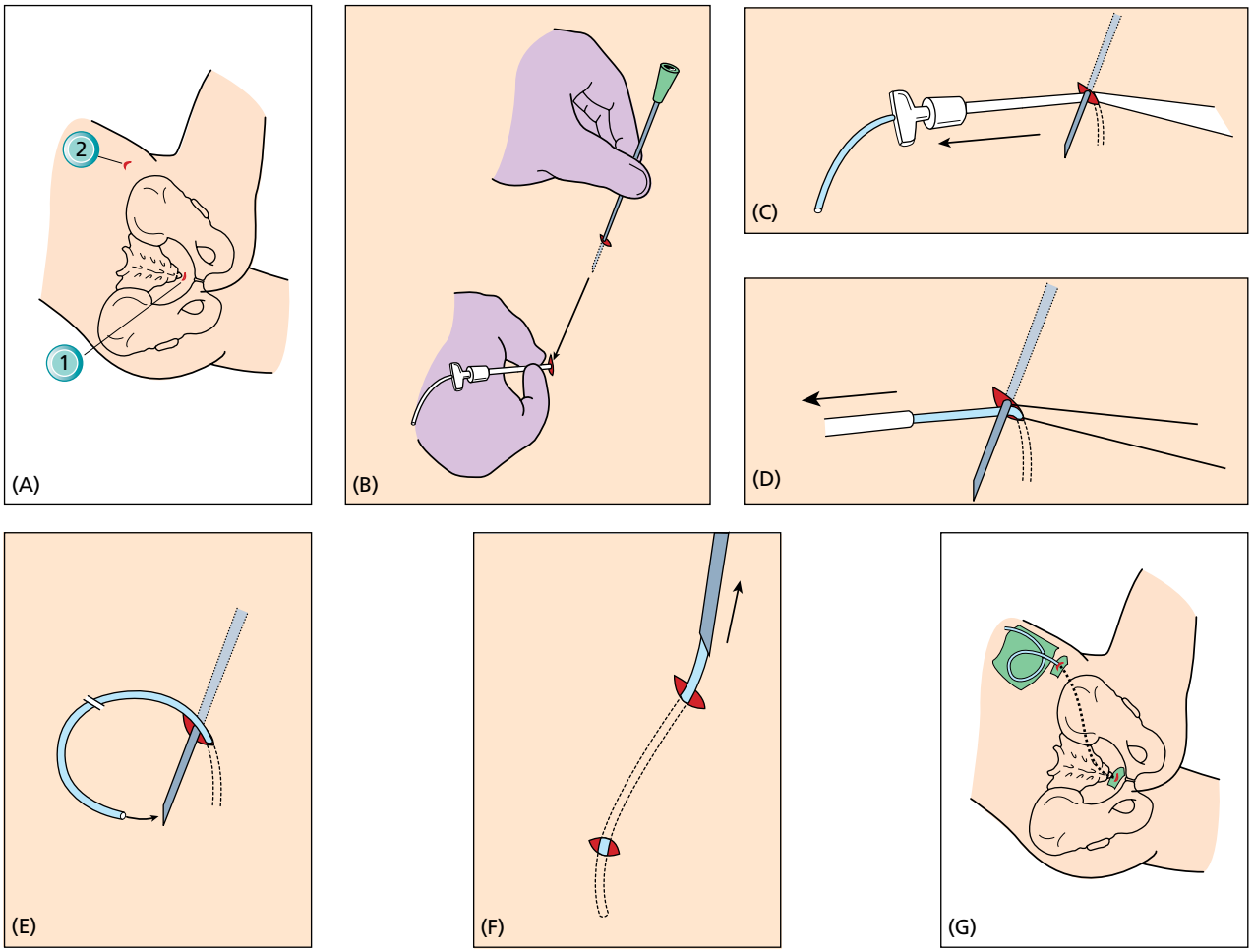


Figure 32.3 Placement of a tunneled caudal epidural catheter. (A) The sacorcoccygeal ligament is punctured at position 1, and then an epidural catheter (approximately 6–10 cm) is threaded through the epidural insertion needle to reach a thoracic dermatomal level of T10–12. (B) The tunneling needle (a 17 or 18 gauge styletted Crawford of Tuohy needle) is inserted on the patient's side, near the posterior superior iliac crest (positon 2 in A). This is the final exit position and should be visible when the child is supine so the the site can be easily inpected. (C) The tunneling needle emerges at the epidural needle insertion (position 1). Note the epidural insertion needle is not removed and is left in place to protect the catheter. An 11 scalpel blade cuts the resididual skin and subcutaneous tissue bridge between the two needles. (D) The epidural insertion needle is removed leaving the caatheter in place, depicted as a dashed line. (E) The stylette from the tunneling needle is removed and the distal end of the epidural cahtered is threaded into the tunneling needle (F). The tunneling needle is removed; the subcutaneous portion of the epidural catheter is depicted with a dashed line. (G) The primary insertion site and the final catheter exit site are secured with adhesive strips and covered with a transparent adhesive dressing. A loop is placed in the catheter to prevent accidental dislodgment. *Source*: Reproduced from Kost-Byerly et al [4] with permission of Elsevier.

neonates. Daily communication between pediatric urology and intensive care unit (ICU) staff, the pediatric pain service, and experienced nursing staff are the prerequisites to providing analgesia and sedation without undue complications for a neonatal population [4,14].

KEY POINTS: BLADDER EXSTROPHY

- Bladder exstrophy imposes significant physical, functional, social, sexual, and psychological burdens on patients and families and a significant burden on the healthcare system despite a small patient population
- Goals of reconstructive surgery are both functional and cosmetic
- Anesthetic considerations involve both postoperative pain control and intraoperative fluid shifts, blood loss, and long operating times

Posterior urethral valves

The most common cause of severe obstructive uropathy in children is posterior urethral valves (PUV). The urethral valves are tissue leaflets fanning distally from the prostatic urethra to the external urinary sphincter. A slit-like opening usually separates the leaflets. Valves are of unclear embryological origin and cause varying degrees of obstruction. The renal changes range from mild hydronephrosis to severe renal dysplasia; their severity probably depends on the severity of the obstruction and its time of onset during fetal development. As in other cases of obstruction or renal dysplasia, there may be oligohydramnios and pulmonary hypoplasia [16].

If the serum creatinine level remains normal or returns to normal after birth without intervention, treatment consists of transurethral ablation of the valve leaflets, which is performed endoscopically under general anesthesia. If the urethra is too small for transurethral ablation, temporary vesicostomy is preferred, in which the dome of the bladder is exteriorized on

the lower abdominal wall. When the child is older, the valves may be ablated and the vesicostomy closed [17].

There are several classifications of this disorder, based on the type and severity of obstruction. The spectrum of abnormalities may represent the different degrees of obstruction, the timing of obstruction, and other genotypic risk factors. Mild obstruction may have a delayed presentation until adolescence. It appears that a partial outlet obstruction can be overcome with bladder wall hypertrophy that generates high voiding pressures [16,17].

An infant with severe PUV may present in the neonatal nursery with anuria and a palpable bladder. The clinical sequelae from PUV result in persistent bilateral hydronephrosis, either from vesicoureteral reflux (VUR) or elevated bladder pressures [17]. When a newborn's condition is especially severe, with associated lung hypoplasia, serial percutaneous needle bladder drainage may be undertaken to decompress the bladder until the newborn is optimized to have surgical repair.

After the diagnosis is established, renal function and the anatomy of the upper urinary tract should be carefully evaluated. In the healthy neonate, a small polyethylene feeding tube (5 or 8 Fr) is inserted through the urethra into the bladder for several days. Passing the feeding tube may be difficult, because the tube tip may coil in the prostatic urethra causing urine to drain around the catheter rather than through it. A Foley (balloon) catheter should not be used, because the balloon may cause severe bladder spasm, which may produce severe ureteral obstruction [18].

Posterior urethral valves are now commonly diagnosed in the antenatal period. The ultrasound findings may include bilateral hydronephrosis, a distended thick-walled bladder, and oligohydramnios [17]. The incidence of PUV is one in 5000 livebirths. Of the 500 new cases of PUV each year, 150 will develop end-stage renal disease (ESRD) and require dialysis or transplantation in the first 18 years of life. Some institutions perform *in utero* interventions. Experimental and clinical evidence of the possible benefits of fetal intervention is lacking, and few affected fetuses are candidates. Prenatal diagnosis of PUV, particularly when discovered in the second trimester, is associated with a poorer prognosis than those detected after birth [18]. While antenatal intervention improves pulmonary function and the restoration of amniotic fluid volume, it does not guarantee an improvement in the renal insufficiency [16,17].

The appropriate treatment of PUV is determined by examining all contributing factors. These include the overall condition of the infant, renal function, hydration status, and lung maturity [17]. Prophylactic antibiotics are started at birth and the bladder may need decompression. Valve ablation may be undertaken if the creatinine falls to less than 1 mg/dL. When the renal function does not continue to improve, usually a vesicostomy is performed as the initial step to decompress the kidneys. Most boys have a good prognosis if they complete a normal gestation and undergo neonatal valve incision.

These patients may present in the neonatal period for PUV incision and also for circumcision which may decrease the rate of UTIs [17]. In the very small infant where the cystoscope will not pass through the urethra, a vesicostomy may be considered, with delayed valve incisions.

These infants may also have some degree of respiratory compromise, relating to the oliguria [18]. It is thought that the urinary obstruction and lack of urine production *in utero* limits the amount of fluid the fetus then aspirates, which helps to stent open the developing lungs. In turn, this leads to pulmonary hypoplasia and respiratory distress syndrome [19]. An appropriate volume of amniotic fluid, which is produced by the kidneys and then excreted as urine, is necessary for the complete and proper branching of the bronchial tree and alveoli. Physical findings can include poor fetal breathing movements, small chest cavity, ascites, limb deformities from compression, and Potter facies [16]. Potter facies develops *in utero* secondary to the effects of oligohydramnios from any cause. Features include micrognathia, hypertelorism, pulmonary hypoplasia, and spade-like hands [20]. Neonates with pulmonary hypoplasia may require perioperative mechanical ventilation. These patients may require high peak pressures, and permissive hypercapnia must be tolerated. The severe patient may even require an oscillating ventilator until the lungs mature further.

The preoperative evaluation of a neonate with PUV should include assessment of renal function including the extent of urinary retention and fluid overload. Appropriate laboratory testing should search for evidence of renal failure. Hyponatremia, azotemia, hypertension, and hyperkalemia must be identified and treated prior to anesthetizing the patient. Patients in renal failure must be treated with appropriate fluid management and judicious use of anesthetic agents affected by renal metabolism.

When PUV cause mild obstruction, the associated complications are also mild or non-existent. The length of surgical intervention is generally less than 1 h, and the anesthetic approach includes general anesthesia with endotracheal intubation or laryngeal mask airway (LMA) for airway management. Postoperative pain is minor for cystoscopy and valve ablation.

Long-term results after surgical repair for PUV vary. Late development of renal failure can present if the following risk factors are present: bilateral VUR, presentation in the first year of life, and diurnal incontinence at 5 years of age [21]. This may result in the need for renal transplantation. Other possible long-term outcomes that may be influenced by PUV repair are sexual function and fertility and urinary continence [21].

KEY POINTS: POSTERIOR URETHRAL VALVES

- The most common cause of severe obstructive uropathy in children is PUV and this may develop into significant renal failure
- Mild obstruction may not present until adolescence; when severe it presents in the first day of life with anuria, palpable bladder, and significant lung hypoplasia
- The appropriate treatment of PUV is determined by examining all contributing factors and may involve long-term antibiotics, decompression of the bladder, vesicostomy placement, and definitive surgical repair

Circumcision

Circumcision is the most commonly performed surgical procedure in the world. There are very few absolute indications for circumcision, especially in the neonate. The American Academy of Pediatrics does not recommend routine circumcision in otherwise healthy boys. In this age group, if hydronephrosis is present, then a circumcision may help decrease the likelihood of UTIs [17]. In older children, persistent phimosis and recurrent balanitis are indications for circumcision [17].

Newborn circumcisions are most often done at the bedside or as outpatients with a Plastibell device or Gomco clamp. These procedures are usually performed by the pediatrician or obstetrician while the infant is still in the newborn nursery. Circumcision in older children usually requires freehand sleeve resection performed under general anesthesia. Common surgical complications of circumcision include bleeding, infection, residual redundant skin, meatal stenosis, and skin bridges [22].

When infants and children require general anesthesia, anesthesia usually is induced via inhalational induction, a peripheral intravenous line is placed, and the airway is secured with an LMA or endotracheal tube. A penile nerve block placed prior to incision is effective in providing intraoperative analgesia and postoperative pain relief [23]. Although caudal epidural anesthesia can be used for analgesia, penile block is usually preferred because less local anesthetic is given and less time is spent performing that block [24]. Many urologists delay this typically elective procedure until the patient is 6 months of age to decrease anesthetic risks and eliminate the need for an overnight stay.

KEY POINTS: CIRCUMCISION

- In spite of circumcisions being one of the most commonly performed surgical procedure in the world, there are very few absolute indications for circumcision
- This is generally an elective procedure in an otherwise healthy population and is completed with a straightforward general anesthestic

Hypospadias

Hypospadias is the abnormal ventral opening of the urethral meatus, which results from incomplete development of the urethra. This defect may be located anywhere from the corona of the glans to the perineum [24]. Therefore, the extent of surgical dissection and the staging of the repair depend on the complexity of the lesion [25]. Hypospadias is often discovered during or after a routine neonatal circumcision. Signs of hypospadias include an abnormal prepuce, a persistent ventral curvature (also known as chordee), and a proximally displaced urethral orifice that is rarely obstructive, but often stenotic [17]. The meatus is located on the glans or distal shaft in 70–80% of cases and in the middle of the shaft 20–30% of the time [17]. Rarely, the meatus is located in the scrotum or more proximally in the perineum.

Hypospadias can be associated with inguinal hernias, cryptorchidism, and low birthweight. The incidence of hypospadias is higher in patients with affected siblings [26].

Early repair of this defect is important for aesthetic considerations and toilet training, and also for long-term psychosexual adjustment [25]. Skilled pediatric urologists perform this repair in healthy term babies as early as 3 months of age. Delaying the repair past 15 months may increase cognitive, emotional, behavioral, and psychosexual issues. In addition, younger infants may develop less scar tissue and have better wound healing than older children [17].

The goals of repair are straightening the ventral curvature and extending the urethra distally. Historically, these operations were done as staged procedures. Currently, the majority are done as one procedure, unless severe. Surgery may be staged if the penis has a curvature greater than 30°. A buccal graft may be needed for tubularization of the neourethra during the second stage, which occurs approximately 6 months later [17]. A recent review of several large series of proximal hypospadias repairs reported complications in 32–68% of patients, including fistulas, diverticulum, meatal stenosis, and glans dehiscience [27]. The complication rate was higher with single-stage repair for proximal hypospadias. Complication rates for distal hypospadias repairs are much lower, at 5–15%.

These patients are usually otherwise healthy. General anesthesia with an LMA and supplemental caudal anesthesia or a penile block is the most common approach. Postoperative urethral instrumentation must be avoided as catheterization of the newly formed urethra could cause disruption of the repair. These patients often have a urethral catheter left in place postoperatively, to allow passive urine drainage through the neourethra for approximately 1 week [17]. The penis is gently compressed with a Telfa® pad and bio-occlusive dressing following the procedure. Complications can include fistulas, meatal stenosis, urethral stricture, dehiscence, and recurrent curvature [17].

Recently, concerns have arisen about a possible increased rate of postoperative urethrocutaneous fistula development with caudal analgesia compared with penile nerve block. The postulated mechanism is increased blood flow leading to penile engorgement with tension on the suture lines, resulting in suboptimal healing and fistula formation. A prospective, randomized study of penile block versus caudal analgesia in 54 patients revealed a 27% increase in penile volume with caudal analgesia versus 2.5% with penile nerve block ($p < 0.001$); analgesia was improved and longer lasting with the penile nerve block [28]. Five cases of urethral fistula were observed; all were in caudal block patients. Subsequently, four retrospective studies describing 3300 patients have reported mixed results, with two indicating increased incidence of fistula with caudal analgesia [29,30], and two not finding a difference [31,32].

KEY POINTS: HYPOSPADIAS

- Hypospadias is the abnormal ventral opening of the urethral meatus and may be located anywhere from the corona of the glans to the perineum
- Hypospadias can be associated with inguinal hernias, cryptorchidism, and low birthweight, but is generally an isolated finding in an otherwise healthy patient
- Caudal analgesia is frequently utilized for hypospadias repair, but recent publications indicate that it may be associated with increased fistula formation

Cryptorchidism

Cryptorchidism (undescended testes, UDT) is the most common disorder of sexual differentiation and occurs in approximately 2% of male births [33]. The consequences of cryptorchidism include degeneration of the testes, impaired fertility, and increased risk for germ cell testicular tumors [18]. Despite the significance of this problem, the etiology of UDT in the majority of patients is unknown. It is unclear whether the pathological changes in the cryptorchid testis occur as a result of a primary defect or from secondary changes produced by the higher temperatures imposed on the undescended testis [18].

Two-thirds of patients present with a unilateral abnormality, and the other third present with bilateral abnormalities [17]. When the undescended testicle is unilateral, the right side is more often affected. The incidence ranges from 3.4% to 5.8% in full-term males. The usual timing for testicular descent into the scrotum is during the 7th month of gestation. Spontaneous descent may occur up until the first 6 months of life. A number of maternal risk factors have been implicated as a cause of undescended testicles. These include advanced maternal age, maternal obesity, breech presentation, low parity, preterm birth, low birthweight, and consumption of cola-containing drinks during pregnancy [17,34].

Cryptorchidism may occur as a single, isolated abnormality in an otherwise healthy patient or be associated with other congenital anomalies such as prune belly syndrome, posterior urethral valves, neural tube defects, gastroschisis, and microcephaly [35].

Treatment is focused on prevention of infertility, testicular malignancy, testicular torsion, and the psychological stigma associated with an empty scrotum. The rate of malignancy is approximately 1% in the cryptorchid patient. It is unknown whether this results from the abnormal position of the testis or an abnormality of the testis itself [17]. The rate of infertility is 38% in patients with bilateral cryptorchidism compared with 11% in unilateral cryptorchidism and 6% in normal males.

Treatment includes surgical exploration for the location of the testis. Sixty percent of the time, the testis is located in the inguinal canal or abdomen and 40% of the time, the testis is absent or comprised of fibrous tissue. The current method of treatment is orchiopexy, or relocation of the testis into the scrotum. If the location of the testis is not easily determined, the vas deferens and testicular vessels are used to help locate it [24]. Vessel length is the determining factor in deciding whether to undertake the procedure in one or two stages. Small, short spermatic vessels lead to the risk of a non-viable testis if placed into the scrotum without staging. In the first stage, the vessels are dissected and the testicle is brought as close to the scrotum as possible. The second stage 1 or 2 years later moves the testicle the remaining distance into the scrotum. The waiting period allows the blood supply to enlarge and form collateral circulation to supply the testicle.

Hormonal treatments intended to stimulate testicular descent include human chorionic gonadotropin, gonadotropin-releasing hormone, and luteinizing hormone-releasing hormone. These hormones stimulate the Leydig cells to produce androgens, but the mechanism for testicular descent is unknown [17]. Recent reviews report that hormonal treatments are not effective in stimulating and maintaining testicular descent, and that early surgery between the age of 3 and 12 months is the preferred approach [36]. Hormone therapy to improve fertility potential has been demonstrated to be effective.

Children who present for orchiopexy are usually otherwise healthy. These children require general anesthesia with either an endotracheal tube or LMA for airway management. Caudal epidural block is helpful to minimize postoperative pain. These procedures may be performed with conventional surgical incisions, or if abdominal position of the testes is suspected, laparoscopic surgery is often performed. If the anesthetic level is insufficient, laryngospasm may occur when the testis is manipulated. Otherwise, the postanesthetic course is generally unremarkable.

KEY POINTS: CRYPTORCHIDISM

- Cryptorchidism or undescended testes can result in degeneration of the testes, impaired fertility, and increased risk for germ cell testicular tumors
- Treatment may involve hormonal replacement or surgical exploration and repair
- Although presenting typically in an otherwise healthy patient, cryptorchidism may be associated with other congenital anomalies such as prune belly syndrome, posterior urethral valves, neural tube defects, gastroschisis, and microcephaly

Testicular torsion

Testicular torsion is a true surgical emergency. The diagnosis is usually made by history, physical examination, and diagnostic imaging studies. There are no definitive diagnostic imaging studies available, although color Doppler, isotope scans, and conventional ultrasound may be useful adjuncts [37]. Testicular torsion is best managed by early exploration, detorsion, and, when the testis is salvageable, fixation. When the testis is not salvageable, the surgeon will proceed with orchiectomy. In either scenario, a contralateral orchiopexy is usually performed [17].

Normally, the tunica vaginalis covers the anterior surface of the testis, epididymis, and spermatic cord, attaching with the gubernaculums and scrotal wall posteriorly, fixing the testis [17]. When these attachments are not secure, torsion may occur, leading to vascular compromise. There is a bimodal distribution in occurrence, with increased frequency during the neonatal period and puberty. During puberty, the rapidly increasing testicular mass increases the chances for rotation. In the neonatal period, the recently descended testis is very motile in the scrotum, increasing the risk of the spermatic cord to rotate en masse [17].

The patient's history should focus on the age of the patient, association with pain, and history of trauma. The onset and severity of pain may help differentiate torsion from epididymitis. The pain in torsion is acute in onset, severe, and ipsilateral [17]. The patient may also have symptoms of abdominal pain, thigh pain, and nausea and vomiting. The orientation and location of the testis in the scrotum must also be evaluated.

Testicular infarction may occur within a few hours of the torsion. After 8 h following the onset of pain, the testicular salvage rate declines precipitously [38]. In addition, studies in rats have confirmed that unilateral torsion can induce bilateral testicular damage and infertility [17]. This may result from reflex vasoconstriction, the formation of autoantibodies, or other chemically mediated mechanisms [17]. Therefore, surgery under general anesthesia with a rapid sequence induction and tracheal intubation should proceed as soon as possible. The goal is to begin surgery within 4–8 h of the time of testicular torsion whenever possible; unnecessary delays to obtain imaging studies when there is high clinical suspicion, or waiting to achieve nil per os status. are to be avoided [39].

KEY POINTS: TESTICULAR TORSION

- Testicular torsion is a true surgical emergency with no exact method for diagnosis. The methods used may include color Doppler or conventional ultrasound, along with a thorough history and physical exam
- There is a bimodal distribution in occurrence, with increased frequency during the neonatal period and puberty
- Surgical exploration and repair must occur within a few hours of symptom onset to have the best chance of testicular survival

Vesicoureteral reflux procedures

Vesicoureteral reflux is the retrograde flow of urine across the ureterovesical junction (UVJ). There is a high rate of familial recurrence, suggesting a genetic component. Risk factors for developing this condition include anatomical and functional abnormalities of the UVJ, high intravesical pressures, and impaired ureteral function [17]. If the VUR is severe, kidney dysfunction and hypertension may be present preoperatively, although the majority of presenting patients are healthy.

The unidirectional flow of urine through the normal ureter depends on both active and passive components. It appears that the tunneling path that the ureter travels through the submucosal layers of the bladder wall is inversely related to the rate of VUR. When the submucosal course is short, and therefore perpendicular to the bladder wall, the flap-valve mechanism normally in place to prevent reflux is absent. Additionally, the intravesical pressure must be lower than that in the ureter for there to be flow in the anterograde direction. Common clinical scenarios when VUR might occur are in patients with posterior valves, in patients with a neurogenic bladder, or when ureteral peristalsis is abnormal [17].

Long-term antibiotic prophylaxis is recommended in these children, especially up to the age of 8 years and in those with frequent recurrences [17]. This is continued until the reflux has resolved spontaneously or has been surgically corrected. This prophylaxis has been shown to decrease the amount of renal scarring and renal damage from repeated infections, helping to minimize the progression to chronic renal insufficiency and hypertension [17].

Management of VUR may be surgical or medical. The main goal is to prevent pyelonephrosis, which can lead to the complications mentioned. The treatment plan depends on gender, age, grade of reflux, concurrence of UTIs, renal function, and likelihood of resolution [17]. If the reflux is sterile, with no associated UTI, this reflux is not harmful to the kidneys and has no significant effect on kidney function and can probably be managed medically. Indications for surgical treatment include breakthrough UTIs despite prophylactic antibiotics, VUR associated with congenital anomalies at the UVJ, renal growth retardation, and the finding of worsening renal scarring. The endpoint of the surgical treatment is to restore the flap-valve mechanism, thereby preventing the VUR. The gold standard for this remains open surgical repair to establish an adequate submucosal tunnel for the ureter.

There are multiple techniques available for surgical repair, however the main component of each is freeing the ureter for mobilization, submucosal tunnel formation, transferring the ureter through the tunnel, and securing the ureter into the new position [17]. A minimally invasive technique for repair is also available. Using either an extravesical or intravesical approach, laparoscopic reimplantation can be undertaken. Endoscopic injection therapy, most frequently using polytetrafluroethylene or silicone, is then introduced submucosally at the 6 o'clock position of the UVJ [17]. By creating a mound at the opening of the UVJ, this narrows the ureteral orifice, thereby decreasing the amount of reflux allowed.

Anesthetic considerations for these cases include duration and blood loss, which can be significant during open repair. An epidural catheter or caudal epidural (catheter or single shot) may be placed to supplement anesthesia intra- and postoperatively. Postoperatively, these patients may have significant bladder spasm. This may be effectively treated in a variety of ways, including with belladonna and opium suppositories, oral or intravesiclular oxybutynin, ketorolac, or bupivacaine via epidural or in the bladder [22,23,40].

KEY POINTS: VESICOURETERAL REFLUX PROCEDURES

- Vesicoureteral reflux is the retrograde flow of urine across the ureterovesical junction and, if severe, can present concurrently with kidney dysfunction, hypertension, and long-term kidney infection
- Management of vesicoureteral reflux may be surgical or medical with the main goal being to prevent pyelonephrosis
- Multiple techniques, both minimally invasive and open surgical techniques, exist for treatment

Ureteropelvic junction obstruction

Ureteropelvic junction (UPJ) obstruction is the most common cause of obstructive uropathy in childhood and usually is caused by intrinsic stenosis. The typical appearance on ultrasonography is grade 3 or 4 hydronephrosis without a dilated ureter. UPJ obstruction most commonly presents on maternal ultrasonography revealing fetal hydronephrosis, as a palpable renal mass in a newborn or infant, as abdominal, flank, or

back pain, as a febrile UTI, or as hematuria after minimal trauma. Approximately 60% of cases occur on the left side, and the male to female ratio is 2:1. In 10% of cases UPJ obstruction is bilateral. In kidneys with UPJ obstruction, renal function may be significantly impaired from pressure atrophy, but approximately half of affected kidneys have relatively normal function [41].

Crossing vessels have been identified in 38–71% of patients with UPJ obstruction and in 19% of patients without UPJ obstruction [42]. Crossing vessels are believed to exacerbate rather than initiate the obstructive process [43]. If not recognized, crossing vessels can cause significant bleeding. These vessels are not excised as part of the repair, but the renal pelvis and ureter are rearranged by dismembered pyeloplasty [44].

The goal of surgery for UPJ obstruction is to preserve renal function by facilitating unobstructed drainage of urine. There are two common techniques: the more popular dismembered pyeloplasty and the flap technique. With the dismembered approach, there is complete severing of the ureter from the pelvis and then reanastamosis. With the flap approach, the renal pelvis is modified with the ureter intact.

The most common surgical approaches are the anterior subcostal, muscle-splitting approach and the dorsal lumbotomy approach. The anterior subcostal approach is performed in a modified supine position with the ipsilateral side at a 15–20° angle. The operating table is flexed at the level of the child's anterior superior iliac spine, and a "bump" placed under the patient. The lumbotomy approach is performed with the child in the prone position.

Pyeloplasty can also be performed by the laparoscopic approach with and without robotics. Potential benefits of the laparoscopic approach include shorter hospital admission, decreased postoperative pain, less superficial scarring, and earlier return to normal activity [45]. Because of the small incision used in the open procedure combined with the rapid convalescence of most children, controversy exists about which approach may be advantageous in this age group. The decision is likely left to surgeon preference and experience. Neither approach is responsible for prolonged extreme pain. The mean length of stay for an open procedure is 25 h [46].

In most children, the general risk of anesthesia is relatively low. These children are usually healthy, but it is always prudent to search for coexisting diseases. Renal failure is not usually an issue, especially with unilateral disease. Because of positioning, length of surgery, and when a laparoscopic approach is planned, tracheal intubation is usually the safest route for anesthesia. Liberal fluid therapy allows free flow of urine. Regional block with local anesthetic via the caudal route with or without opioids and clonidine provide excellent postoperative pain relief. Because the mean length of hospitalization is about 25 h, epidural catheter placement usually is not necessary [22]. Ben-Meir and others demonstrated that a regimen of opioids and non-steroidal anti-inflammatory drugs in children after open pyeloplasty has efficacy similar to that of epidural analgesia [46,47].

KEY POINTS: URETEROPELVIC JUNCTION OBSTRUCTION

- Ureteropelvic junction obstruction is the most common cause of obstructive uropathy in childhood and usually is caused by intrinsic stenosis; it can even be observed on maternal ultrasound
- The majority occur on the left side and more often in females than males
- The goal of surgery for UPJ obstruction is to preserve renal function by facilitating unobstructed drainage of urine and this can be done by a variety of techniques

Wilms tumor

Wilms tumor or nephroblastoma is the most common renal tumor of childhood and the seventh most common pediatric malignancy overall, accounting for about 5% of all childhood malignancies [48]. There are approximately 500 new cases of Wilms tumor each year. Most (75%) newly diagnosed patients are under 5 years of age, and usually aged between 2 and 3 years. Commonly, the tumor presents as a painless mass which is noticed by the parents as an abdominal bulge or a palpated mass. Some patients may exhibit signs and symptoms including malaise, fever, weight loss, and frank hypertension. Classic associations with Wilms tumor include crytorchidism or hypospadias, aniridia, and/or hemihypertrophy [49]. Table 32.1 lists the characteristics associated with

Table 32.1 Occurrence of characteristic congenital anomalies in Wilms tumor patients according to subgroups of the National Wilms Tumor Study

Subgroup	No. of patients evaluated	Percentage of patients in subgroups with			
		Aniridia	Cryptorchism/ hypospadias*	Hemihypertrophy	Beckwith–Wiedemann
Unilateral, unicentric	4165	1.3	5.0	2.6	0.5
Unilateral, multicentric	516	1.0	8.6	6.2	2.3
Bilateral at onset	315	1.3	16.8	8.6	1.6
Late bilateral	43	4.7	15.4	4.7	4.7
Familial Wilms tumor	61	1.6	5.1	3.3	0.0
ILNR (±) PLNR	552	2.0	12.2	4.2	2.5
PLNR only	446	0.4	2.3	7.2	1.6
Neither ILNR/PLNR	1748	0.4	3.8	1.8	0.2

* Percentage of male patients.

ILNR, intralobar nephrogenic rests; PLNR, perilobar nephrogenic rests.

Source: Reproduced from Breslow et al [49] with permission of John Wiley and Sons.

different types of Wilms tumor. The tumor usually involves one kidney but may affect both kidneys in about 5% of cases. As the tumor grows it may spread by local invasion and in 12% may demonstrate hematogenous spread to the lungs and less commonly to the brain (0.5%) [50]. Children with tumors that are solitary, unilateral, and have a low-risk genotype have an excellent prognosis. Bilateral masses and those with higher risk tumors (by genotype) are associated with significant morbidity and mortality. Common morbidities include recurrence of tumor, complications secondary to chemotherapy or radiotherapy, and spread to other organs, particularly the lungs. Recent advances in molecular biology have improved understanding of factors that can affect the outcome of children with Wilms tumor. In particular, the loss of heterozygocity (LOH) of chromosome 1p and/or 16q is associated with anaplastic Wilms tumors, which have a worse prognosis than those without LOH. Older children also are more likely than younger ones to have LOH, and, therefore, a worse prognosis. Patients who exhibit LOH at both the 1p and 16q loci have a significant chance of relapse after therapy and, therefore, a worse prognosis. The epidemiological and genetic factors have been used to stratify the risk associated with Wilms tumor. These are summarized in Box 32.1. Current survival rates for Wilms tumor according to staging are presented in Table 32.2 [51].

Children with Wilms tumor may require anesthesia for a variety of conditions, including primary tumor resection, radiological imaging (magnetic resonance imaging), diagonostic bone marrow biopsy and lumbar puncture, placement of central lines (percutaneously inserted central catheters), or radiotherapy. Usually the child will present to the operating room for surgical resection and staging. The main responsibility of the surgeon is to remove the primary tumor completely, without spillage, and to accurately assess the extent to which the tumor has spread, with particular attention to adequately assessing lymph node involvement. There is a difference in approach to the timing of initial surgery between the guidelines of the Children's Oncology Group (COG) in the USA and

Box 32.1: Wilms tumor staging system

I. Tumor limited to kidney and completely excised. The surface of the capsule is intact. Tumor was not ruptured before or during removal. There is no residual tumor apparent beyond the margins of excision
II. Tumor extends beyond the kidney, but is completely excised. There is regional extension of the tumor, i.e. penetration through the outer surface of the renal capsule into perirenal soft tissues. Vessels outside the kidney substance are infiltrated or contain tumor thrombus. The tumor may have been biopsied or there has been local spillage of tumor contained to the flank. There is no residual tumor apparent at or beyond the margins of excision
III. Residual non-hematogenous tumor confined to the abdomen. Any one or more of the following occur:
    a. Lymph nodes on biopsy are found to be involved in the hilus, the periaortic chains or beyond
    b. There has been diffuse peritoneal contamination by tumor such as by spillage of tumor beyond the flank before or during surgery, or by tumor growth that has penetrated through the peritoneal surface
    c. Implants are found on the peritoneal surfaces
    d. The tumor extends beyond the surgical margins either microscopically or grossly
    e. The tumor is not completely resectable because of local infiltration into vital structures
IV. Hematogenous metastases. Deposits beyond stage III, i.e. lung, liver, bone, and brain
V. Bilateral renal involvement at diagnosis. An attempt should be made to stage each side according to the above criteria on the basis of extent of disease prior to biopsy

Source: Reproduced from Davidoff [50] with permission of Wolters Kluwer.

Table 32.2 Wilms tumor survival rates from the Children's Oncology Group studies

Study	Number of patients	Chemotherapy regimen*	4-year EFS/OS
Very low-risk, surgery-only, FH (study ARENO532)	116	None	EFS 89.7% OS 100%
Stage I and II: combined 1p and 16q, LOH positive, FH (study ARENO533)	35	DD4A	EFS 83.9% OS 100%
Stage III: combined 1p and 16, LOH positive (study ARENO533)	52	M plus XRT	EFS 91.5% OS 97.8%
Stage IV: lung nodules, incomplete responders (study ARENO533)	183	M plus XRT	EFS 88% OS 92%
Stage IV: lung nodules, complete responders at 6 weeks (study ARENO533)	119	DD4A	EFS 80% OS 98.3%
High-risk, AH:			
Stage II	23	Revised UH-1	OS 85%
Stage III	24	± XRT	OS 74%
Stage IV (study ARENO321)	46		OS 46%

* Chemotherapy regimens: DD4A = vincristine, dactinomycin, doxorubicin; M = vincristine, dactinomycin, doxorubicin, cyclophosphamide, and etoposide; Revised UH-1 = vincristine, dactinomycin, doxorubicin, cyclophosphamide, carboplatin, and etoposide.
AH, anaplastic histology Wilms tumor; EFS, event-free survival; FH, favorable histology Wilms tumor; LOH, loss of heterozygosity; OS, overall survival; XRT, radiotherapy.
Source: Reproduced from Irtan et al [51] with permission of Elsevier.

those of the International Society of Pediatric Oncology (SIOP) in Europe. The American practice is to perform primary resection and staging before administering chemotherapy. The SIOP recommends preoperative chemotherapy because the tumor then is easier to resect and may be associated with a decreased incidence of tumor spill and a lower mortality and morbidity rate [50].

Commonly, anesthesia for primary tumor resection is similar to that for any major open laparatomy or radical nephrectomy. Proper preoperative assessment is crucial. The anesthesiologist should be aware of the extent of the tumor and whether it is adherent to surrounding organs. The tumor may involve a good portion of the kidney as well as the inferior vena cava, mesenteric arteries, and a portion of the liver or right atrium. Patients with atrial involvement or atrial thrombus may need cardiopulmonary bypass support during the surgical procedure. Bilateral tumors or ones crossing the midline of the abdomen may affect the great vessels, adding potential risk of significant blood loss. In addition, the anesthesiologist should be aware of any associated anomalies and the nature of any preoperative chemotherapy or radiotherapy. Chemotherapeutic agents such as actinomycin, doxorubicin, and vincristine are used for preoperative and postoperative treatment. These drugs may be associated with myelosuppression, cardiotoxicity, pulmonary effects (pleural effusion, pneumonia, and interstitial pneumonitis), hepatotoxicity, and neurotoxicity in children [52]. The incidence varies and may depend both on dose and the patient's individual response to the agent [52–54].

The anesthetic plan depends on the preoperative condition of the patient and the surgical plan. These patients will require endotracheal intubation and general anesthesia with standard monitors. Two intravenous lines are useful, one to provide maintenance IV solutions and the second for rapid infusion of fluids or blood products. If there is intraatrial involvement or if thoracotomy or cardiopulmonary bypass is required, an arterial line is useful to closely monitor the patient's blood pressure and obtain blood specimens for testing. Central venous access, if not present preoperatively, may be desirable to monitor central pressures and provide longer term venous access. For the abdominal approach, patients are positioned supine and commonly the surgical approach is through a transverse abdominal transperitoneal incision. Epidural analgesia for intraoperative and postoperative pain management may be quite useful. The level of the catheter is determined by the site of the incision. The tip of the catheter is best located at the mid or low thoracic level in order to provide adequate analgesia. Despite proper planning and execution, up to 12% of cases may have a perioperative complication. Table 32.3 lists some of the possible surgical complications and reported incidence [55]. In addition to these, the anesthesiologist should be mindful of possible injury related to patient positioning and take proper precautions to minimize the risk. Patients may have significant postoperative pain and discomfort depending on the location of the incision and extent of the surgical dissection. Postoperative use of patient- or nurse-controlled epidural analgesia may result in more comfort and rapid return to activity by avoiding the common side-effects of intravenous opioid analgesia. Without surgical complications, patients usually recover from surgery within 3–5 days. Postoperative therapy is determined by the stage of the tumor and risk stratification.

Table 32.3 Incidence of surgical complications following surgery for Wilms tumor

Complication	*n*	%
Bowel obstruction	27	5.1
Extensive hemorrhage	10	1.9
Wound infection	10	1.9
Vascular injury	8	1.5
Splenic injury	6	1.1
Hypotension	3	0.6
Diaphragmatic tear	2	0.4
Liver injury	1	0.2
Chylous ascites	1	0.2
Incisional hernia	1	0.2
Pulmonary embolus	1	0.2
Respiratory failure	1	0.2
Pleural effusion	1	0.2
Pneumothorax	1	0.2
Urinary tract infection	1	0.2
Pancreatitis	1	0.2
Staph. sepsis	1	0.2

Seventy-six complications occurred in 68 of 534 children: 12.7% had at least one complication.
Source: Reproduced from Ritchey et al [55] with permission of Elsevier.

KEY POINTS: WILMS TUMOR

- As one of the most commonly diagnosed childhood tumors, the majority are noticed by the parents of children age 2–3 years with a significant abdominal bulge
- Morbidity is determined by laterality. Children with a solitary tumor have an excellent prognosis; those with bilateral masses have potential significant morbidity and mortality
- Genetic testing and molecular biology has become more important in the work-up of Wilms tumor and helps to determine potential chemotherapy treatments

Chronic renal failure and dialysis

Children in acute or chronic renal failure may require peritoneal dialysis or hemodialysis. The insertion of the appropriate catheter in non-critically ill patients is usually performed in the operating room under general anesthesia. The critically ill child may require a procedure in the operating room while undergoing continuous renal replacement therapy (CRRT) in the ICU. This section will describe the types of renal replacement available, the mechanism by which dialysis is performed, and finally a discussion of the types of dialysis catheters used for the pediatric patient. The perioperative care of children in renal failure requiring surgery will also be addressed.

Renal replacement therapy defines dialysis therapies. However, some authors now refer to dialysis as renal support therapy because only fluid removal and filtering wastes are performed by dialysis and not the endocrine functions [56]. Dialysis employs only two physiologies for solute and fluid

movement. Both methods require blood being exposed to a semi-permeable membrane against a dialysate solution of different concentration. Regardless of the modality employed, the goal of renal replacement therapy is to precisely control serum electrolytes, clear toxins, and provide fluid removal for the patient in renal failure.

Dialysis employs a diffusive clearance while hemofiltration employs convective clearance. Hemodialysis and peritoneal dialysis involve the diffusion of solutes across a concentration gradient from high to low concentration. Dialysate is passed across the semi-permeable membrane counter current to blood flow allowing equilibration of the plasma and dialysate solute concentrations. This process may remove or add solute to the plasma water space depending upon the composition of dialysate compared to the plasma. Water will also move along a gradient in effect "following" the solute (ultrafiltration). Diffusive clearance is effective for removal of the small solutes, including serum ions and urea, with subsequent fluid removal. In addition, other solutes such as antibiotics, narcotics, and other medications will cross the membrane. Diffusion gradients change dependent upon blood flow rates, dialysate flow rates, and starting concentration gradients. CRRT employing countercurrent dialysate for solute clearance is called continuous venovenous hemodialysis[57].

Hemofiltration uses a pressure gradient for fluid movement instead of solute concentration gradients. It is considered part of the CRRT modalities. A positive hydrostatic pressure drives water across the membrane from the blood side to the filter side and the solutes follow the water through the membrane. Due to the possibility of large shifts of volume during convective therapies, a filter replacement fluid is often utilized to replace fluid lost by convection. In patients undergoing CRRT, bicarbonate is lost in the ultrafiltrate. Therefore, the replacement fluid is usually an isotonic, buffered electrolyte solution. The buffer used in the replacement fluid may be acetate, citrate, lactate, or bicarbonate. The use of citrate is becoming more commonplace because it may be used as both a buffer and an anticoagulant to help prevent hemodiafilter clotting [58]. There are multiple names for the types of hemofiltration performed including slow extended hemofiltration, slow continuous ultrafiltration, continuous venovenous hemofiltration, and continuous venovenous hemodiafiltration [57].

Thresholds for the timing of dialysis in acute renal failure (ARF) are controversial and not well defined [56,59,60]. Indications for renal replacement therapy include: volume overload with evidence of hypertension and/or pulmonary edema refractory to diuretic therapy, persistent hyperkalemia, severe metabolic acidosis unresponsive to medical management, neurological symptoms (altered mental status, seizures), and the presence of progressive azotemia. The modulation of inflammatory mediators in ARF with sepsis or multiorgan system failure may be another indication [61]. An additional indication for dialysis is the inability to provide adequate nutritional intake because of the need for severe fluid restriction. In patients with ARF, dialysis support may be necessary for days or weeks [62].

In chronic renal failure, ESRD represents the state in which a patient's renal dysfunction has progressed to the point at which homeostasis and survival can no longer be sustained with native kidney function and maximal medical management. Relative indications for renal replacement therapy include weight loss, malnutrition, persistent nausea and vomiting, refractory metabolic disturbances, refractory hypertension, fluid overload, school performance failure, and chronic fatigue. Absolute indications include progressive uremic encephalopathy, bleeding diathesis related to uremia, pericarditis, pulmonary edema, and life-threatening hyperkalemia [56]. The ultimate goal for children with ESRD is successful kidney transplantation because it provides the most normal lifestyle and possibility for rehabilitation for the child and family.

Seventy-five percent of US children with ESRD require a period of dialysis before transplantation can be performed. It is recommended that plans for renal replacement therapy be initiated when a child reaches a glomerular filtration rate of between 29 and 50 mL/min/1.73 m^2 [62]. The optimal time to actually initiate dialysis, however, is based on a combination of the biochemical and clinical characteristics of the patient including refractory fluid overload, electrolyte imbalance, acidosis, growth failure, or uremic symptoms, including fatigue, nausea, and impaired school performance [56]. In general, most nephrologists attempt to initiate dialysis early enough to prevent the development of severe fluid and electrolyte abnormalities, malnutrition, and uremic symptoms. Pre-emptive transplantation before initiation of dialysis is increasingly observed [62]. Management of anesthesia for renal transplantation is discussed in Chapter 30.

The selection of dialysis modality must be individualized to fit the needs of each child. In the United States, two-thirds of children with ESRD are treated with peritoneal dialysis, whereas one-third are treated with hemodialysis. Age is a defining factor in dialysis modality selection: 88% of infants and children from birth to 5 years of age are treated with peritoneal dialysis, whereas 54% of children older than 12 years of age are treated with hemodialysis [63]. In ARF each modality has its indications, contraindications, and challenges (Table 32.4) [61].

Peritoneal dialysis involves the transport of solutes and water across the peritoneum. The blood in the peritoneal capillaries are exposed to the dialysis solution in the peritoneal cavity, which typically contains sodium, chloride, and lactate or bicarbonate along with glucose to make the solution hyperosmolar. During the course of a peritoneal dialysis dwell, three transport processes occur simultaneously: diffusion, ultrafiltration, and absorption. The amount of dialysis achieved and the extent of fluid removal depends on the volume of dialysis solution infused (called the dwell), how often this dialysis solution is exchanged, and the concentration of osmotic agent present [64].

Peritoneal dialysis requires less clinical expertise, fewer equipment resources, and decreased cost. It can be used in all pediatric patients including neonates and stable postoperative heart surgery patients. It can be performed in patients with a venticuloperitoneal shunt and also in patients with prone belly syndrome. Peritoneal dialysis provides gradual solute clearance and ultrafiltration, thus causing less hemodynamic instability. Slow solute clearance and ultrafiltration is an obvious disadvantage for patients with severe fluid overload or severe lactic acidosis requiring

Table 32.4 Comparison of the advantages and disadvantages of continuous renal replacement therapies (CRRT), peritoneal dialysis (PD), and intermittent hemodialysis (IHD)

Variable	CRRT	PD	IHD
Continuous therapy	Yes	Yes	No
Hemodynamic stability	Yes	Yes	No
Fluid balance achieved	Yes, pump controlled	Yes/no, variable	Yes, intermittent
Easy to perform	No	Yes	No
Metabolic control	Yes	Yes	Yes, intermittent
Optimal nutrition	Yes	No	No
Continuous toxin removal	Yes	No/yes, depends on the nature of the toxin – larger molecules not well cleared	No
Anticoagulation	Yes, requires continuous anticoagulation	No, anticoagulation not required	Yes/no, intermittent anticoagulation
Rapid poison removal	Yes/no, depending on patient size and dose	No	Yes
Stable intracranial pressure	Yes	Yes/no, less predictable than CRRT	Yes/no, less predictable than CRRT
ICU nursing support	Yes, high level of support	Yes/no, moderate level of support (if frequent, manual cycling can be labor intensive)	No, low level of support
Dialysis nursing support	Yes/no, institution dependent	Yes/no, institution dependent	Yes
Patient mobility	No	Yes, if IPD used	No
Cost	High	Low/moderate. Increases with increased dialysis fluid used	High/moderate
Vascular access required	Yes	No	Yes
Recent abdominal surgery	Yes	No	Yes
VP shunt	Yes	Yes/no, relative contraindication	Yes
Prune belly syndrome	Yes	Yes/no, relative contraindication	Yes
Ultrafiltration control	Yes	Yes/no, variable	Yes, intermittent
PD catheter leakage	No	Yes	No
Infection potential	Yes	Yes	Yes
Use in AKI-associated inborn errors of metabolism	Yes	No	Yes
Use in AKI-associated ingestions	Yes	No	Yes

AKI, acute kidney injury; ICU, intensive care unit; IPD, intermittent peritoneal dialyss; VP, ventriculoperitoneal.
Source: Reproduced from Walters et al [59] with permission of Springer Nature.

precise fluid balance and controlled ultrafiltration that can only be attained with intermittent hemodialysis or continuous renal replacement therapy [59]. Peritoneal dialysis can worsen respiratory distress by limiting diaphragmatic movement. Diaphragm defects are a contraindication to peritoneal dialysis. Because peritoneal dialysis can result in the loss of immunoglobulins, peritonitis is a risk. Catheter malfunction is common resulting in leaks, hernias, and catheter obstruction.

Intermittent hemodialysis has the clear advantage of rapid ultrafiltration and solute removal when compared with peritoneal dialysis or CRRT. The hemodialysis circuit is comprised of the patient's blood compartment, access in the form of a surgically placed arteriovenous fistula or arteriovenous graft, or a venous catheter, and the polyethylene tubing through which the patient's blood travels to and from the dialyzer. The dialysate consists of highly purified water into which sodium, potassium, calcium, magnesium, chloride, bicarbonate, and dextrose have been introduced. The low molecular weight waste products that accumulate in uremic blood are absent from the dialysis solution. For this reason, when uremic blood is exposed to dialysis solution, the flux rate of these solutes from blood to dialysate is initially much greater than the backflux from dialysate to blood. During dialysis, concentration equilibrium is prevented, and the concentration gradient between blood and dialysate is maximized, by continuously refilling the dialysate compartment with fresh dialysis solution and by replacing dialyzed blood with undialyzed blood. Normally, the direction of dialysis solution flow is opposite to the direction of blood flow. The purpose of "countercurrent" flow is to maximize the concentration difference of waste products between blood and dialysate in all parts of the dialyzer [65].

Like peritoneal dialysis, intermittent hemodialysis can be performed outside the ICU. This modality is useful in children with toxic ingestions, tumor lysis syndrome, and inborn errors of metabolism [66,67]. Rapid solute and fluid removal afforded by intermittent hemodialysis can lead to disequilibrium syndrome. Careful dosing, dialysate solution selection, judicious use of mannitol, and monitoring are required to prevent the dangerous osmolar fluctuations leading to this complication [68,69].

CRRT refers to any continuous mode of extracorporeal solute or fluid removal. The common denominator to all forms of CRRT is an extracorporeal circuit connected to the patient via an arterial or venous access catheter. A variety of alternative CRRTs have been developed to address many of the problems associated with intermittent hemodialyisis and peritoneal dialyisis discussed above. CRRT provides better metabolic control of azotemia and fluid removal without compromising intravascular volume and facilitates fluid and electrolyte management and nutritional

support in critically ill patients. CRRT is an invaluable means of supporting critically ill children with a variety of illnesses, including ARF, drug intoxication, inborn errors of metabolism, liver failure, and multiorgan failure. However, the ideal method of applying the technique is unknown [70,71]. On the basis of the successful use of CRRT in patients with ARF, it is now occasionally used to facilitate fluid removal in patients without renal failure but for whom diuretic therapy alone has been unsuccessful or is contraindicated [70].

KEY POINTS: CHRONIC RENAL FAILURE AND DIALYSIS

- Placement of the hemodialysis catheter may occur urgently for acute renal failure or more electively for those with chronic renal failure
- Regardless of the modality employed, the goal of renal replacement therapy is to precisely control serum electrolytes, clear toxins, and provide fluid removal for the patient in renal failure
- The ultimate goal for children with ESRD is successful kidney transplantation because it provides the most normal lifestyle and possibility for rehabilitation for the child and family
- In the United States, two-thirds of children with ESRD are treated with peritoneal dialysis, whereas one-third are treated with hemodialysis. This is also dependent on age, with the vast majority of those under the age of 5 years being treated with peritoneal dialysis

Dialysis catheter placement in the operating room

For children who do not undergo pre-emptive renal transplantation or who initially present with ESRD, establishment of adequate dialysis access is of paramount importance because it is directly linked to the quality of life and health of the patient. With respect to hemodialysis, all attempts should be made to create a primary arteriovenous fistula. For patients without adequate veins, a polytetrafluoroethylene graft is required. A native fistula is clearly preferred because of superior patency rates, although this option does require the presence of suitable veins, which excludes infants and small children under 20 kg [65]. Vascular catheters are the predominant vascular access in children. In children with ESRD, renal transplant is the first line of therapy. As an arteriovenous graft is recommended for long-term dialysis, such grafts are inappropriate for children who will undergo renal transplantation within a year [73,74].

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines recommend that the order of vascular access be sequential: the right internal jugular vein, right external jugular vein, left internal and external jugular veins, subclavian veins, femoral veins, or translumbar access to the inferior vena cava. This order is based on complication rates from lowest to highest [75]. Additionally, these catheters can lead to central venous stenosis and thrombosis, which can make future permanent upper extremity vascular access more difficult to achieve.

Peritoneal dialysis is performed after placement of a Tenckhoff catheter. A double-cuffed peritoneal dialysis (PD) catheter is inserted via an open or laparoscopic surgical procedure under general anesthesia. The loop of the catheter is placed in the pelvis. During the procedure it is important to ascertain that fluid can run freely through the catheter into the abdomen and drain freely as well.

The laparoscopic technique appears to afford no advantage for successful catheter function in the early postoperative period [76]. In addition, other factors that that do not influence catheter function include previous PD catheter placement, previous abdominal surgery, type of catheter, or location of catheter exit site. However, Arog et al showed that use of the laparoscopic technique was helpful in children with an *in situ* ventriculoperitoneal shunt [77].

The most common cause of catheter failure is occlusion: either from an internal fibrin plug or obstruction by omentum, bowel, or other structures. The single controllable factor that was associated with a decreased risk of occlusion was the performance of simultaneous omentectomy. Overall, children weighing less than 10 kg have a higher risk of PD catheter failure than children weighing more than 10 kg.

The annualized infection rate decreases with age. Tenckhoff straight and Tenckhoff curled catheters have similar times to first peritonitis infection. Overall, first time peritonitis infection took longer for catheters with two cuffs compared with one, for swan neck tunnels compared with straight tunnels, and for down exit sites compared with up and lateral exit sites [63,78].

Children who are scheduled for PD catheter insertion are usually in a stable condition with chronic renal failure and have a catheter for renal replacement therapy in anticipation for renal transplantation. Occasionally, a child in acute renal failure will require surgical insertion of a dialysis catheter, such as the patient with new-onset hemolytic uremic syndrome.

The preoperative evaluation includes a physical exam and review of the patient's metabolic status. The timing of the patient's most recent dialysis session, if any, is very important. Of particular importance are serum potassium concentration, fluid status, and dosing of drugs that undergo predominately renal clearance. The patient requiring a PD catheter or hemodialysis catheter will require standard ASA (American Society of Anethesiologists) monitoring but usually not invasive monitoring. Arterial catheters are normally avoided in these patients, as are blood pressure cuffs on the extremity of an existing arteriovenous fistula or graft. Of critical importance is a preoperative discussion with the patient's nephrologist or surgeon about vascular access sites to be avoided. It is critical to maintain long-term patency of major veins and arteries in these patients, who may undergo a number of vascular access procedures over a lifetime. It is also important, when anesthetizing a patient with an existing dialysis fistula, to monitor blood flow during the anesthetic, and maintain blood pressure and intravascular

volume status to ensure arteriovenous fistula or graft patency. Tracheal intubation is prudent since many children in acute and chronic renal failure have delayed gastric emptying and thus have a pulmonary aspiration risk. The need for rapid sequence induction or modified rapid sequence must be made on an individual patient basis. While succinylcholine may be used for rapid sequence induction if the serum potassium is at normal levels, rocuronium may be a better choice. Neuromuscular blockade with rocuronium is of similar duration or only slightly prolonged in patients with chronic renal failure as compared to patients with normal renal function [79]. Fentanyl and hydromorphone are not metabolized by the kidney and are reasonable choices for perioperative analgesia [80].

KEY POINTS: DIALYSIS CATHETER PLACEMENT IN THE OPERATING ROOM

- For children who do not undergo pre-emptive renal transplantation or who initially present with ESRD, establishment of adequate dialysis access is of paramount importance because it is directly linked to the quality of life and health of the patient
- A native fistula is clearly preferred because of superior patency rates, but cannot be obtained in infants and small children under 20 kg because of a lack of suitable vessel sizes. Vascular catheters are generally used in this population
- Important anesthetic considerations include the timing of the patient's most recent dialysis session, which can influence serum potassium concentration, fluid status, and dosing of drugs that undergo predominately renal clearance

Continuous renal replacement therapy in the operating room

Most patients receiving CRRT are critically ill, may be on mechanical ventilator support, and are often receiving a myriad of vasoactive agents. These patients are challenging because they may have underlying coagulopathies, yet CRRT requires anticoagulation for filter patency. If these children need surgical procedures, in most instances, CRRT treatment can be discontinued while in the operating room. However, in some procedures, for example liver transplantation, CRRT may be used during surgery to optimize fluid and electrolyte management [81].

Most anesthesiologists and operating room personnel are not familiar with CRRT or the equipment needed to provide the therapy. It is imperative that a meaningful discussion occurs among the intensivists, nephrologists, and surgeons involved in the procedure, in order to outline the operative care of the patient. At the Monroe Carell Jr Children's Hospital at Vanderbilt University Medical Center, a technician familiar with the CRRT device manages the apparatus in the operating room. Careful monitoring of arterial blood gases and electrolytes is essential to ensure normal acid–base balance [72].

KEY POINTS: CONTINUOUS RENAL REPLACEMENT THERAPY IN THE OPERATING ROOM

- Most patients receiving CRRT are critically ill, may be on mechanical ventilator support, and are often receiving a myriad of vasoactive agents. These patients are challenging because they may have underlying coagulopathies, yet CRRT requires anticoagulation for filter patency
- Most anesthesiologists are not intimately familiar with CRRT so it is imperative that a meaningful discussion occurs among the intensivists, nephrologists, anesthesiologists, and surgeons involved in the procedure, in order to outline the operative care of the patient

Priapism

Ischemic (veno-occlusive, low-flow) priapism is a non-sexual, persistent erection causing a compartmental syndrome that is a medical, and sometimes surgical, emergency in any episode lasting more than 4 h. Patients typically report associated pain. In children, the etiologies include sickle cell disease, oncological disease, and neuroleptic drugs. Unlike normal erections which involve engorgement of the corpora cavernosa and the corporus spongiosum, priapism only involves the engorgement of the corpora cavernosa.

Trazodone is a triazolopyridine derivative that holds considerable appeal for treatment of depressive illness and as an adjunct for chronic pain because it has little anticholinergic activity and few cardiovascular side-effects. However, trazodone possesses significant α-blocking activity. Trazodone-induced priapism resembles priapism due to sickle cell hemoglobinopathy [82].

In general, since ischemic priapism of more than 4 h in duration irrespective of etiology implies a compartment syndrome, decompression of the corpora cavernosa is recommended for counteracting and preventing ischemic injury. Definitive first-line treatment consists of evacuation of blood and irrigation of the corpora cavernosa along with intracavernous injection of an α-adrenergic sympathomimetic agent. A dorsal nerve block or local penile shaft block is generally performed prior to penile maneuvers. Priapism resolution employing aspiration with or without irrigation is approximately 30%.

Sympathomimetic agents can be expected to exert contractile effects on the cavernous tissue and thus facilitate detumescence. Among these, phenylephrine, as an α1-selective adrenergic agonist, is the preferred drug for this application since it minimizes the risk of cardiovascular side-effects compared with other sympathomimetic agents having β-adrenergic effects as well. Evacuation of stagnant intracorporal blood may be required for the medication to be most effective [83,84].

In patients with an underlying etiological disorder, intracavernous treatment of ischemic priapism should be provided concurrent with appropriate systemic treatment. This recommendation applies to priapism associated with sickle cell

disease as well as that associated with other hematological diseases, metastatic neoplasia, or other causes having standard treatments. Support for this recommendation is provided by literature review showing that ischemic priapism resolved in 37% or less of patients with sickle cell disease managed with systemic medical treatments, whereas much better resolution rates were achieved with therapies directed at the penis [82]. Thus, for priapism related to sickle cell disease, conventionally recommended medical therapies such as analgesia, hydration, oxygenation, alkalinization, and even transfusion may be performed, but these interventions should not lead to delays in intracavernous treatment if prolonged periods of ischemia have occurred [84].

The surgeon may proceed with surgical intervention once it is apparent that intracavernous treatment has failed [83]. A surgical shunt has the objective of facilitating blood drainage from the corpora cavernosa, bypassing the veno-occlusive mechanism of these structures [84]. Surgical correction involves connecting the engorged cavernosal tissue with the glans, corpus spongiosum, or dorsal or saphenous vein. This surgically created fistula will allow blood to drain from the corpora cavernosa until the pathological process has resolved. Ideally, the surgically created fistula will spontaneously close after the priapism-causing factors have resolved [85].

KEY POINTS: PRIAPISM

- Ischemic priapism is a non-sexual, persistent erection causing a compartmental syndrome that is a medical, and sometimes surgical, emergency in any episode lasting more than 4 h
- In children, the etiologies include sickle cell disease, oncological disease, and neuroleptic drugs
- Definitive first-line treatment consists of evacuation of blood and irrigation of the corpora cavernosa along with intracavernous injection of an α-adrenergic sympathomimetic agent. Surgical intervention is required if medical treatment fails

Robotic surgery

Laparoscopic and robot-assisted laparoscopic surgeries have gained increasing popularity for pediatric urological procedures. Compared with traditional open techniques, minimally invasive surgery offers the advantages of shorter hospitalization, decreased postoperative pain medication requirements, fewer postoperative respiratory complications, and smaller incisions with improved cosmetic outcome [86].

The first robotic procedure in a child was described by Meininger et al in 2001 for a robotic Nissen fundoplication [87]. Improvements offered by the robotic system over traditional laparoscopic surgery include enhanced dexterity, tremor filtration, motion scaling, and superior depth perception and magnification (Fig. 32.4) [88,89]. Disadvantages include inferior haptic feedback, a relatively limited selection of laparoscopic tools, and cost [88,90]. Many pediatric urological procedures have been successfully performed with a robot-assisted approach. These include pyeloplasty, ureteral reimplantation (intra- and extravesical), nephrectomy or partial nephrectomy, ureteroureterostomy, orchidopexy, bladder augmentation, and appendicovesicostomy [91]. The surgical outcomes for robot-assisted pyeloplasty are recognized as at least equivalent to the open or traditional laparoscopic approach while other procedures are still undergoing evaluation [92]. In 2013, a literature review of robotic surgery in children by Cundy et al found a conversion rate to a traditional laparoscopic or open approach of 2.5% [89]. Compared with gastrointestinal and thoracic surgery, genitourinary procedures demonstrated the lowest rate of conversion at 1.5% [89].

Co-morbidities leading to decreased tolerance of pneumoperitoneum and increased intra-abdominal pressure might make robotic surgery a less feasible option for some patients. Examples of such co-morbidities include bronchopulmonary illness with poor respiratory reserve, uncorrected congenital heart disease, and pulmonary hypertension. While small patient size can lead to challenging port placement and an increased risk of instrument collision, it is not a contraindication to robotic surgery [91,92]. Abdominal robotic procedures on a patient weighing 2.2 kg as well as on a 1-day-old neonate have been reported [93]. Prior abdominal surgery may complicate port placement; it is, however, not a contraindication to robotic surgery [91].

The anesthetic considerations in robotic surgery depend on the type of surgical procedure being performed. Some general considerations pertain to every case and focus on patient positioning requirements and the respiratory, cardiovascular, and neuroendocrine changes accompanying the creation of a pneumoperitoneum. The robot's reach is often a limiting factor, so the bed may need to be tilted to an extreme laterally. Some surgeries require a steep Trendelenburg or reverse Trendelenburg position for portions of the procedure. It is critical to pay close attention to securing and padding extremities to avoid inadvertent movement or pressure injury. The same is true for head positioning since the head may slide off the pillow if not secured and monitored (Fig. 32.5) [94]. Depending on the size and layout of the operating room, the anesthesia provider's access to the patient may be exceptionally limited. The operating room team should have a coordinated and practiced plan in place for optimum positioning of the robotic system (Figs 32.6 and 32.7) and to allow for quick disengagement of the robot and access to the patient in case of airway emergencies or the need to rapidly convert to an open procedure [95].

Effects of retro- or intraperitoneal CO_2 insufflation include hypercarbia and an increase in intra-abdominal pressure. Hypercarbia can increase systemic vascular resistance and mean arterial pressure [96,97]. If uncorrected, hypercarbia can result in acidosis, which in turn can decrease cardiac contractility, increase the risk of arrhythmias, and cause vasodilation [96]. CO_2 increases the release of catecholamines and vasopressin [97]. Children under the age of 4 years have an increased CO_2 absorption rate due to a high absorption surface to body weight ratio and a shorter distance between the absorbent membrane and capillaries [98]. CO_2 insufflation can lower core temperature and care must be taken to maintain normothermia.

Intra-abdominal pressures exceeding 15 mmHg can decrease venous return and lead to a decrease in cardiac output [86,98]. Recommended insufflation pressures are

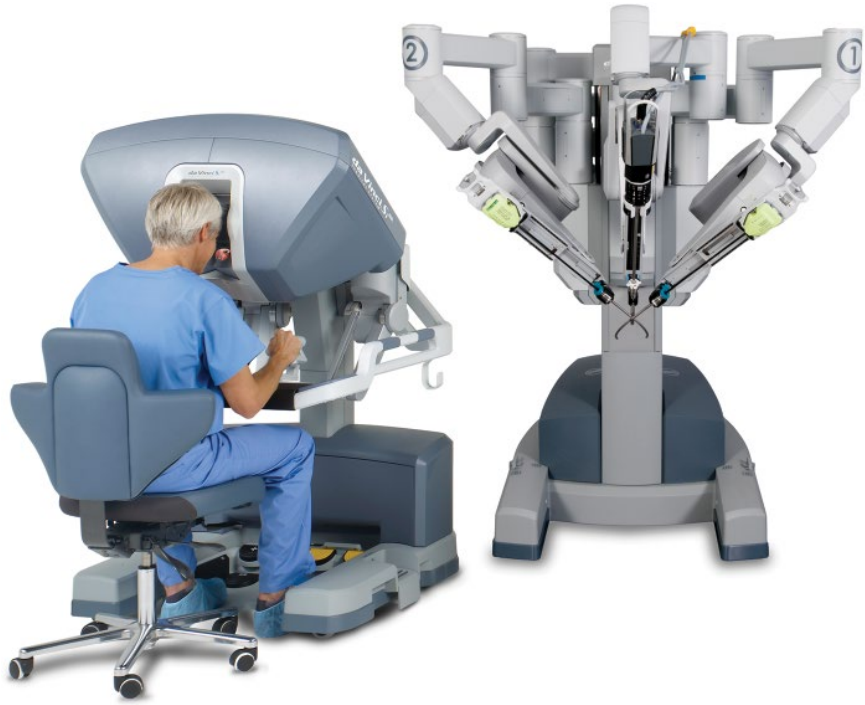


Figure 32.4 Robotic surgical system. The surgeon sits at a control console remote from the surgical field, either inside the operating room or outside in a control room. *Source*: Reproduced with permission from The DaVinci® Surgical System [90]. DaVinci Surgical, https://en.wikipedia.org/wiki/Da_Vinci_Surgical_System#/media/File:Cmglee_Cambridge_Science_Festival_2015_da_Vinci.jpg. Licensed under CCBY SA 3.0.

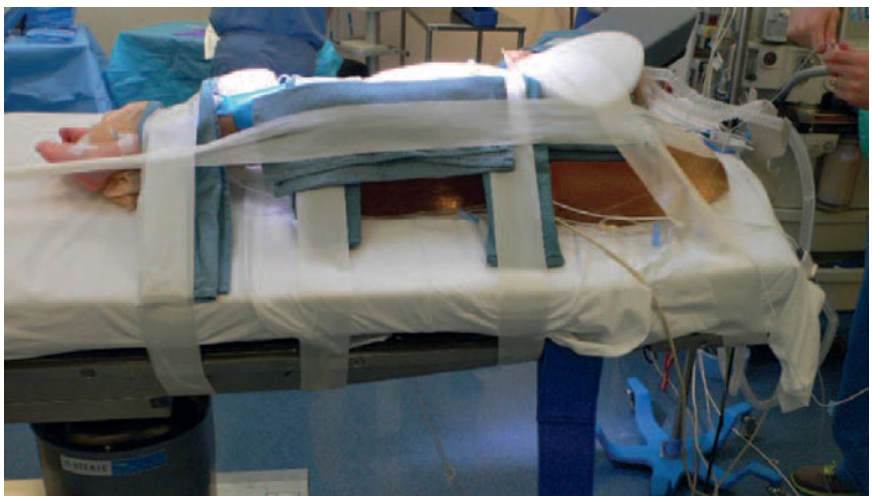


Figure 32.5 Patient positioning for robotic surgery. Lateral view of patient after positioning and taping just prior to robot docking. Note the large gel rolls placed behind the patient's back and head in order to prevent patient movement from the lateral displacement of the operating room table. *Source*: Reproduced from Muñoz et al [94] with permission of Wolters Kluwer.

8–10 mmHg for infants (0–2 years), 10–12 mmHg for children (2–10 years) and 15 mmHg for adolescents (>10 years) [99].

The peritoneal stretch during insufflation can cause transient bradycardia, which is poorly tolerated in neonates and infants given their rate-dependent cardiac output. Cephalad displacement of the diaphragm during insufflation can decrease functional residual capacity below closing volumes, causes atelectasis, and increases dead space [96]. Possible consequences include hypoxemia and right-to-left shunting [96,97]. Increased intra-abdominal pressure has also been shown to reduce the glomerular filtration pressure and may temporarily decrease urine output [96,100]. This makes urine output a poor indicator for volume status during robotic procedures. Tables 32.5 and 32.6 summarize the respiratory, cardiovascular, and renal effects of pneumoperitoneum [94].

Monitors for robot-assisted laparoscopic procedures in children include standard ASA monitors. The addition of a precordial stethoscope allows for early recognition of inadvertent mainstem intubation [95]. End-tidal CO_2 ($ETCO_2$) monitoring can be unreliable as an indicator for $PaCO_2$ in small infants and the setting of respiratory pathology or high intra-abdominal pressure requirements. Arterial line placement for blood gas sampling can be indicated for select patients or long procedures [97]. Induction of anesthesia can be intravenous or inhalational. Care must be taken to avoid gastric distension during mask ventilation. Both inhalational

and intravenous maintenance are good options. Some sources prefer total intravenous anesthesia to increase hemodynamic stability during pneumoperitoneum [87]. Peripheral intravenous access is preferably placed in an upper extremity given a possibly delayed effect of medications administered via lower extremity access in the setting of increased intra-abdominal pressure. Placement of a second peripheral IV access prior to procedure start is recommended [96,101].

Patients require intubation for most laparoscopic and nearly all robot-assisted laparoscopic procedures. Cuffed endotracheal tubes are preferred to ensure adequate controlled ventilation. Proper endotracheal tube position must be reconfirmed after patient positioning is completed and should be checked at the expected extremes of table positioning to rule out inadvertent endobronchial migration of the endotracheal tube tip during the case. Foam padding around the face can help prevent contact of the robot or a surgical assistant with the endotracheal tube [101]. Muscle relaxation minimizes the risk of patient movement and facilitates adequate

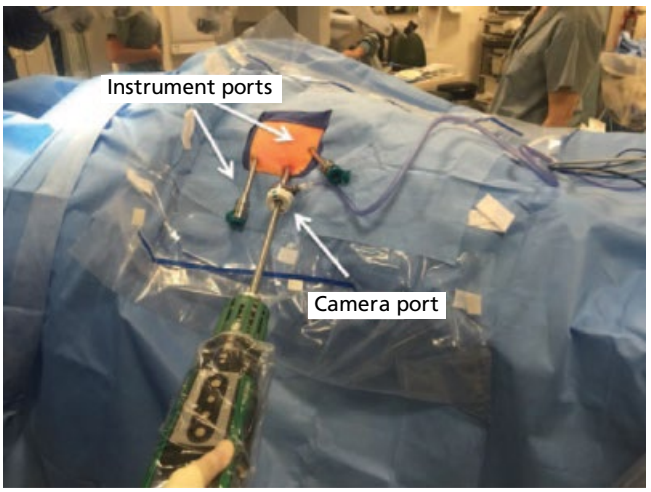


Figure 32.6 Intraoperative placement of the camera and instrument ports for pediatric robot-assisted urological surgery. Many surgeries can be accomplished with three ports but a fourth port may be necessary for more complex procedures. *Source*: Reproduced from Muñoz et al [94] with permission of Wolters Kluwer.

Table 32.5 Summary of the respiratory effects of pneumoperitoneum

Parameter	Change
Peak inspiration pressure	Increase
Chest wall mechanical resistance	Increase
Pulmonary compliance	Decrease
Pulmonary dead space	No change or increase
Functional reserve capacity	Decrease
Vital capacity	Decrease
Shunting	Increase
Ventilation/perfusion mismatch	Increase

Source: Reproduced from Muñoz et al [94] with permission of Wolters Kluwer.

Table 32.6 Summary of the cardiovascular and renal effects of pneumoperitoneum

Parameters	Change
Heart rate	No change or increase
Mean arterial pressure	Increase
Systemic vascular resistance	Increase
Venous return	Increase or decrease
Central venous pressure	Increase
Cardiac output	Increase or decrease
Glomerular filtration rate	Decrease
Urine output	Decrease

Source: Reproduced from Muñoz et al [94] with permission of Wolters Kluwer.

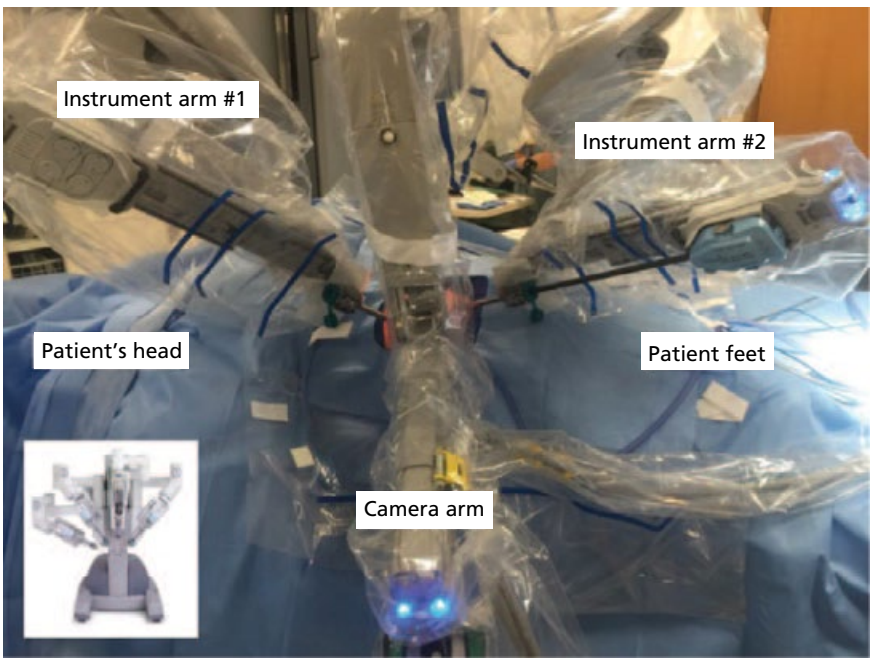


Figure 32.7 The surgical field after attachment of the robotic arms to the laparoscopic ports of the surgical robot ('docking'). Inset: Moveable robotic tower of the DaVinci® robot prior to docking. *Source*: Reproduced from Muñoz et al [94] with permission of Wolters Kluwer.

CO_2 insufflation [88]. It also improves conditions for controlled ventilation to maintain normocapnia [88,97].

It is recommended to decompress the bladder before obtaining surgical access to minimize the risk of bladder injury and to improve visualization of pelvic structures during the procedure since the bladder is in a more abdominal position in infants [99]. A distended stomach can similarly obstruct the surgeon's view of the operative field. Placement of a nasogastric or orogastric tube after induction decreases the stomach [95,102]. Nitrous oxide is frequently avoided given the risk of bowel dilation and an increased risk of postoperative nausea and vomiting [96].

Many of the complications seen with robot-assisted laparoscopic surgery in children are associated with the establishment of the pneumoperitoneum. This begins with possible vascular or bowel injury during trocar placement. The open "Hasson" technique is generally preferred for initial trocar placement in the pediatric population [88,97]. The anesthesiologist must be prepared for occult bleeding after access is obtained. Maintenance of adequate insufflation during instrument change can be more challenging in children than adult patients due to their thinner abdominal wall [99]. Port site hernias have been reported but are a rare complication [88,92]. Subcutaneous tissue emphysema, pneumothorax, and pneumomediastinum can occur during insufflation. The anesthesia team must be vigilant for the event of a venous gas embolism (Table 32.7) which can present with hypotension, hypoxemia, or sudden decrease in $ETCO_2$ [94,96]. $ETCO_2$ monitoring has been suggested by many to be a sensitive and non-invasive means of detecting gas embolism [103–110]. Several sources state an abrupt rise in $ETCO_2$ will occur [104]. However, most of the literature suggests there will be a significant decrease in $ETCO_2$ with carbon dioxide embolism and compromised cardiac output [103–110]. Tissue injury can occur from retraction, puncture, and during instrument change, as well as from cautery devices [88,92]. The anesthesiologist also must be prepared for emergent opening of the abdomen to address acute vascular injury and hemorrhage (Table 32.8) [94].

In infants, a limited amount of gas is available to dissipate heat from cautery devices. Cautery settings and active cautery time should be reduced [111].

Hypercapnia increases cerebral blood flow [97]. Significant increases in intracranial pressure during laparoscopic procedures have been reported in patients with ventriculoperitoneal shunts [112]. Robot malfunction as a complication is rare, with a reported incidence of 0.38–0.5% [91,92].

Table 32.7 Detection and management of CO_2 embolism

Signs and symptoms	Treatment
Sudden rise in $ETCO_2$	Inform surgeon and call for help
Acute hypotension	Deflate the pneumoperitoneum
Hypoxemia	Hyperventilation with 100% O_2
Dysrhythmias	Left lateral decubitus position with Trendelenberg
Pulmonary edema	Full cardiopulmonary resuscitation
'Mill-wheel' murmur on auscultation	Placement of central venous catheter to aspirate CO_2
Cyanosis of head and neck	Cardiopulmonary bypass if unresponsive to above

$ETCO_2$, end-tidal carbon dioxide.
Source: Reproduced from Muñoz et al [94] with permission of Wolters Kluwer.

Table 32.8 Detection and treatment of acute vascular injury/hemorrhage

Signs and symptoms	Treatment
Acute hypotension Tachycardia Arrhythmias Cardiovascular collapse	Notify the surgeon and call for help 100% O_2 Bolus intravenous fluids: crystalloid or colloid Turn off inhaled anesthetics, consider IV midazolam or diazepam to prevent recall Vasopressors: ephedrine, neosynephrine, or epinephrine depending on mean arterial pressure Obtain hematocrit and consider blood transfusion with O negative blood Cardiopulmonary resuscitation if perfusion is inadequate Prepare for laparotomy if bleeding not easily controlled

Source: Reproduced from Muñoz et al [94] with permission of Wolters Kluwer.

Two common pediatric urological procedures for which the robot-assisted laparoscopic approach has gained popularity are pyeloplasty and ureteral reimplantation. Technically challenging portions of both procedures, namely intracorporeal suturing during pyeloplasty and dissection and suturing of the bladder during reimplantation, benefit from the technical enhancements of robotic surgery over traditional laparoscopy [90,92].

The gold standard for pyeloplasty to treat ureteropelvic junction obstruction has traditionally been open dismembered pyeloplasty, with a success rate of 90–100% [92]. Transperitoneal and, less commonly, retroperitoneal robotic approaches have been described. In a multicenter observational study in 2015, Avery et al reported a 91% success rate for reduction or resolution of hydronephrosis and an 11% complication rate for the transperitoneal robot-assisted approach [111]. Robotic pyeloplasty has been associated with longer operating room time, but shorter length of stay and decreased total opioid requirement [113]. Children are generally placed on a clear liquid diet for 24 h prior to the surgery, and younger patients are given either a laxative or suppository [114]. The procedure typically includes retrograde or anterograde stent placement. Retrograde stent placement occurs during a cystoscopy at the beginning of the case [99]. Positioning for the robotic portion requires elevation of the affected side of 20–45°. The ipsilateral arm is extended [111]. Different options for port placement have been described. Triangular placement involves port insertion at the umbilicus, between the xiphoid and umbilicus, and in the ipsilateral lower quadrant. In smaller infants (<10 kg) an all midline placement (subxiphoid, umbilical, and suprapubic) approach is sometimes preferred [111]. Postoperative complications include ileus, evidence of bowel injury, urine leak, and persisting hydronephrosis [114].

Intra- or extravesical ureteral reimplantation is one of the treatment modalities for vesicoureteral reflux. The open approach has a reported success rate of 95–98% [115]. The

robotic intravesical approach is limited by challenges in maintaining pneumovesicum [90]. Patients with a bladder capacity of less than 130 mL are not considered good candidates [90,92,102]. In a small series, Marchini et al saw shorter urinary catheter drainage times, decreased bladder spasms, and shorter hospital stay in their robot-assisted intravesical ureteral reimplant patients compared with patients undergoing an open procedure [115].

Extravesical robotic ureteral reimplantation is more frequently performed than intravesical. Success rates are similar to open ureteral reimplantation [90]. The procedural steps are the same as for the open Lich–Gregoir technique [102]. Ports are placed at the umbilicus and in the midclavicular line bilaterally, approximately 1 cm below the level of the umbilicus. In small patients, the camera port may have to be placed above the umbilicus to avoid instrument collision [102]. The robot is positioned over the patient's feet [102]. Extravesical ureteral reimplantation can be associated with postoperative voiding dysfunction. Improved visualization with the robot may help avoid injury to the pelvic plexus [101]. In 2008, Casale et al reported robot-assisted extravesical ureteral reimplantation in 41 patients with a success rate of 97.6% and no occurrence of postoperative urinary retention [116].

KEY POINTS: ROBOTIC SURGERY

- Minimally invasive surgery is associated with less postoperative pain, shorter recovery, and better cosmesis
- Robotic surgery offers technical improvements over traditional laparoscopic surgery. However, space requirements, cost, and the lack of pediatric-specific equipment are limiting factors
- Good communication between the surgical team, anesthesia team, and operating nursing staff is essential
- Key anesthetic considerations are the management of the physiological changes associated with pneumoperitoneum, limitations in access to the patient, and proper patient positioning

CASE STUDY

An 18-month-old boy weighing 11 kg presents for robotic pyeloplasty for left ureteropelvic junction (UPJ) obstruction. He is an otherwise healthy product of a full-term birth without any complicatons. He has left hydronephrosis diagnosed on prenatal ultrasound, which has been followed with serial examinations and ultrasound; he has not had a urinary tract infection. Renal ultrasound a month before surgery demonstrated marked left intrarenal collecting system distension consistent with UPJ obstruction. He is taking no medications and has no drug allergies. Baseline vital signs and physical examination are normal.

The pediatric anesthesiologist explained the anesthetic plan to the parents, which included general endotracheal anesthesia, local anesthetic infiltration of the port sites by the surgeon, and parenteral analgesia. The low risk of acute anesthetic complications was discussed. Because the procedure was anticipated to last longer than 3 h, the anesthesiologist discussed the 2016 US Food and Drug Administration (FDA) warning about prolonged anesthesia in patients less than 3 years of age, and the theoretical risk of longer term neurodevelopmental problems. The surgery could not be deferred until a later date, and the parents had received a preanesthetic educational brochure that included the FDA warning information, and the surgeon had also discussed this with them during the office visit to schedule the surgery. They did not have any further questions and agreed to proceed, signing the anesthesia consent form.

After an oral midazolam premedication, an inhalation induction with sevoflurane was performed, after attaching standard ASA monitors. Two 22 g peripheral IVs were inserted and after muscle relaxation with rocuronium a 4.0 mm cuffed endotracheal tube was placed. After a dose of cefazolin was administered, a cystoscopy was performed in the supine position, confirming normal bladder and ureterovescicular junction anatomy. A left retrograde ureterogram confirmed UPJ obstruction. An orogastric tube to decompress the stomach, and Foley catheter to decompress the bladder, were placed. The patient was then postioned supine, and his left side was elevated on a gel roll such that he was at a 45° angle to the table. A right-sided axillary roll was then placed. He was carefully padded at all pressure points, including a gel pad under his head, and then he was secured to the table with silk tape across the chest, hips, and legs. The operating room bed was then airplaned 45° to the right side and to the left side to ensure that his position was stable and that he would not fall off the table. Endotracheal tube security and ventilator tube connections were checked carefully before draping, because access to the patient's head would be limited by the surgical robot. Final bed position was tilted left 45° to allow the surgical robot access to the field.

After sterile prep and draping, an infraumbilical port was placed and CO_2 pneumoperitoneum was achieved. The robotic camera scope was then placed in the infraumbilical port, and two additional robotic ports were placed, one in the midline just below the xyphoid process, and one in the left lower quadrant. An accessory laparoscopic port was placed in the right upper quadrant. The surgical robot was then docked into position for the surgery. A dismembered left pyeloplasty was performed, and a stent placed from the renal pelvis into the bladder. After inspection for intra-abdominal injury, the robotic instruments were removed and the robot undocked, and the port sites were closed. Estimated blood loss was 5 mL.

The anesthetic course was uncomplicated, with sevoflurane end-tidal concentration between 2.6% and 3.3% for anesthesia maintenance, and dense neuromuscular blockade was maintained with rocuronium to ensure motionless

operating conditions. No nitrous oxide was used to avoid bowel distension; and air–oxygen at a total flow of 2 L/min, with FiO_2 of 0.4–0.5, was utilized. Ventilation was with pressure control mode, and during CO_2 pneumoperitoneum peak inspiratory pressures were 24–25 cmH_2O, with tidal volumes of 65–75 mL (6–7 mL/kg) with end-tidal CO_2 values of 52–57 mmHg. Hemodynamic status was stable during the case, with a heart rate 120–130 bpm and systolic blood pressure of 75–90 mmHg. Ketorolac 0.5 mg/kg and morphine 0.2 mg/kg were administered at the beginning of the case, and the port sites infiltrated with 0.25% bupivacaine by the surgeon at the end of the case. A total of 450 mL of lactated Ringer solution was administered and the patient had 80 mL of urine output. At the end of the case the neuromuscular blockade was reversed, and the trachea was extubated with the patient awake. The total anesthetic time was 3 h 32 min.

The patient was transferred to the postanesthesia care unit (PACU) where he received two additional doses of 0.5 mg morphine for analgesia. After a 1 h PACU stay he was transferred to the surgical ward for overnight admission. Analgesia was with one dose of morphine, and then oral hydrocodone-acetaminophen and ibuprofen. He resumed a normal diet by the morning after surgery and was discharged home later that day with instructions to use acetaminophen and ibuprofen first for pain, and only use the hydrocodone-acetaminophen for significant pain.

This case illustrates the anesthetic considerations for robotic surgery: a long anesthetic period in a young child that may necessitate discussion of potential anesthetic neurotoxicity, very careful positioning and padding to ensure security of the patient with extremes of operating room bed position, a cuffed endotracheal tube to maintain ventilation during pneumoperitoneum, maintenance of neuromuscular blockade, vigilance for hemodynamic changes from CO_2 insufflation or bleeding, and the general lack of severe pain, and rapid recovery and discharge home after a hospital stay of less than 24 h. Although surgical duration may be longer with the robotic technique, in experienced hands the difference is minimal compared with conventional laparoscopic techniques.

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A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 33
Anesthesia for Orthopedic Surgery

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Introduction

Orthopedic surgery procedures are among the most common anesthetics that many pediatric anesthesiologists perform, and include a wide variety of surgeries, and patients. This includes many patients with significant neuromuscular diseases and multiple co-morbidities, healthy children with fractures, fractures from non-accidental trauma, and very healthy teenaged athletes with sports injuries. This chapter presents the major neuromuscular and genetic diseases that result in patients presenting for orthopedic surgery. It also covers orthopedic surgeries in otherwise healthy children such as fractures and septic joints. Non-accidental trauma as a cause of fractures is also discussed. Anesthesia for spinal surgery is presented in Chapter 29.

Clubfoot

Clubfeet or congenital talipes equinovarus are classified as being positional or rigid. Rigid abnormalities are either flexible or resistant. The incidence of clubfoot is 1/1000 livebirths in the United States but may be higher in certain ethnicities (e.g. Polynesian islanders). Males are twice as affected as females. There is bilateral involvement in 30–50% of cases. Parents of a child with clubfoot have a 10% chance of having another child with clubfoot [1]. The etiology is often unknown. Most infants have no identifiable genetic syndrome or extrinsic cause. Extrinsic causes include oligohydramnios, congenital concentric rings, and teratogenic agents. Pathophysiological theories include arrest of fetal development, defective cartilage production, changes in innervation leading to paresis, increased fibrous tissue in muscles and ligaments, abnormal tendon insertion, and possible prenatal polio-like condition; the latter is based on changes in the motor neuron of the anterior horn in the spinal cord [2].

On physical examination, the foot is supinated in the varus position and adducted (Fig. 33.1). Dorsiflexion is limited. The navicular, cuboid, and anterior aspects of the calcaneus are displaced medially [3]. There are contractures of the medial plantar soft tissues. The heel is small and empty. The medial malleolus is difficult to palpate and is often in contact with the navicular bone. The tibia is often internally rotated. The leg muscles are frequently atrophied, especially the peroneal muscle group. Although the number of muscle fibers is normal, they are smaller in size. The calf is often small and remains small even after successful correction of the lesion [4].

The goal of therapy is to correct the deformity early and maintain alignment of the foot until growth ceases [5]. The Pirani scoring system is used to identify the severity of the clubfoot and is based on the curvature of the lateral border, medial crease, uncovering of the lateral head of the talus, posterior crease, emptiness of the heel, and degree of dorsiflexion [6]. Non-operative treatment (splinting and casting) begins 2–3 days after birth with forefoot adduction, followed by forefoot supination, and then correction of the equinus [7]. Gentle manipulation of the foot is needed to avoid producing a rocker-bottom foot. If splinting and casting are unsuccessful, surgery is indicated, usually at 6 months of age when the anatomy is more identifiable. In children younger than 5 years of age, soft tissue procedures are indicated. In children older than 5 years, bony reshaping or osteotomy of the calcaneum may be needed. Lateral wedge tarsectomy or triple fusion is required in children older than 10 years [8]. Complications of surgical correction are wound breakdown, infection, avascular necrosis, stiffness, and residual deformity.

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

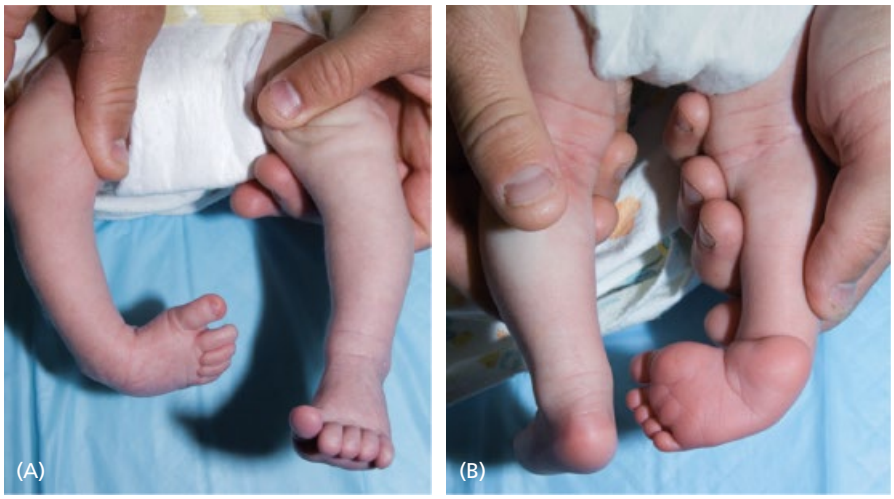


Figure 33.1 Clubfoot. (A) Anterior view of a baby with clubfoot. (B) Posterior view of the same child.

Preoperatively, one looks for co-morbid conditions (e.g. arthrogryposis, myelomeningocele) that include cardiovascular, respiratory, hematological, and neurological problems that have their own anesthetic implications. Although both general and regional anesthesia may be performed for clubfoot surgery, peripheral nerve blocks like posterior sciatic and femoral nerve blocks are generally avoided because the surgeons must examine the patient for postoperative neurological changes and for possible compartment syndrome with casting. While spinal and epidural anesthesia have been used for clubfoot surgery, there was no significant decrease in postoperative opiate use [9]. Tourniquets must be used cautiously in patients who have fragile bones. Postoperatively, pain is minimal and amenable to standard doses of opiates and acetaminophen.

KEY POINTS: CLUBFOOT

- A relatively common disorder that requires early treatment
- Initial treatment is splinting or casting at 2–3 days of age
- Failed correction with casting requires surgery
- Femoral and sciatic nerve blocks are avoided because surgeons must examine patients postoperatively

Hip dysplasias/dislocations

Hip dysplasia refers to a hip that can be dislocated from or relocated into the acetabulum. Hip dislocation describes a non-reducible hip that is associated with shortening, decreased abduction, and asymmetry of skinfolds. The normal hip joint consists of a femoral head and the acetabulum which develop from the same primitive mesenchymal cells. In the 11th week of fetal life, the hip joint is fully formed and may begin to dislocate if predisposed to do so [10]. Subluxation of the hip occurs in 1% of newborn infants. Patients with dysplasia or dislocation of the hip do not have the normal tight fit between the femoral head and the acetabulum. The majority of abnormalities in developmental hip dysplasia or dislocation are on the acetabular side. Acetabular shape is determined by 8 years of age in most children. Growth of the acetabulum is affected by abnormal acetabular cartilage, which is influenced by several factors, including the presence of a spherical femoral head, interstitial growth within the acetabular head, appositional growth under the perichondrium, and growth of adjacent bones (ileum, ischium, pubis). The dysplastic hip has a ridge (the limbus) in the superior, posterior, and inferior aspects of the acetabulum that is made of cellular hyaline cartilage. The limbus is a hypertrophied labrum [11].

Increased risk for abnormalities of the hips is indicated by female gender, first born, breech delivery, oligohydramnios, a positive family history for hip dysplasia, persistent hip asymmetry, torticollis, and lower limb deformity. All newborns are now screened for hip dyslplasia and dislocation with the Ortlani and Bartlow signs [12]. The *Ortlani sign* is positive when the hip is abducted, the trochanter is elevated, and the femoral head glides back into the acetabulum with a characteristic click. The *Barlow sign* is positive when the femoral head exits the acetabulum with the hip flexed and adducted. Ultrasonography helps to confirm the diagnosis and identify more subtle forms of dysplasia or dislocation. This should be performed in suspected cases at 4–6 weeks of age. If the diagnosis is missed at birth, there are four possible outcomes. The hip may become normal, subluxate or develop partial contact, completely dislocate, or remain located in the hip with dysplastic features. Physical findings of late diagnosis include shortened limb, asymmetry of gluteal, thigh, or labial skinfolds, and limited hip abduction. Patients with bilateral involvement have a waddling gait and hyperlordosis.

The Pavlik harness is the treatment of choice for infants and neonates with developmental hip dysplasia or dislocation. This device consists of a chest strap, shoulder straps, and anterior and posterior stirrup straps that maintain the hips in flexion and abduction while restricting extension and adduction (Fig. 33.2) [13].

Contraindications to the Pavlik harness include major muscle imbalance (e.g. myelomeningocele), major stiffness (e.g. arthrogryposis), ligamentous laxity (e.g. Ehlers–Danlos), patients older than 10 months of age, and lack of family support and care. The harness is worn until there are no positive findings on clinical, ultrasonographic, or radiographic

(A) (B)

Figure 33.2 Pavlik harness: (A) posterior and (B) anterior aspects.

examinations. If the hip remains unstable with use of a Pavlik harness, a hip abduction brace is recommended. Complications of the harness include inferior dislocation, femoral nerve palsy, and avascular necrosis of the hip from excessive hip flexion [14].

An abduction orthotic is an alternative for infants who are more than 9 months of age. This maintains abduction while allowing the child to walk. Skin traction is recommended for older infants who have a dislocated hip and have failed to improve with a Pavlik harness or for children more than 9 months old. Skin traction is followed by adductor tenotomy, closed reduction of the abnormality, and spica cast application [15]. Children more than 2 years old are treated with primary femoral shortening, open reduction of the hip, capsulorrhaphy (suture of capsule tear in order to prevent dislocation), and pelvic osteotomy [16,17]. The decision to perform open reduction of the hip is made in the operating room after arthrography and failed closed hip reduction [18].

Preoperatively, it is important to identify co-morbid conditions or underlying bone pathology that may affect the overall anesthetic. Baseline laboratory studies, such as complete blood count, chemistry, and coagulation studies, are not necessary for healthy children but will help identify abnormalities if co-morbidity exists. Intraoperative anesthesia technique includes general anesthesia with the possible addition of regional anesthesia during correction of hip pathology, if no contraindications exist. Spinal or epidural anesthesia may help with postoperative pain control in inpatients. If an epidural catheter is placed, care must be taken to cut a hole posteriorly in the spica cast so that the catheter can be removed from the patient. While the child is being placed in a spica cast under anesthesia, care must be taken during cast application to ensure that the arms are supported and head and neck are in alignment to prevent injury to major nerves. Postoperatively, oral pain medication can include acetaminophen, opioids, and short-term non-steroidal anti-inflammatory drugs (NSAIDs).

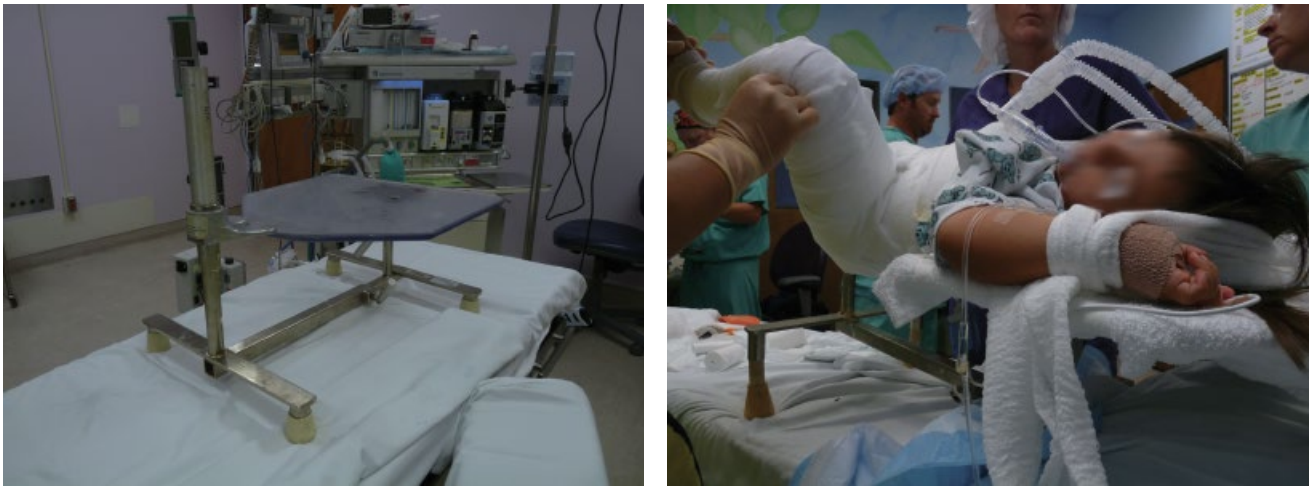
KEY POINTS: HIP DYSPLASIA

- Diagnosed at birth (ideal): Pavlik harness, serial ultrasounds, no surgery
- Older than 10 months: hip abduction brace, closed hip reduction with spica; if surgery then skin traction, adductor tenotomy, closed reduction of abnormality, spica cast
- Older than 2 years: primary femoral shortening, open reduction of the hip, capsulorrhaphy, pelvic osteotomy
- Surgical decisions in the operating room should be made with arthrography if closed hip reduction has failed
- Anesthesia: consider intrathecal or epidural for osteotomy postop pain

Spica cast

Spica casts create stability and immobilize femoral fractures or hip abnormalities (Fig. 33.3).

Contraindications to these devices include unacceptable shortening or angulation of the lower extremities, open fractures, thoracic or intra-abdominal trauma, and large or obese children [19]. Anesthesia is usually required to apply a spica cast. Fluoroscopy is used to determine optimal position, i.e. the affected limb or hip is placed in mild abduction. Too much abduction results in lateral bowing of the femur due to pull of the adductors. The degree of hip flexion, hip adduction, and external rotation depends on the location of the femoral fracture or hip abnormality [20]. A folded towel is placed on the anterior thorax and abdomen and padding and casting material are placed over the towel. When the towel is removed (after the cast is applied) this creates space between the cast and the thorax/abdomen, allowing for free breathing. Two layers of stockinette are placed to ensure that the cast padding can be pulled over the edges of the cast. Gore-Tex™ soft wrap



(A) (B)

Figure 33.3 (A) Spica cast table and (B) with a child on the table.

is often applied prior to applying a thick felt belt across the chest, sacrum, posterior superior iliac spine, and anterior superior iliac spine. The casting material is often placed over the non-affected side for stability. A wooden stick is placed between both legs and covered in cast material. This reinforces the cast and prevents breakdown of the cast at the hip joint. In small children, spica casts are applied while the child is on a portable, elevated, narrow table that provides very little head support.

The goals of anesthesia during cast placement include hemodynamic stability, appropriate amnesia and analgesia, and safe positioning of the patient. The choice of anesthetic technique is dictated by the patient's health status and by any coexisting disease. With elevation of the patient off the operating room table, vigilance is required to assure that the upper extremities and neck are in alignment with the long axis of the body to prevent nerve injury and paralysis.

Blount disease

Blount disease is a growth disorder of the medial aspect of the tibia in children. It causes the legs to bow outwards below the knees [21]. Normal infants have a small amount of physiological bowing that usually resolves by 2 years of age. In Blount disease the legs remain bowed, and the inner surface of the legs bulge outward just below the knee. A metaphyseal–diaphyseal angle greater than 11° is more indicative of Blount disease [21]. The toes also begin to point inwards as internal tibial rotation and asymmetrical leg shortening develop. Most patients are healthy, without congenital abnormalities, and may not experience much pain. If pain is present, it is usually related to the knee joints.

Blount disease usually affects children younger than 4 years old, in which case it is called infantile tibia vara. Adolescent tibia vara occurs after 4 years of age. Blount disease is more common in Africa, the West Indies, and Finland. Sixty to 70% of cases are bilateral and symmetrical [22]. Risk factors for Blount disease include female sex, African-American race, obesity, early age at walking, and a positive family history for this problem. The cause of Blount disease is unknown but may be related to a combination of genetic, environmental, and mechanical factors [23]. The medial aspect of the growth plate fails to develop properly, while the lateral aspect grows normally. This results in deviated growth of the tibia. If untreated, the disease results in the onset of osteoarthritis in the third decade of life. In the USA, the estimated prevalence of infantile Blount disease is less than 1% and adolescent disease is 2.5%. The disease is non-existent in non-ambulatory people. Adolescent tibia varus differs from Blount disease in that patients with varus complain more about knee pain, have unilateral involvement in 80% of cases, have shortened leg length, and may be obese [24–26].

Under 2 years of age, observation of the patient and follow-up with an orthopedic surgeon are recommended to distinguish physiological bowing from abnormal bowing. If bowing persists during ages 2–4 years, orthotic braces from the top of the thigh to the tips of the toes are recommended [27]. In children with severe bowing or who are more than 4 years of age, osteotomies of the tibia and occasionally the fibula are most commonly performed to correct the misalignment [28]. Other operative treatments include removing the epiphysis to stop abnormal growth or an osteotomy followed by external fixation [29,30]. If treated early, patients develop fully functioning lower limbs and have no limitations of movement. Complications of treatment include loss of alignment of lower extremities, vascular impairment, pathological fractures, and wound infection.

Preoperatively, the anesthetic implications of existing comorbidities must be considered. Concurrent obesity may lead to airway difficulties, respiratory problems, obstructive sleep apnea, increased risk of aspiration, and difficulty inserting an intravenous catheter. Intraoperatively, both general and regional anesthesia can be utilized if they are not contraindicated. Fat or venous air embolism must always be suspected if acute decompensation in the patient's condition occurs during surgery. Presenting symptoms of fat embolism under general anesthesia may include hypoxemia, petechial rash, and hypotension. Presenting symptoms of venous air embolism under general anesthesia may include decreased end-tidal carbon dioxide and hypotension. Surgical blood loss is usually minimal. Postoperatively, it is important to perform a neurovascular examination to make sure that no important

vascular or neural structures were damaged during corrective repair. Pain control can be managed with intravenous patient-controlled analgesia or regional blocks. Obesity with or without the diagnosis of obstructive sleep apnea puts the patient at increased risk of respiratory depression with opiates. NSAIDs such as ketorolac and ibuprofen in addition to acetaminophen can be administered around the clock to minimize the cumulative dose of opiates.

KEY POINTS: BLOUNT DISEASE

- Associated with obesity/obstructive sleep apnea with increased risk of respiratory depression with opiates
- Fat or venous air embolism risk

Slipped capital femoral epiphysis

Slipped capital femoral epiphysis (SCFE) consists of a defect of the proximal femoral growth plate, which causes instability of the femoral head. The femoral head is displaced posteriorly and inferiorly from the femoral neck. SCFE presents with hip, medial thigh, and knee pain. The range of motion of the hip is limited and causes a limp. The incidence of SCFE is 10.8/100,000 children. Higher rates of prevalence exist in males, African-Americans, Hispanics, and people who live in the west and north-east of the United States [31]. The average age of occurrence of SCFE is between 10 and 16 years. Twenty percent of patients have bilateral involvement. High-risk patients include those with obesity, hypothyroidism, low concentrations of growth hormone, pituitary tumors, craniopharyngioma, Down syndrome, renal osteodystrophy, and adiposogenital syndrome [32–34]. The left hip is affected more commonly than the right. Familial involvement is present in 5–7% of patients with SCFE. In patients younger than 10 years of age, SCFE is associated with metabolic endocrine disorders. Unstable SCFE produces a non-ambulatory patient and has a higher risk of avascular necrosis [35]. On physical examination, internal rotation of the affected leg is very painful.

Emergency treatment is necessary. If surgical correction is performed within 24 h of onset, the risk of avascular necrosis decreases. Immediate internal fixation with a screw is the treatment of choice [36]. Repair of SCFE permits early stabilization of slippage, prevention of further slippage, increased physeal closure, and improvement of symptoms [37]. The fixation may require revision if the child outgrows the screw. Prophylactic fixation of unaffected hips should only occur if patients have endocrine or metabolic conditions and are outside the usual age group of 10–16 years [38,39]. Osteotomy of the proximal femur may be required to reposition the femoral head and improve functional range of motion. Bone graft epiphysiodesis and internal fixation can be performed but may result in avascular necrosis, chondrolysis, poor initial fixation, prolonged operative time, increased intraoperative blood loss, and loss of epiphyseal position [40].

Preoperatively, a thorough history and physical examination elucidate significant co-morbidities that may affect anesthetic technique. Given that obesity has a high association with SCFE, one must evaluate and prepare for an obstructed airway, restrictive lung disease, and a difficult airway. Some obese patients also have type 2 diabetes. In rare cases hypothyroidism and renal osteodystrophy may also be present. Preoperative studies should include baseline hematocrit, serum electrolytes, and a type and screen for blood.

Intraoperatively, the patient may be placed supine or in lateral position. During positioning of the patient, care must be taken to avoid nerve compression or injury, especially in obese patients. The Chick fracture table (Fig. 33.4) or the Hana fracture table (Fig. 33.5) are often used and require careful padding and securing of the patient to the table. Access to the airway during surgery can be limited. Tracheal intubation is usually done prior to transfer to the fracture table both for patient comfort and better access to the head of the bed.

The choice of anesthetic technique is influenced by the patient's baseline health status and co-morbidities. General anesthesia, in conjunction with regional anesthesia if an open procedure is being done, may be performed if there are no contraindications to regional anesthesia. A one-time caudal injection of local anesthetic can be helpful; inserting caudal catheters is usually unnecessary. If the repair is achieved with pinning, pain control is generally good without regional block. If the patient is obese or has a difficult airway, a modified rapid-sequence induction may be considered. Third space fluid losses are usually 3–6 mL/kg/h. Blood loss is typically minimal. Postoperative pain is usually controlled with opioids and acetaminophen. Short-term NSAIDs may also be helpful and have not been shown to significantly affect epiphyseal growth.

KEY POINTS: SLIPPED CAPITAL FEMORAL EPIPHYSIS

- Obesity association: increased risk of respiratory depression with opiates and occurrence of obstructive sleep apnea
- Fracture table limits patient access
- Emergent case to decrease risk of avascular necrosis
- Internal fixation with a screw (pinning) is most common approach; open repair for complex SCFE

Figure 33.4 Chick table.

Figure 33.5 Hana® fracture table. *Source*: Courtesy of Mizuho OSI, Union City, CA, USA.

Hand surgery

Many different types of disorders that require hand surgery exist in childhood (Box 33.1). These include, but are not limited to, extra fingers (polydactyly), webbed fingers (syndactyly), missing fingers (symbrachydactyly – hand or arm deficiency), abnormal thumbs, stiff joints, and nerve and skeletal injuries [41,42]. The abnormalities range from mild to severe in their presentations. Given the complexity and variation of each deformity, only a few of them will be described in detail in this text. Although most hand malformations cause little functional deficit, surgery is usually performed within the first 2 years of life to improve growth and reduce scarring, and to reduce psychological trauma. Early surgery also improves adaptation to the use of the newly formed part [43].

Syndactyly surgery is performed after a child is 2 years old and growth of the hand has slowed [44]. Syndactyly is twice as common in boys as in girls and occurs in 1/2000 livebirths. It commonly affects the long and ring fingers [45]. Skin grafts may be required to close the defects caused by separation of the digits. About half of treated children return for surgery during adolescence for further cosmesis once the hand reaches full size [46]. Symbrachydactyly is a condition in which a child is born with small or missing fingers, a short forearm, or a missing hand. It is the most common form of hand or arm deficiency [47]. The cause is unknown and is not attributed to genetic inheritance. It is usually unilateral; muscular abnormalities may be present on the ipsilateral side. Although surgery is often not required, it can help to deepen the webs between the fingers and to stabilize the fingers when bone grafts are used. Thumb polydactyly has varying forms, ranging from a broad fingernail to complete double thumbs [48]. Reconstructive surgery sometimes combines parts of the two different thumbs to create one functional thumb. Surgery is usually delayed until the thumb is large enough to allow the surgeon to reconstruct the nerves, ligaments, and bone.

Trigger thumb occurs when a nodule on the tendon causes the thumb to jump or lock into a bent position with movement. This condition develops after birth and is present at 1 year in 3.3/1000 livebirths. Hand surgeons must evaluate and treat this condition promptly to prevent contracture, but 30% of these lesions resolve spontaneously. Treatment involves surgery to enlarge the tendon sheath and to allow the tendon to move more smoothly. This is performed usually between the ages of 1 and 3 years.

Radial club hand is a deficiency of the radius in the forearm. It occurs 1/30,000–1/100,000 livebirths and includes an absent or incomplete radius, absent or incomplete thumb, deviation of wrist toward the radial side, and some degree of neuromuscular deficiency. The cause of radial club hand is unknown, but it has been suggested that irradiation or environmental and nutritional factors may be involved. Radial club hand may be associated with other genetic syndromes such as VACTER (vertebral, anal, cardiac, tracheoesophageal, and renal anomalies), Holt–Oram syndrome (heart and hand syndrome), thrombocytopenia with absent radius syndrome, and Fanconi anemia [49]. Therefore a thorough investigation of other possible organ abnormalities must be undertaken. Treatment of radial club hand starts with splinting, casting, and non-surgical manipulation of the hand. If needed, surgery is typically performed between 6 months and 1 year of age. The procedure is called centralization/radialization of carpus on ulnar epiphysis, which relocates the hand over the

Box 33.1: Hand malformations

- Cerebral palsy contractures
- Arthrogryposis contractures
- Juvenile arthritis
- Madelung's deformity – malformed wrist bones
- Ulnar longitudinal deficiency
- Bite wounds
- Retained foreign objects
- Ganglion cysts
- Hemangiomas
- Lipomas
- Vascular malformations
- Amputations
- Crush injury
- Nailbed injury
- Mallet finger – damage to extensor tendon
- Rugger jersey finger – damage to flexor tendon
- Burn wound and scar management
- Polydactyly
- Symbrachydactyly
- Syndactyly

ulna [50]. The affected limb is usually shorter than the contralateral limb after this repair. If too severe, a procedure can be done between 6 and 8 years of age to lengthen the extremity. If the thumb is absent or underdeveloped, the hand surgeon can also make the index finger into a thumb ("pollicization") to allow grasping.

Preoperative evaluation consists of gathering information about other possible co-morbidities and evaluating the child's maturity and social environment. All may affect the type of anesthesia chosen. For example, it must be determined if children with congenital hand deformities have associated heart, lung, kidney, or airway problems that must be addressed. If there are vascular malformations of the hand, one must be suspicious that there are other vascular malformations (e.g. oropharyngeal) and that the child may have a high output state and heart failure. In trauma, full stomach aspiration risks need to be addressed. The child's maturity will also dictate whether a procedure should be performed with sedation or local anesthesia, with or without general anesthesia. If the surgery is elective or semi-urgent, laboratory tests are performed if anemia or coagulopathy is suspected. If other co-morbidities exist, an electrocardiogram and chest x-ray should be considered if indicated. A baseline neurovascular examination should be performed to evaluate sensation and perfusion to the affected hand. The findings of the examination should be documented in the anesthetic record.

Intraoperatively, combined regional and general anesthesia has been shown to improve postoperative recovery and decrease the need for postoperative analgesics. Most children who undergo surgery require general anesthesia. Small cases, such as distal fingertip amputation, can be performed with local anesthesia and sedation if the child is cooperative. More extensive cases are amenable to using a combined regional and general anesthetic if there are no contraindications. Contraindications to peripheral blocks include hand infection, generalized sepsis, coagulopathy, predisposition to compartment syndrome, parental/child dissent, or the surgeon's need to perform an immediate postoperative examination of the extremity [51].

The nerve supply to the hand includes three major branches of the brachial plexus (Table 33.1). The median nerve originates from the lateral and medial cords of the brachial plexus (C5–T1). It innervates the muscles involved in pinching and grasping (i.e. flexor carpi radialis, palmaris longus, flexor digitorum superficialis, flexor pollicis longus, flexor digitorum profundus, and pronator quadratus). It provides sensation to the lateral aspect of the palm, including the thenar eminence and the distal ends of the first three and a half fingers dorsally. The ulnar nerve originates from the medial cord of the brachial plexus (C8–T1). Motor branches innervate the flexor carpi ulnaris, flexor digitorum profundus, and the hypothenar muscles. This nerve provides sensation to the medial dorsal aspect of the hand and to the last one and a half fingers. The radial nerve originates from the posterior cord of the brachial plexus (C6–8) and innervates the wrist extensors and provides sensation to the lateral dorsal aspect of the hand and proximal portion of the first three and a half fingers (Fig. 33.6) [131].

Regional anesthetic techniques appropriate for hand surgery include Bier block (intravenous local anesthetic), axillary block (Fig. 33.7), infraclavicular block, wrist block, elbow block, and digital block (Table 33.2) [51]. Of these, the infraclavicular block is best suited to catheter placement because the area is generally cleaner, and it is easier to secure the catheter. Regional anesthesia is relatively contraindicated in children less than 1 year old due to systemic local anesthetic toxicity. It may also be contraindicated in children susceptible to tourniquet injury (e.g. osteogenesis imperfecta). Most hand surgery requires use of a tourniquet, which is associated with hyper/hypotension and respiratory and lactic acidosis from repeated inflation and deflation of the tourniquet. If not properly applied, tourniquets can lead to paralysis, sensory loss, excessive edema, skin problems, and muscle damage. Chapter 20 presents a detailed discussion of regional anesthetic approaches to the brachial plexus including ultrasound-guided techniques.

Postoperatively, it is important to determine if there are new or worse neurovascular deficits. Pain can be controlled with residual regional anesthetic, intravenous patient-controlled analgesia, and oral medication.

Supracondylar femur fractures

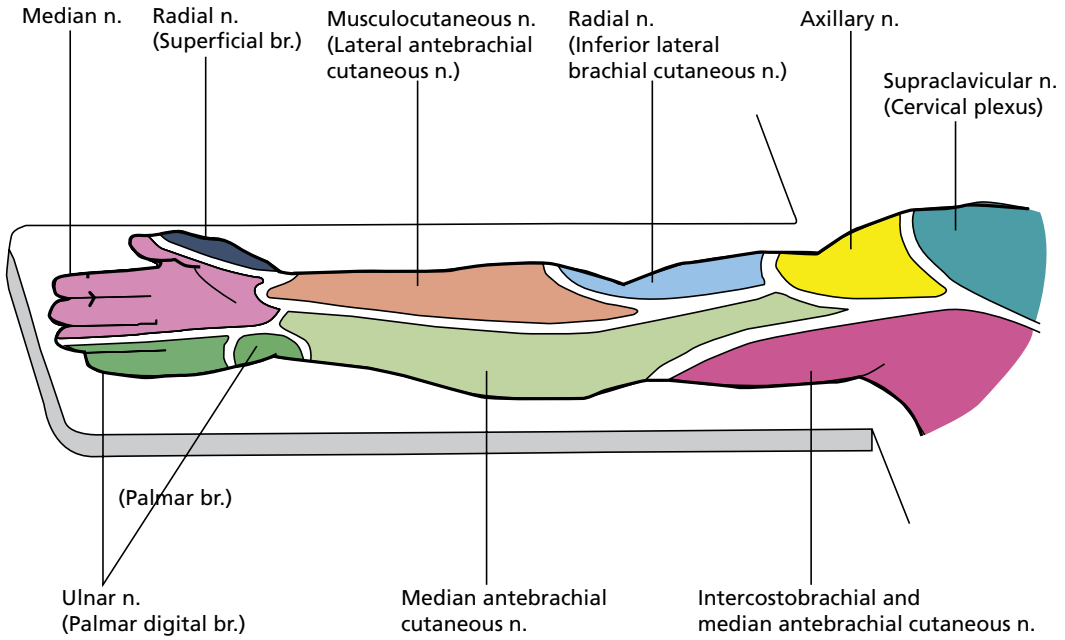
A supracondylar fracture represents 12% of femoral fractures in children and is the most common femur fracture in infants less than 1 year old, often due to non-accidental trauma (child

Table 33.1 Nerve supply to the hand: three branches of the brachial plexus

	Origin	Motor	Sensory
Median nerve (MN)	Lateral and medial cords of the brachial plexus (C5–T1)	Flexor carpi radialis Flexor digitorum superficialis and profundus Flexor pollicis longus Pronator quadratus	Lateral aspect of the palm Thenar eminence First three fingers, dorsal aspect Lateral half fourth finger
Ulnar nerve (UN)	Medial cord of the brachial plexus (C8–T1)	Flexor carpi ulnaris Flexor digitorum profundus Hypothenar muscles	Medial dorsal and palmar sides of the hand Fifth finger Medial half fourth finger
Radial nerve (RN)	Posterior cord of the brachial plexus (C6–8)	Wrist extensors	Lateral dorsal aspect of the hand Proximal portion first three and a half fingers

Figure 33.6 Upper extremity peripheral nerve and osteotome innervation. (A) Peripheral nerve innervation with arm supinated on an arm board. (B) Peripheral nerve innervation with arm pronated on an arm board. (C) Osteotomes with arm supinated on an arm board. (D) Osteotomes with arm pronated on an arm board. *Source*: Reproduced from Brown [131] with permission of Elsevier.

(A)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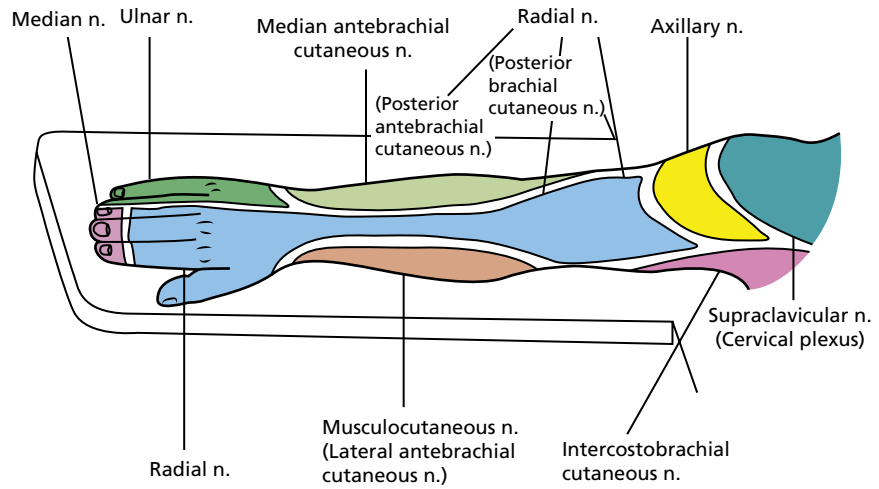
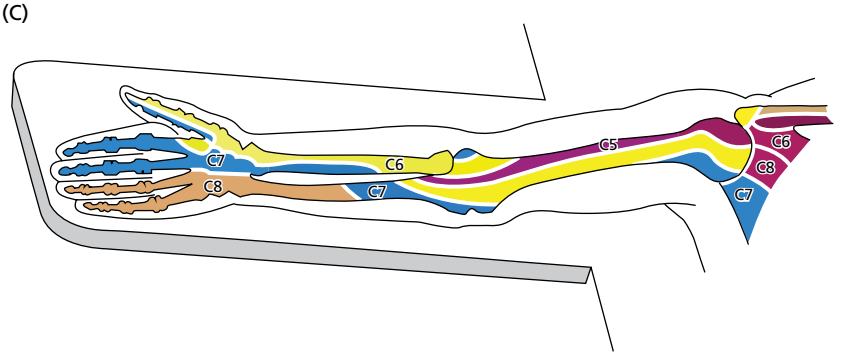
(Superficial br.)
Musculocutaneous n.
(Lateral antebrachial
cutaneous n.)
Radial n.
(Inferior lateral
brachial cutaneous n.)
Axillary n.
Supraclavicular n.
(Cervical plexus)
(Palmar br.)
Ulnar n.
(Palmar digital br.)
Median antebrachial
cutaneous n.
Intercostobrachial and
median antebrachial cutaneous n.

(B)


Median n.
Ulnar n.
Median antebrachial
cutaneous n.
Radial n.
(Posterior
brachial
cutaneous n.)
(Posterior
antebrachial
cutaneous n.)
Axillary n.
Supraclavicular n.
(Cervical plexus)
Radial n.
Musculocutaneous n.
(Lateral antebrachial
cutaneous n.)
Intercostobrachial
cutaneous n.

(C)


C7
C8
C6
C7
C5
C6
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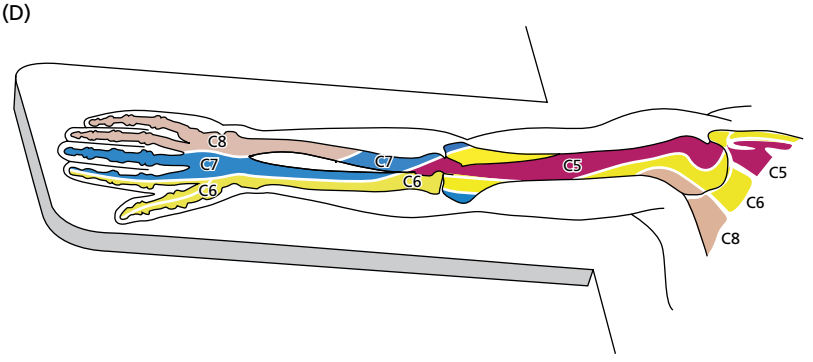
C7

(D)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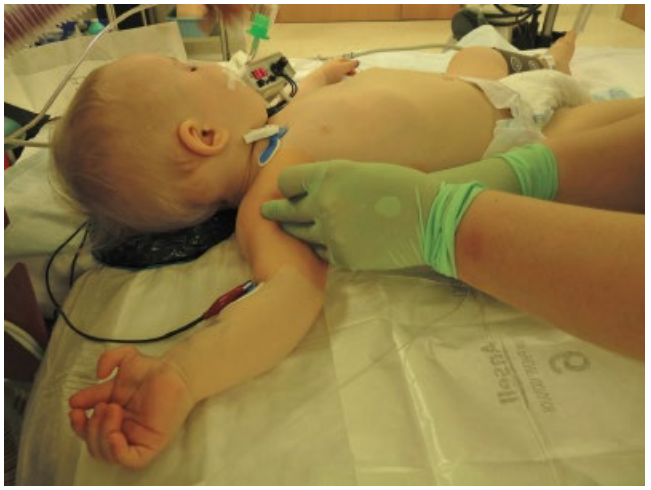

Figure 33.7 This patient with thumb polydactyly is undergoing an axillary nerve block.

Table 33.2 Regional anesthetic techniques appropriate for hand surgery

Block	Technique details
Bier block (intravenous local anesthetic)	Limited use in pediatric patients due to volume of local anesthetic needed to achieve surgical anesthesia Provides little postoperative analgesia
Axillary block	Effective block due to the proximity of axillary artery to median, ulnar & radial nerves Musculocutaneous nerve spared Not amenable to catheter placement
Infraclavicular nerve block	Brachial plexus block at the level of all three cords Stable location for catheter placement
Forearm blocks	Include radial, ulnar and median nerve blocks Anesthetize proximal palmar and dorsal cutaneous nerves of the hand Spare flexors/extensors of the arm at the elbow

abuse) [54]. Although the incidence is slightly less, it is still very common at ages 1–4 years. The American Academy of Orthopedic Surgeons recommends screening children younger than 36 months of age with femoral shaft fracture for non-accidental traume. In adolescents, motor vehicle accidents (cars, bicycles) are the leading cause of femoral shaft fractures. Other causes of femoral shaft fracture include falling hard on the playground and in contact sports. Fractures are described by location, shape of fractured ends, and number of fractured parts [55].

Non-surgical treatment of some femoral fractures includes closed reduction, a Pavlik harness, or spica casting (see earlier) [56]. Pathological bone is often treated with closed methods, due to abnormal bone fragility. Closed reductions are often done under sedation, but the child may require general anesthesia if they are uncooperative or the defect is extreme. Pavlik harnesses are soft restraints that go around the patient's shoulders and body and hold the hips in a flexed position. Spica casts typically begin at or below the nipple line of the chest and extend to slightly beyond the fracture or defect [57]. They hold the broken bone in alignment while it heals. The broken bones should not overlap by more than 2 cm when in the cast. Increased growth of the damaged femur will overcome the initial shortening caused by the overlap [58]. If casting causes greater than 3 cm shortening or misalignment of the bones, traction may help to align the bones properly. Children who are older, large, or obese and have multiple trauma, head injury, and/or soft tissue damage usually require operative fixation of the bones.

Recently, there has been a trend towards more surgical stabilization than in previous years, due to earlier mobilization, faster rehabilitation, and less time spent in hospital [59]. Flexible intramedullary nails are used in 6–10-year-old children [60]. If the bone is broken into many pieces (comminuted), other options include a plate with screws to bridge the fracture, an external fixator, or prolonged traction with a temporary pin in the femur [61]. Once skeletal maturity is achieved (about 11 years of age), there is less risk of vascular compromise to the growth plate. Treatment options at this point include flexible or rigid locked intramedullary nails. Rigid locked intramedullary nails allow walking immediately. Most children with femoral shaft fractures will heal, regain normal function, and have legs of equal length. The intramedullary nails may need to be removed after healing if skin or tissue irritation occurs [62]. If there is significant leg length discrepancy, angulation or rotation of the leg, or if infection or non-union persist, further surgical intervention will be required [63].

Preoperatively, it is important to note the mechanism of injury, as this may provide clues to other associated injuries (e.g. neck or skull injury). Conditions associated with bone fragility require care in positioning the patient, care in the use of non-invasive versus invasive blood pressure monitoring, and care in the use of a tourniquet. In addition to thorough airway, respiratory, and cardiovascular examinations, it is important to perform and document a neurovascular examination that will provide the baseline for evaluating postoperative changes. A preoperative hematocrit and a type and cross-match of blood should be obtained because hemorrhage can occur into the thigh with femur fractures.

Intraoperatively, either general or regional anesthesia may be used to provide anesthesia. Spinal anesthesia works well in older, cooperative children if there are concerns for a full stomach or a difficult airway. Peripheral nerve blocks plus general anesthesia work well, but a thorough discussion with the surgeon should take place beforehand, as there is a high risk of compartment syndrome (which can be masked by a nerve block) and coagulopathy. Adequate intravenous access must be present for infusing fluid and blood products. Depending on the location of the fracture and the size of the patient, a tourniquet may be used to limit the amount of blood loss. The anesthesiologist must be prepared for the hemodynamic changes that are sometimes associated with using a tourniquet. Fat and venous air embolism from bone manipulation may also cause adverse hemodynamic effects. Postoperatively, patients are typically placed into casts to stabilize the fracture site. Opioids and acetaminophen are usually adequate for pain control.

KEY POINTS: SUPRACONDYLAR FEMUR FRACTURE

- Preoperative hemoglobin, blood type, and cross-match packed red blood cells
- Tourniquet to limit blood loss
- Preoperative neurovascular exam; may limit regional anesthesia options
- Fat/venous air embolism risk

Septic arthritis

Septic arthritis usually occurs in the first 3 years of life or during teenage years (gonococcal infections). Septic arthritis is a true clinical emergency because it can have serious implications for future joint mobility and organ dysfunction [64]. Pain with passive motion is the most common finding on physical examination. Prior to the introduction of antibiotics, septic arthritis was often severely incapacitating and/or fatal [65]. *Haemophilus influenzae* type b (Hib) was previously the most common causative organism associated with septic arthritis but since the institution of Hib vaccination in the 1970s, *Staphylococcus aureus* is now the foremost culprit [66,67]. Other less common pathogens include *Streptococcus* species, *Pseudomonas aeruginosa*, pneumococci, *Neisseria meningitidis*, *Escherichia coli*, *Klebsiella* species, and Enterobacter. Newborns can acquire *Neisseria gonorrhoeae* from an infected birth canal. *Kingella kingae*, a fastidious aerobic gram-negative micro-organism, has rapidly become a formidable pathogen that is difficult to grow in culture but must be suspected and treated, if septic arthritis is present, in children aged 3 years and younger [68].

Septic arthritis may develop after a penetrating wound or from trauma, surgery, or adjacent cellulitis. However, the most common cause is hematogenous spread from transient bacteremia. Usually in healthy individuals, the bacteremia is quickly eliminated by intrinsic immune defense mechanisms. In immunocompromised and extremely young patients (neonates), the defense mechanisms are too overwhelmed or immature to eliminate the infection. Developing pediatric bone has vascular loops that provide nutrients to the metaphyseal side of the growth plate. The blood supply to this area is relatively slow, and the growth plate is not well covered by the reticuloendothelial system. This leaves the area vulnerable to infection. From 0 to 18 months of age, an abscess in the metaphyseal area may spread into the epiphysis through blood vessels that cross the cartilaginous physis and enter the joint. Those blood vessels disappear after 18 months of age. An abscess in the metaphyseal area will only cause septic arthritis in the areas where the joint capsule is attached to the metaphyses, such as the hip, shoulder, ankle, and elbow joints [65].

Once in the joint, the pathogens and the counteracting leukocytes release proteolytic enzymes that degrade the articular cartilage. Damage can occur in as little as 8 h. The synovial membrane becomes edematous and hypertrophied and produces increased amounts of exudative fluid and pus. Increased pressure within the joint can interrupt the blood supply to the epiphysis. This causes bone destruction, loss of adjacent growth plate, dislocated joints, and injury to the capsule ligament. Rupture of the synovium can lead to extracapsular infections, such as myositis, soft tissue abscesses, and bacteremia.

Presenting symptoms that should make one suspicious of septic arthritis include fever, malaise, erythema, swelling, and tenderness of the joint. Pain with passive motion of the joint is the most common finding. As in the hip, the child will hold flexion, abduction, and external rotation to diminish pain and increase intracapsular volume. Refusal to move the affected joint is called pseudoparalysis, which can be mistaken for a neurological problem. Differential diagnosis of septic arthritis includes, but is not limited to, juvenile rheumatoid arthritis (more gradual onset), Legg–Calvé–Perthes disease (avascular necrosis of the proximal femoral head), Lyme disease, mycobacterial or fungal infections, abscess of the psoas muscle (presents with bladder irritability or a femoral nerve neuropraxia [69]), or transient synovitis from a self-limiting viral infection, mostly involving the hip [70]. A high index of suspicion must be present for neonates and immunocompromised patients, as they can have multiple sites affected without fever and without an elevated white blood cell count [71].

Septic arthritis is a true surgical and/or procedural emergency. Aspiration of the joint in the emergency room, interventional radiology suite, or operating room must be accomplished quickly to insure prompt diagnosis and appropriate therapy. Typically these cases are completed within several hours of being scheduled. Frequently it is necessary to keep the child anesthetized while a gram stain and initial pathological evaluation of the aspirated fluid are performed. Treatment includes appropriate antibiotic therapy and drainage of the affected joint to prevent degradation of joint and bone. Open drainage of the joint is more effective than percutaneous aspiration and is indicated if the hip, shoulder, and peripheral joints fail to respond to percutaneous aspiration. Open drainage is also indicated for patients with systemic illness, *Staphylococcus aureus*, and gram-negative bacteria that produce cartilage-destroying enzymes. Patients with pus in fascial layers have a high mortality rate, as these pockets of infection can lead to venous thrombosis.

Preoperative assessment includes assessment for comorbidities. Patients can be quite ill with multiple manifestations of sepsis. Hematogenous spread of bacteria can cause lung involvement that manifests as pleural effusion, pneumatoceles (lung abscesses), pneumothorax, wheezing, inflammation, and edema-induced stridor. If respiratory symptoms present, a chest x-ray may help to identify the problem. Cardiac involvement includes pericardial effusion, myocarditis, endocarditis, and pericarditis, which can all limit cardiac function. An echocardiogram is recommended for patients with congenital defects, unresolved fever, or prolonged bacteremia without a known source. Renal function may be affected through hematogenous spread of infection, decreased intravascular volume, or medication-induced injury. Baseline laboratory studies and a coagulation profile are helpful as they can be adversely affected by infection. Chronically ill anemic patients may require blood transfusions. Platelets and coagulation factors may be decreased. Disseminated intravascular coagulation is a major complication of dispersed infection so blood products should be available prior to surgery and administered if needed. Adequate venous access must be available for giving volume support, blood products, and inotropes if necessary.

Shoulder or neck septic arthritis may cause cervical ligamentous laxity that can cause C1–2 subluxation during tracheal

intubation. Intravascular volume must be repleted prior to induction of anesthesia to avoid hypotension. Chronic illness-induced decreased concentrations of intrinsic catecholamines may also cause acute decompensation of vital signs with induction of anesthesia. Intraoperative manipulation of the infected joint during surgery may release pathogens and their toxins into the bloodstream and produce acute hemodynamic changes. General anesthesia is typically required for these types of surgeries because regional anesthesia may obscure a possible compartment syndrome or lead to a new infectious point of entry/spread or a hematoma if coagulation abnormalities exist. Although positive pressure ventilation may predispose to pneumothorax and decreased venous return, it is still preferred over spontaneous ventilation, which may be associated with breath holding, laryngospasm, and bronchospasm.

Intraoperatively, the choice of anesthetic drugs can vary. Ketamine should be avoided for induction of anesthesia if catecholamine stores are depleted or are suspected to be depleted, as this can cause hypotension after induction of anesthesia. Succinylcholine should also be avoided if renal dysfunction and chronic illness exist because hyperkalemia can lead to significant injury and/or death.

Postoperatively most patients improve quickly after drainage and removal of infectious material. Fluid, blood products, and inotropes should be continued if needed. Pain is controlled with opioids and acetaminophen. NSAIDs are avoided when renal dysfunction or abnormal coagulation status is present. Although chronic NSAID use has been suggested to inhibit osteogenesis, new evidence indicates that perioperative use of these drugs for 48 h use may not significantly affect osteoblasts and bone formation. This should be addressed with the surgeon on a case-by-case basis.

KEY POINTS: SEPTIC ARTHRITIS

- Emergent drainage or surgery to preserve the joint
- Aspiration of joint for diagnosis
- Often remain anesthetized while awaiting gram stain
- If gram stain is positive usually use open incision and drainage
- Possible sepsis and hemodynamic instability
- Neonates and immunocompromised are the most susceptible

Osteogenesis imperfecta

Osteogenesis imperfecta (OI), also called brittle bone disease, blue sclera syndrome, fragile bone disease, and Lobstein disease, is a relatively common skeletal dysplasia. It has long been documented in human history and was found in a partially mummified infant's skeleton from Egypt. Oral historians believe that a Viking chieftain named Ivan the Boneless (865 AD) may also have had the disease (Fig. 33.8).

Osteogenesis imperfecta is most commonly identified by three characteristics: blue sclerae, bone fragility, and hearing loss. Less common symptoms include triangular facies, macrocephaly, defective dentition, barrel chest, scoliosis, joint laxity, growth retardation, constipation, and sweating. Type 1 collagen is an important component of bone, ligament, dentin, and sclera. In OI, there is a decrease in either quality or quantity of type 1 collagen. Most cases of OI are autosomal dominant mutations of the genes encoding type 1 collagen [72]. Quantitative defects typically cause mild clinical disease, while qualitative defects cause severe clinical disease.

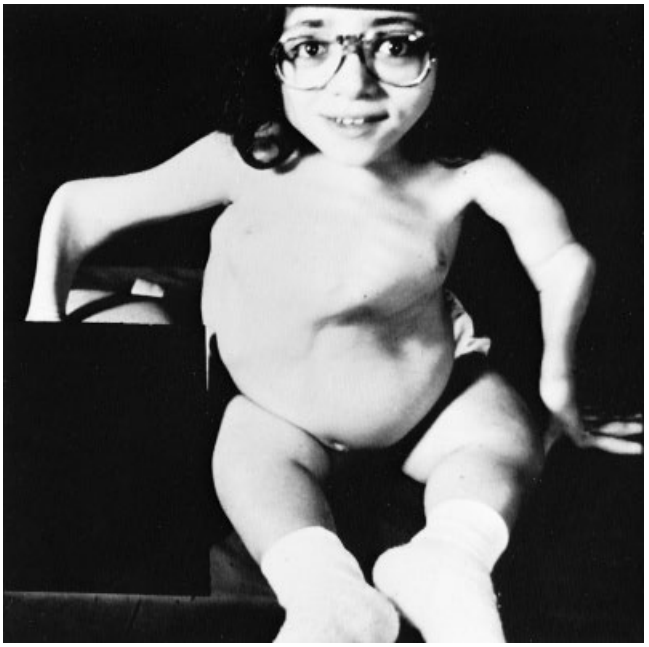

Figure 33.8 Child with osteogenesis imperfecta. Note abnormal chest and extremities.

Osteogenesis imperfecta (types I–IV) occurs in 1/20,000 births. There is no predilection for OI by race, gender, or age. More severe forms present at a younger age [73]. Types I and IV have milder clinical presentations, while types II and III are more severe (Table 33.3).

Recently, bisphosphonates have been used to increase bone mass and strength. Intravenous pamidronate, a synthetic analog of pyrophosphate, inhibits osteoclast-mediated bone resorption on the endosteal surface of bone by binding to hydroxyapatite. This allows unopposed osteoblastic new bone formation on the periosteal surface and increases cortical bone thickness. Bisphosphonates decrease the number of fractures by increasing bone mineral density [74]. This decreases bone pain and increases height. Physiotherapy, in conjunction with bisphosphonate therapy, promotes gross motor development and maximizes function. Adverse effects of bisphosphonate therapy include acute febrile reaction, leukopenia, a transient increase in bone pain, mild hypocalcemia, and scleritis. Other medical therapies under investigation include growth hormone, a recombinant human form of parathyroid hormone, bone marrow transplantation, and gene therapy.

Orthopedic goals for osteogenesis imperfecta include improving strength and preventing fractures. The aim of surgical intervention is to improve function [75]. Release of lower limb contractures improves mobility. Bony deformities and fractures are treated with intramedullary stabilization with or without corrective osteotomies [76]. Rods, pins, and wires are preferable to nails, plates, and screws as the former are less frequently associated with bone fractures. Complications of rods include breakage, rotational deformities, and migration.

Table 33.3 Osteogenesis imperfecta

	Clinical features	Bone fragility	Presentation
Type I	Blue sclera Normal birthweight Moderate bone deformity	Variable degree of bone fragility Fracture onset when child begins to walk Fractures may diminish with puberty	Mildest form Up to 20% have scoliosis May have dentinogenesis imperfecta
Type II	Blue sclera Dwarfism Bowed limbs at birth	Multiple fractures at birth	Most severe form Usually fatal during perinatal period (either at birth or shortly after)
Type III	Blue sclera (become white in adulthood) Short stature Bowed limbs Wheelchair bound May have mild pectus carinatum	Severe bone fragility Bone fractures at birth Progressively deforming	Severe presentation Dentinogenesis imperfecta Chest and rib cage involvement spared
Type IV	White sclera	Mild to moderate bone fragility	Milder severity Kyphoscoliosis common

Table 33.4 Preoperative considerations in osteogenesis imperfecta

Organ system	Clincial features	Consideration
Airway: potential for difficult airway	Short neck Macrocephaly Macroglossia Fragile dentition Decreased neck mobility	Consider x-ray of craniovertebral junction if symptoms of upper cervical cord compression are present (odontoid complex)
Pulmonary	Chest wall deformities may result in restrictive lung disease	Consider chest x-ray and pulmonary function tests
Cardiovascular	Rare, usually related to aortic root dilation causing aortic insufficiency	Echocardiogram indicated if murmur present, suspicion/known aortic insufficiency
Hematological: increased risk for bleeding diathesis	Abnormal collagen on platelet–endothelial cell interaction Increased capillary fragility Defective platelet aggregation Defective contraction of small blood vessels	Normal prothrombin time Normal partial thromboplastin time Platelet count may be normal Abnormal platelet function

With the use of bisphosphonates, non-extendable rods are being used more often than extendable rods [77]. Posterior spinal arthrodesis is preferable to ineffective bracing for scoliosis. Arthrodesis is done in mild OI patients with greater than 45° curvature or in severe OI with greater than 35° curvature.

Preoperatively, it is important to identify the type of OI and the severity of clinical symptoms. Often the patient has required previous medical care. Lung function may be restricted due to chest wall deformities. A chest x-ray and pulmonary function tests, although not required, may help predict postoperative respiratory failure. Airway examination includes neck mobility, dentition, and mouth opening, as there may be a high likelihood of difficult tracheal intubation due to a short neck, macrocephaly, macroglossia, and fragile dentition. Ventral brainstem compression by an invaginating clivus–odontoid complex may further make tracheal intubation difficult. Therefore, evaluation of the patient for symptoms of upper cervical cord compression and x-rays of the craniovertebral junction may help prevent injury. Cardiovascular abnormalities, although not significantly increased in comparison to healthy individuals, are usually related (when present) to aortic insufficiency caused by aortic root dilation. If a murmur is present or suspicion of aortic insufficiency is high, echocardiography is indicated. Patients with OI have an increased risk for bleeding diathesis [78]. The abnormal collagen on platelet–endothelial cell interaction results in increased capillary fragility, defective contraction of small blood vessels, and defective platelet aggregation. Typical coagulation studies (prothrombin time (PT) and partial thromboplastin time (PTT)) will be normal but platelet function will be abnormal. Patients at risk should avoid NSAIDs for at least 7 days preoperatively (Table 33.4).

Intraoperatively, care must be taken to position and pad the patient so no further fractures occur. Non-invasive blood pressure monitoring may cause fractures [79] so less frequent monitoring or invasive arterial blood pressure monitoring is preferred. Tourniquets may produce fractures and should be placed on top of a soft material, such as Kerlix™ or Coban™. Facemasks may damage fragile mandibles and maxillae. Laryngeal mask airways have been used successfully in lieu of facemasks to prevent facial fractures. Tooth guards are used when patients have fragile dentition. The increased incidence of difficult tracheal intubation warrants having a wide variety of airway equipment immediately available, including multiple sizes of tracheal tubes, multiple laryngoscope blades, gum elastic bougies, laryngeal mask airways, video laryngoscopy, and fiberoptic laryngoscopes. See Chapter 16 for additional discussion of management of the difficult airway.

Hyperthermia and lactic acidosis have occurred in patients with OI, possibly from an increased metabolic rate or associated hyperthyroidism. Hyperthermia is more often associated with the administration of anticholinergic drugs and with inhaled anesthetics. A cooling blanket should be used to treat

hyperthermia. Succinylcholine is avoided due to the theoretical risk of fasciculation-induced fractures.

Postoperatively, patients may also have febrile responses from the increased metabolic rate or hyperthyroidism. Because these patients suffer from chronic pain, they should be treated with their baseline opioid plus adjuvant pain medications, as needed. The patient's respiratory status should be carefully evaluated postoperatively to detect obstruction that is caused by residual anesthesia or by decreased hypercapneic-hypoxic respiratory drive from restrictive lung disease. Caution must be exercised during transfer from one bed to another to prevent additional fractures occurring.

KEY POINTS: OSTEOGENESIS IMPERFECTA

- Difficult airway potential
- Restrictive lung disease
- Careful padding and positioning
- Blood pressure cuff and tourniquets can fracture bones
- Increased metabolic rate/hyperthyroidism
- Hyperthermia and lactic acidosis reported

Arthrogryposis

Arthrogryposis is a clinical finding that can be separated into two groups: arthrogryposis multiplex congenital (AMC) and distal arthrogryposis syndromes (DAS). AMC is more severe and tends to involve multiple joints and to have other coexisting syndromes and diseases. It is present in 1/3000 livebirths and is more common in isolated populations such as in Finland and the Bedouin community in Israel [80]. Males and females are affected equally. Thirty percent of cases have a genetic abnormality [81].

The major cause of arthrogryposis is fetal akinesia (decreased fetal movement *in utero*) [82]. The etiologies of arthrogryposis are many, often unknown, and include neurogenic, muscular, connective tissue abnormalities, mechanical limitations, or maternal factors such as infection, drugs, trauma, and other illnesses. Malformations of the central and peripheral nervous systems are the most common cause of arthrogryposis [83]. Decreased fetal movement can also cause polyhydramnios, pulmonary hypoplasia, micrognathia, ocular hypertelorism, and short umbilical cord. Lack of fetal movement results in the development of extra connective tissue around the joints, which limits joint movement and fixes it in a contracted state [84]. Half of patients with associated central nervous system abnormalities die within the first year. Infants born to mothers with myotonic dystrophy, myasthenia gravis, or multiple sclerosis are at high risk for developing resistant contractures. Exposure of mothers to hyperthermia, such as hot tubs or prolonged hot baths, can cause abnormal nerve growth and decreased fetal movement.

Patients with arthrogryposis have cylindrical extremities, decreased subcutaneous tissue, and absent skin creases. Defects are symmetrical and are more severe distally in the hands and feet. Joint dislocation may occur in the hips and knees [85]. Sensation is present but deep tendon reflexes may be decreased or absent. Limb malformations include deletion anomalies, radioulnar synostosis, syndactyly, and short digits. Deformities associated with fetal akinesia include intrauterine growth retardation, pulmonary hypoplasia, short gut syndrome, scoliosis, genital deformities, and hernias (both inguinal and umbilical). Congenital cardiac anomalies and cardiomyopathy may be present. The genitourinary system may have structural abnormalities. Musculoskeletal abnormalities include decreased muscle mass, soft muscle texture, fibrous bands, and abnormal tendon attachments. The skin is often soft, doughy, and thick with webs and dimples over affected joints.

Goals of orthopedic treatment for arthrogryposis are lower limb alignment, stability for ambulation, and upper limb function for self-care [86]. Early gentle manipulation of the contractures after birth helps passive and active range of motion [87]. Physical therapy is indicated for most forms of arthrogryposis but recurrence of the contractures can be high following stretching, necessitating surgery. Soft tissue surgery should be undertaken early and osteotomies performed when growth plates have fused. The most common deformity in the foot is a rigid talipes equinovarus deformity. The goal is to make the foot plantigrade and braceable. Casting often fails early on and typically the patient has to undergo an extensive medial and lateral release of ankle tendons with postoperative bracing. Recurrence of talipes equinovarus is common and other procedures, such as lateral column shortening (distal calcaneal resection), may be required. In an older child in whom the bone is skeletally mature, a triple arthrodesis (fusion of talocalcaneal, talonavicular, and calcaneocuboid joints) is performed. In the knees, flexion deformities are more common than fixed knee deformities and are more resistant to treatment. Moderate contractures of between 20° and 60° require soft tissue release with posterior capsulotomies. Severe contractures of greater than 60° may require femoral shortening in addition to soft tissue release. Older children with severe deformity may require a knee disarticulation. Extension deformities, if unresponsive to physical therapy, will need quadricepsplasty if the child is younger than 6 months of age.

Hip deformities should be addressed after foot and knee deformities have been corrected [88]. Intervention to improve the hip should take place before 1 year of age to make ambulation easier. Hip flexion greater than 35° requires soft tissue release. Bilateral hip dislocations that exceed 35° and the presence of a flexion contracture should be treated with soft tissue release but no reduction [89]. Unilateral hip dislocation requires reduction to avoid the development of scoliosis and pelvic deformity. Upper extremity surgery should be done when the patient is older than 5–6 years. With elbow contractures, the goal is to make possible arm flexion for feeding and extension for hygiene needs. Extension is corrected with either a capsulotomy or capsulotomy plus triceps or pectoralis major transfer. Wrist deformities are usually flexed with ulnar deviation [90]. A severe deformity requires proximal row carpectomy with or without fusion. For severe finger deformities, soft tissue releases and proximal interphalangeal fusions are done. In scoliotic spines, curvatures greater than 35° are treated with spinal fusion.

Preoperatively, any co-morbid conditions that would affect an anesthetic must be identified (Table 33.5). Intraoperatively, care with positioning and tourniquet use is needed, as these children have osseous hypoplasia and are prone to fractures.

Table 33.5 Anesthesia implications in arthrogryposis (consider etiology – neurogenic versus muscular)

Organ system	Clinical features	Consideration
Airway	Limited jaw motion Micrognathia Craniofacial anomaly Laryngeal/tracheal cleft Airway stenosis High arched palate	Difficult airway preparation
Vertebral instability	Hypoplastic cervical vertebrae C1/C2 Decreased muscle mass	Videoscope, fiberoptic bronchoscope, or direct laryngoscopy with midline neutral stabilization Minimize neck extension/flexion
Pulmonary	Scoliosis /restrictive lung disease Hypoplastic diaphragm	Consider chest x-ray and pulmonary function tests
Cardiovascular	Cardiomyopathy Congenital anomalies	Echocardiogram
Neuromuscular junction upregulation	Decreased muscle mass	Increased sensitivity non-depolarizing muscle relaxants Hyperkalemia with succinylcholine
Hyperthermia (10% incidence)	Hypermetabolic Typically unrelated to malignant hyperthermia (MH) unless underlying etiology is susceptible to MH (e.g. King–Denborough, central core disease)	Cooling blankets Avoid triggers if MH
Genitourinary anomaly	Structure and function	Basic metabolic panel Decreased metabolism and excretion of anesthetic drugs
Contractures Decreased subcutaneous tissue "Doughy" skin Gastrointestinal reflux	Difficult IV access Difficult regional block access	Careful positioning Foam padding

Intraoperative hyperthermia is usually caused by hypermetabolism, not malignant hyperthermia (MH), unless there is an underlying predisposing neuromuscular disorder like King–Denborough [91]. Hyperthermia occurs regardless of the type of anesthetic used. A cooling blanket should always be available. There are controversial, anecdotal case reports of MH in patients with arthrogryposis. The majority of temperature increases are not MH and respond to cooling blankets. Due to the extensive list of etiologies for arthrogryposis that are often undiagnosed, one should remain vigilant for hyperthermic events that do not respond to cooling and consider other diagnostic criteria for MH and proceed with treatment. Challenging the traditional belief that arthrogryposis patients have an increased incidence of hyperthermia, a recent retrospective review of 369 arthrogryposis anesthetics (264 AMC, 105 DAS) reported a similar incidence of hyperthermia in the AMC (10%) and DAS (11%) groups. However, the AMC anesthetics were also compared with matched controls without arthrogryposis (n = 222) and showed no increased incidence of hyperthermia compared with AMC cases [92].

Choice of anesthetic agent depends on co-morbid conditions. Ventilation may be affected by scoliosis-induced restrictive lung disease. Pneumothorax, during either spontaneous or mechanical ventilation, may be the result of pulmonary hypoplasia. Postoperatively, there is an increased risk of aspiration when the cause of arthrogryposis is neurogenic or muscular. Therefore, full return of baseline neuromuscular function and ability to protect the airway is required before emergence from anesthesia and tracheal extubation. Patients will be in casts postoperatively for approximately 6 weeks. Preoperative pain medication should be continued into the postoperative period and enough pain medication given to treat surgical pain. This helps prevent opiate withdrawal and a wind-up phenomenon.

Cerebral palsy

Cerebral palsy (CP) describes the movement and posture disorder that is the result of a motor deficit caused by brain injury *in utero*, at birth, or postnatally. It is present in approximately 2/1000 births [93]. The clinical features of CP are classified by the number of extremities with motor deficits (mono-, di-, tri-, or quadri-). Involvement of one side of the body is hemiparesis. Spastic quadriparesis is the most common form of CP, requiring multiple surgeries. The causes of CP are many, but the exact etiology is often difficult to define in any given infant. The functional limitations from paresis include hypotonia or hypertonia and occasionally extrapyramidal symptoms. Function can frequently be improved by multiple surgical procedures that address the extremities. Surgeries to straighten the spine help maintain posture and lung volumes. Anesthesia is often required to inject medications for treatment of spasticity and contractures (e.g. botulinum toxin-A or baclofen) [94].

Preoperative assessment and medical optimization should occur ahead of the surgery, since the majority of surgeries are elective (Box 33.2). Anesthetic challenges include appropriate communication with children who can have either normal cognitive abilities or severe developmental delay. A particularly challenging group of CP patients are cognitively intact, non-verbal patients. Patients with hypotonic CP often have the most severe developmental delay. Preoperative discussions with the family should include estimation of the child's developmental level and the best means of communicating

Box 33.2: Typical procedures in cerebral palsy

- Heel cord lengthening
- Contracture releases
- Tendon lengthen/transfer
- Botulinum injection
- Nissen fundoplication
- Gastrostomy tube
- Scoliosis repair

with them. Ideally a pain scale is identified that will be used postoperatively so the child and family can become familiar with its use.

Patients with CP may also have epilepsy. Their scheduled antiepileptic drugs are administered, despite preoperative fasting, and should be given either orally or converted to IV doses in the preoperative area if missed. A history of recent seizure patterns and frequency is obtained. Many of the antiseizure medications increase activity of cytochrome P450 degradation pathways. Drugs utilizing these pathways for elimination include non-depolarizing neuromuscular relaxants; train-of-four monitoring and more frequent dosing are desirable to achieve the desired effects due to the fact that the duration of action of the non-depolarizing agent may be shortened [95].

Pulmonary pathology includes the usual incidence of childhood diseases (e.g. reactive airway disease), and they may be exacerbated by anatomically scoliosis-induced restricted airways. Feeding dyscoordination increases the risk of aspiration and recurrent respiratory infections. Gastroesophageal reflux is common, difficult to control medically, and often requires fundoplication. Respiratory muscle strength may also be compromised. Poor oropharyngeal function often causes excessive drooling. This is controlled with antisialogogues or salivary gland surgery. Premedication with glycopyrrolate facilitates tracheal intubation and decreases pooling of secretions intraoperatively.

Patients with severe CP may be chronically underhydrated, since most of them are tube fed and empirically hydrated. Preoperative rehydration may be required. Complete blood count and coagulation studies are indicated for potentially bloody procedures because the incidence of prolonged PT/PTT in this patient group is increased.

Scoliosis surgery is discussed in Chapter 29. Other orthopedic procedures often required include extremity surgeries to address contractures and gait abnormalities. Historically, these procedures have been done serially as the child grows and movement is evaluated. Some centers are now undertaking elaborate gait and movement studies preoperatively to plan and perform a single operation that addresses multiple extremities simultaneously. The advantage of doing this is that the child can be mobilized more quickly and there is one recovery process instead of several. An important component of this approach is close coordination with a pediatric acute pain service to optimize pain management postoperatively, often with regional analgesia.

Clubfoot and hip dislocations are common acquired deformities in CP and often require surgery. They are described in detail earlier in this chapter. Heel cord lengthening, adductor myotomy, and hamstring lengthening are the most common surgeries needed. For clubfoot, the foot is rotated inward, the back of the heel is moved up, and the forefoot deviates medially. During the newborn period the heel cord is cut under local anesthesia and the lower extremity is serially casted. For surgical correction of clubfoot, general anesthesia, with or without caudal block, is usually used. Acquired clubfoot is the result of the paralysis associated with CP.

Contracture releases are performed to facilitate patient comfort, positioning, and mobility. Ober fasciotomy is done for flexion at the hip that is abducted and externally rotated (frog leg in appearance). Incision is anterolateral and just distal to the iliac crest. The fascial attachments are loosened to obtain neutral extension. The iliotibial band may be tight, causing flexion of the knee. In the Yount procedure, a distal midlateral longitudinal incision is made above the knee, and a segment of the iliotibial band and lateral intermuscular septum is removed and not repaired. Tendon lengthening/transfer is done to release contractures. Tendon transfers are done to change the direction of muscle force to compensate for paralysis or paresis of muscle groups.

Intraoperative considerations for CP include maintaining body temperature since these patients tend to be hypothermic (Table 33.6). Using warm blankets and forced-air warming devices in the preoperative area facilitates venous cannulation. Non-depolarizing neuromuscular relaxants are less potent in patients with CP, with or without the presence of chronic anticonvulsants. Contractures present positioning problems and make vessel cannulation difficult.

The use of succinylcholine is controversial and best avoided in CP patients. There are anecdotal reports of succinylcholine-induced cardiac arrest in CP patients [96]. Moreover, Theroux et al reported increased sensitivity of CP patients to succinylcholine due to CP patients having a lower effective dose (ED50) [97]. The relative immobility of CP patients may also upregulate their acetylcholine receptors [98]. However, Dierdorf did report normal plasma potassium concentrations before and after succinylcholine administration in CP patients as well as normal controls [96]. Muscle biopsies demonstrate variable neuromuscular junctions in CP patients undergoing spinal fusion, with about 30% of them having abnormal apposition of the acetylcholine receptor compared to normal control patients undergoing spinal fusion [99]. When the risk for aspiration is increased, sufficient rocuronium can be used to safely allow a modified rapid-sequence induction of anesthesia and tracheal intubation considering the potential risk of hyperkalemia.

Postoperative concerns include resumption of all preoperative medications, with close attention paid to the dosing of antiseizure medication and to spasticity regimens. Serum drug levels may be indicated if medications were discontinued for a prolonged period. Postoperative spasms can be painful and may require acute and chronic pharmacological therapy. Current oral regimens include diazepam, baclofen, tizanidine, and dantrolene. Intrathecal pumps are used to deliver baclofen for chronic spasticity. Baclofen overdosing or underdosing can be life threatening, particularly with abrupt withdrawal of the drug. Regional anesthesia supplementation decreases spasms in some instances.

Table 33.6 Perioperative considerations in cerebral palsy

Organ system	Clinical feature	Consideration
Muscular	Spasticity	Baclofen, botulinum injections, diazepam Source of pain postop
Pulmonary	Scoliosis/restrictive lung disease Aspiration pneumonia Reactive airway disease Inadequate cough	Consider chest x-ray and pulmonary function tests Consider ICU postop At risk for respiratory depression with opiates
Neuromuscular junction acetylcholine upregulation	Decreased muscle mass Relative immobility	NDMR: TOF monitor and increased redosing if seizure meds affect P450 degradation Succinylcholine is controversial: may be at risk for increased plasma K^+ concentrations
Contractures	Difficult IV access Difficult regional block access	Careful positioning
Neurological	Seizures	Insure a.m. meds oral or IV were given
Aspiration risk	± GERD	Consider rapid-sequence induction with NDMR
Oropharyngeal dyscoordination	Copious secretions	Consider glycopyrrolate
IV fluids	Chronic dehydration	Continue G-tube clear liquids per fasting protocol
Hematological	± Prolonged PT/PTT	CBC and coags for case with increased EBL

CBC, complete blood count; EBL, estimated blood loss; G-tube; gastrostomy tube; GERD, gastroesophageal reflux disease; ICU, intensive care unit; IV, intravascular; NDMR, non-depolarizing muscle relaxants; PT, prothrombin time; PTT partial thromboplastin tie; TOF, train-or-four.

KEY POINTS: CEREBRAL PALSY

- May have chronic aspiration of secretions
- Less sensitive to non-depolarizing muscle relaxants
- Avoid depolarizing muscle relaxants as they may elevate K^+
- Gastrostomy-fed patients may be dehydrated due to limited administration of fluid

Neuromuscular diseases

Perhaps one of the most common dilemmas in pediatric anesthesia is the anesthetic choice for a patient with neuromuscular disease, including those with hypotonia of unknown etiology [100–102]. The potential for anesthetic complications, based on choice of anesthetic technique, is present, and yet the recommendations are still varied and controversial. Each technique carries its own risk profile. Furthermore, regardless of anesthetic technique, these patients have a higher incidence of cardiomyopathy and arrhythmias from disease effects on the heart muscle. Respiratory function can also be compromised, due to both decreased respiratory muscle strength and to restrictive function associated with advanced spine and rib cage deformity induced by the diseases.

Neuromuscular diseases can be divided into muscular dystrophy (progressive and congenital), developmental myopathy, and metabolic myopathy.

Progressive muscular dystrophies (Duchenne and Becker)

Progressive muscular dystrophies include the dystrophinopathies (absent or deficient dystrophin such as Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy), limb–girdle muscular dystrophies, fascio-scapulo-humeral muscular dystrophy, and oculopharyngeal muscular dystrophy. Most expert opinions now agree that there is not an increased risk of malignant hyperthermia, but life-threatening rhabdomyolysis can occur. Frail muscle membranes break down with exposure to halogenated volatile agents. Thus, in clinical practice many anesthesiologists still choose to deliver a trigger-free anesthetic (i.e. avoidance of succinylcholine and volatile anesthetics). The risk of rhabdomyolysis is highest in young children with more muscle mass. As the child ages and the disease progresses, muscle mass decreases and is replaced with fibrosis. An elevated creatine kinase (CK) is common in this group of patients.

Duchenne muscular dystrophy is the most common and severe muscle disease presenting in childhood and is caused by a complete absence of dystrophin protein in muscle. Disease severity progressively worsens over time. Typical presentation occurs in a toddler or early school-age boy with delayed walking or global motor delay. The incidence is approximately 30 per 100,000 births [103]. Patients have progressive lower extremity weakness, pseudohypertrophy of the calves, and markedly elevated CK levels. A waddling gait and proximal muscle weakness are hallmark signs. The Gower sign is common and describes the process of using the arms to rise from the floor. Approximately one-third will develop cardiomyopathy and/or arrhythmias by 14–18 years of age. However, cardiac disease does not necessarily correspond to the severity of skeletal muscle disease.

Early intervention and surveillance of cardiac status is warranted with electrocardiogram and echocardiogram. Cardiac magnetic resonance imaging can also be used to assess both function and arrhythmia potential and may be more sensitive than echocardiogram. At about age 10 years, empirical afterload reduction with an angiotensin-converting enzyme (ACE) inhibitor is generally started regardless of cardiac function status. Once systolic or diastolic dysfunction is diagnosed, patients are assessed every 6 months. Additionally, aldactone or eplerenone may be added for cardiac remodeling effects. In severe dysfunction, carvedilol or digoxin may be needed. Holter monitors are indicated for moderate to severe dysfunction. Patients with severe dysfunction and dilation may also be on aspirin therapy. Close coordination of preanesthesia

planning with the cardiology team is essential to optimize the patient's cardiac function prior to anesthesia. Some teams elect to admit patients with moderate to severe dysfunction preoperatively to begin milrinone. Corticosteroid regimens are also sometimes prescribed for muscular dystrophy patients, and despite their beneficial effects on disease progression, side-effects must be evaluated preoperatively. Deflazacort is a heterocyclic glucocorticoid prodrug of the oxazoline steroid class. In a randomized controlled trial of deflazacort, prednisone, and placebo in 196 boys aged 5–15 years with DMD, deflazocort and prednisone were equally efficacious in increasing muscle strength but deflazocort was associated with less weight gain [104].

Historically, patients typically died in early-adulthood (mid-20s) due to cardiac disease and heart failure. In the past two decades, life expectancy has increased by enhanced multidisciplinary clinical management and the use of corticosteroids (prednisone, prednisolone, deflazacort) with some patients now surviving into their 30s (Box 33.3) [105–115].

Becker muscular dystrophy is similar to DMD in its clinical presentation but presents in the adolescent years and progresses more slowly, due to a partial loss of dystrophin. It is less common, with an incidence of 3–6 per 100,000 births. Cardiomyopathy generally presents about age 30 with most patients surviving to 30–60 years of age.

Anesthetic risks for progressive muscular dystrophy, in addition to succinylcholine-induced hyperkalemia and rhabdomyolysis, are related to the degree of cardiac and respiratory compromise. Preoperative preparation includes an annual cardiac assessment for cardiomyopathy and/or arrhythmias and pulmonary function tests. Cardiac condition should be medically optimized prior to anesthesia and surgery. Postoperative planning should include longer observation times after surgery and the possible need for ventilatory assistance in an intensive care setting.

KEY POINTS: DUCHENE AND BECKER MUSCULAR DYSTROPHY

- Late onset of walking
- Baseline CK is elevated
- DMD is primarily found in males
- Consider use of a trigger-free anesthetic
- Close coordination with cardiologists and pulmonologists is important
- Close postoperative observation is needed

Box 33.3: Corticosteroid regimens and muscular dystrophy

- Corticosteroids improve and prolong ambulation in both Duchenne and Becker muscular dystrophies
- Corticosteroids reduce the incidence and severity of scoliosis
- Corticosteroids increase the incidence of pathologic fractures
- Duchenne muscular dystrophy patients are more prone to fat embolism syndrome
- Corticosteroids suppress the hypothalamus–pituitary–adrenal axis (HPA)
- Deflazacort was approved for use in the USA in February 2017

Congenital muscular dystrophies

These are characterized by early infancy presentation and slow progression and are sometimes associated with central nervous system anomalies. The incidence is only about four per 100,000 births; thus much less is known and/or written about preferred anesthesia techniques for patients with congenital muscular dystrophy. CK levels are usually elevated. There is a case report of an undiagnosed hypermetabolic response with volatile agent use and a report of rhabdomyolysis.

Congenital myopathies (central core disease and core-rod myopathies)

These infants primarily have contractures with decreased muscle strength; diagnosis is based on the histology of a muscle biopsy. The CK level is normal or only mildly increased, and the disease progresses slowly. Patients with central core disease and core-rod myopathy are at high risk for MH. Other congenital myopathy patients have milder MH or no association with MH. However, given the difficulty for the anesthesiologist to track down and interpret specific genetic testing, a trigger-free anesthetic is prudent in the known or suspected congenital myopathy patient.

Myotonias

There are several variants, both autosomal dominant and recessive, and they are divided into dystrophic and non-dystrophic forms. Myotonia congenita is a non-dystrophic form. The primary symptom for all myotonia patients is impaired muscle relaxation following sudden contraction.

Myotonic dystrophies are chronic, slowly progressing muscular dystrophies characterized by myotonia, posterior iridescent cataracts, cardiac conduction defects, and endocrine derangements [116–118]. They are best known for their skeletal muscle manifestations (distal skeletal muscle atrophy) and are the most common form of muscular dystrophy to present in adulthood with an estimated prevalence of one in 8000. Clinical presentation is highly variable with type I being more severe than type II. Cardiac involvement is always present and is a common cause of mortality after respiratory failure (Table 33.7). Treatment is primarily symptomatic.

Myotonic dystrophy patients are exquisitely sensitive to hypnotic/sedative medications as well as opioids, there may be prolonged emergence, and the drugs should be carefully titrated to effect [117]. Propofol-associated pain on injection may cause myotonia. Reported use of etomidate and ketamine is limited. Anticholinesterase drugs have been reported to cause sustained contraction, and adverse response after administration is poorly predictable. Therefore if neuromuscular blockade is necessary, the use of short-acting non-depolarizing muscle relaxants is preferred. The dose should be adjusted based on the severity of the muscle wasting. Succinylcholine is avoided as it may result in total body sustained contraction and/or masseter muscle rigidity. Halogenated agents have been used safely in these patients, but there are also some case reports of hypermetabolic reactions. Neuraxial techniques have been successfully utilized in myotonic dystrophy patients and offer both intraoperative

Table 33.7 Features of myotonic dystrophy type I (Steinert's disease)

	Features
Age at onset	
Congenital	Profound hypotonia at birth
	Delayed motor and speech development
	Hypotonia usually improves
	Most patients are eventually able to ambulate
Childhood	Onset between 1 and 10 years of age
	Uneventful neonatal period, mild hypotonia may be present
	Facial and neck muscle weakness
	Early motor development may be delayed or normal
Adult	Onset of symptoms between 10 and 40 years
	"Classic" form of myotonic dystrophy
Non-skeletal muscle manifestations	
Pulmonary	Hypoxemia and altered response to CO_2
	Respiratory muscle weakness
	Centrally mediated dysregulation of control of breathing
	Sleep apnea
	High risk for anesthesia-related pulmonary complications
Cardiac	Conduction abnormalities
	Dilated cardiomyopathy
	Little correlation between severity of cardiac involvement and peripheral muscle disease
	Annual EKG is advisable
	Symptomatic patients may benefit from echocardiogram, Holter monitoring, electrophysiology studies
Endocrine	Insulin resistance, glucose intolerance
	Dysthyroidism (usually hypothyroidism)
	Hypogonadism
Gastrointestinal	Dysphagia and delayed gastric emptying
	Pseudo-obstruction
	Increased incidence of prolonged ileus

and postoperative analgesia. Use of intrathecal additives to local anesthetic medications need to be weighed against the increased risk of respiratory/sedative adverse effects.

KEY POINTS: MYOTONIC DYSTROPHY TYPE I

- There is respiratory weakness and central apnea
- Avoid succinylcholine and neostigmine
- Volatile agents and propofol have been used
- There is no MH association (hypermetabolic reaction is reported)
- Volatile agents may cause prolonged sedation/weakness
- Aspiration risk – consider rapid-sequence induction
- Shivering, pain from propofol, etc. can elicit dystonia
- Cardiac conduction delays/arrhythmias – consider pacer pads
- Post-anesthesia intensive care unit is warranted

King–Denborough syndrome

This rare autosomal dominant disease has a high association with MH, so succinylcholine and halogenated agents are avoided. The muscle disease is non-specific and mild. These patients are characterized by short stature, pectus carinatum, kyphosis, cleft palate, low-set ears, ptosis, down-slanting palpebral fissures, and delayed motor development.

Metabolic myopathy (mitochondrial and carnitine disorders)

Mitochondrial diseases interact either with the energy supply to the muscle (adenosine triphosphate synthesis) or with ion channels involved in the process of contraction and relaxation. These patients develop progressive dysfunction in organs with high-energy requirements such as brain and muscle. All anesthetic agents interfere with mitochondrial function so there is no ideal anesthetic for these patients [119–122]. However, many anesthetics have been conducted safely with all anesthetic agents. There is increasing evidence that propofol infusion syndrome results from mitochondrial dysfunction and thus propofol should be avoided or used cautiously [120] in patients with mitochondrial disease. These patients do not have a clear genetic or clinical association with MH, although there are two case reports of possible MH [121,122]. One suggested anesthetic technique is to use ketamine and a low-dose volatile agent and avoid using propofol. Dexmedetomidine can also be added as another adjuvant agent when titrated carefully with prolonged postoperative observation. Ketamine, midazolam, and dexmedetomidine used together for muscle biopsies can be titrated to a depth sufficient to allow muscle biopsy without the use of a volatile agent. Spinal, caudal, or epidural anesthesia can also be employed.

Carnitine deficiency or any problem with its transport makes patients dependent on glucose for energy needs. The most common of these rare disorders is carnitine-palmitoyl transferase II deficiency that also has been associated with rhabdomyolysis following stress, exercise, or anesthesia. There is one case report of MH.

Other forms of metabolic myopathy include potassium-related periodic paralysis, glycogenoses, and lipid myopathies.

Undiagnosed hypotonia

Clinical experience and a recent retrospective study suggest that a cerebral cause for hypotonia is far more frequent than a peripheral neuromuscular cause in a neonate or infant with undiagnosed hypotonia who is presenting for muscle biopsy [100–102,123]. Since many infants/small children who present for muscle biopsy are not diagnosed, the best anesthetic choice is difficult to determine [124,125]. Taking a careful family history and reviewing genetic or neurological consultations, as well as laboratory results, are critical. An elevated CK may represent the presence of an undiagnosed progressive muscular dystrophy, such as DMD or Becker muscular dystrophy. A recent review article recommends that all children with motor delay who are not walking at 18 months of age should undergo neurological evaluation and/or genetic evaluation prior to elective general anesthesia or sedation [125]. An elevated serum lactate concentration may be indicative of metabolic myopathies such as mitochondrial diseases. Discussion with the infant or child's pediatrician or neurologist, in addition to obtaining CK and lactate levels, may help elucidate a more exact clinical suspicion or diagnosis to help guide anesthetic planning for diagnostic examinations and elective surgeries.

Anesthetic complications associated with neuromuscular diseases

Succinylcholine-induced hyperkalemic cardiac arrest following succinylcholine administration to patients who have neuromuscular disease still occurs despite the US Food and Drug Administration black box warning initiated in 1992 (Box 33.4). The hyperkalemic response is proportional to the upregulation of the nicotinic acetylcholine receptors (nAChRs). Pretreatment with a non-depolarizing neuromuscular relaxant does not prevent succinylcholine-induced hyperkalemia. Thus succinylcholine is avoided for any patient with a known condition associated with upregulation of these receptors and patients who have weakness and/or hypotonia without a diagnosis.

Acute rhabdomyolysis occurs due to the breakdown of the muscle surface membrane and causes the release of myoglobin, potassium, and CK. This can be life threatening and difficult to differentiate from malignant hyperthermia.

Hypermetabolic response with unexplained fever can mimic MH but is distinguished by the absence of acidosis and the presence of a normal CK. This condition has been described during anesthesia in both primary neuromuscular conditions and orthopedic syndromes such as osteogenesis imperfecta and arthrogryposis.

Malignant hyperthermia (see Chapter 45) has been associated with most neuromuscular diseases but most experts now classify only central core disease and King–Denborough as being high risk for MH.

Juvenile rheumatoid arthritis

Juvenile rheumatoid arthritis (JRA) (also known as Still disease) is diagnosed approximately three times per 100,000 children under the age of 15 years, and approximately 70% of these patients are female [126]. In addition to the usual childhood surgeries, JRA patients require general anesthesia for surgery on multiple affected joints as well as diagnostic examinations. Intra-articular corticosteroid injection in very young children may also require general anesthesia.

The usual age for presentation of JRA is 2–4 years of age. It is a systemic condition that is characterized by fever, rash, joint redness, leukocytosis, and increased erythrocyte sedimentation rate. It affects collagen and the connective tissues of joints and organs. About 36% of JRA patients have cardiac involvement, with pericarditis being the most common cardiovascular presentation. Severe disease may also include splenomegaly, lymphadenitis, and polyarthritis. JRA is an autoimmune disease that causes deposition of autoantibodies (antinuclear antibodies and rheumatoid factor) in the affected joints. Reactive lysosomal enzymes are released and ultimately damage the joints.

Preoperative preparation includes careful assessment of the airway with regard to neck and jaw mobility because temporomandibular ankylosis, mandibular hypoplasia, and cricoarytenoid arthritis can be present. Fiberoptic intubation of the trachea may be indicated. JRA patients may have atlantoaxial or low cervical subluxation, so extension of the neck should be limited or avoided. Anemia is also common. Children may be on multiple medical therapies, including steroids, NSAIDs, and methotrexate.

Postoperative analgesia can be challenging due to the preexisting chronic pain. Continuous regional anesthesia has been used to provide acute pain relief for larger surgeries, such as hip arthroplasty.

Box 33.4: Neuromuscular and orthopedic diseases associated with anesthetic complications

Succinylcholine-induced hyperkalemic cardiac arrest (upregulation of nAChR)
- Muscular dystrophy
- Acute burn patients
- Denervation
- Muscle atrophy

Rhabdomyolysis
- Duchenne and Becker muscular dystrophies
- Dystrophinopathies (absent or deficient)

Hypermetabolic response with unexplained fever but no acidosis or increase in CK
- Duchenne muscular dystrophy
- Osteogenesis imperfecta
- Arthrogryposis

Malignant hyperthermia
- Central core disease (and core-rod myopathies)
- King–Denborough

Genetic syndromes and orthopedic surgery

There are many syndromes with accompanying orthopedic problems. Table 33.8 contains a listing of these syndromes. The reader is referred to Chapter 43 for a discussion of the anesthetic approach to patients with these conditions.

Fractures in healthy children: supracondylar humerus fracture

Among the most common fractures requiring surgical intervention are the supracondylar humerus fractures, which account for 3% of all pediatric fractures, and most commonly involve a fall onto an outstretched hand with the elbow in extension (97–99% of cases) [127]. These fractures are classified as Gartland type I through IV, depending on the degree of displacement; with type I non-displaced fractures treated nonoperatively with casting (Fig. 33.9A). Type II fractures have slight displacement and may be treated operatively, while types III and IV are always treated operatively. Closed reduction with internal fixation with K wires is the standard treatment, and general anesthesia is required. Because these patients will frequently be considered to have full stomachs, appropriate precautions to protect the airway must be taken, and endotracheal intubation with rapid sequence, or modified rapid-sequence induction of anesthesia is often indicated. Although these fractures are often treated as emergencies, if there is no neurovascular compromise, studies have reported no outcome differences with up to 24 h of delay between fracture and surgery. Analgesia may be provided with opioids or NSAIDs. In a retrospective study of 221 pediatric fractures repaired operatively, ketorolac use was not associated with risk of non-union or delayed union, infection, or bleeding [128].

Table 33.8 Orthopedic syndromes with potential anesthetic implications

Syndrome	Potential anesthetic implications
Achondroplasia	Chronic respiratory infection, hydrocephalus, long narrow mouth with high arched palate, limited head extension, prominent mandible and forehead, constrictive thoracic cage, cyanotic and apneic episodes, dwarfism
Apert	Facial, limb, and cardiac anomalies, hydrocephalus, choanal atresia, craniosynostosis
Arnold–Chiari	Vocal cord paralysis, stridor, respiratory distress, apnea, abnormal swallowing, recurrent aspiration pneumonia, possible increased intracranial pressure, unstable blood pressure, weakness → paralysis
Cri du chat	Microcephaly, micrognathia, facial asymmetry, high vaulted palate, cleft lip/palate, feeding and swallowing difficulties with chronic aspiration, congenital heart defects, seizures, severe retardation
Crouzon	Facial and ocular anomalies, upper airway obstruction, choanal atresia, seizures, craniosynostosis, mental retardation
Cornelia de Lange	Facial and cardiac anomalies, micrognathia, seizures, choanal atresia, contractures, hypertonia
Ehlers–Danlos	Joint laxity, fragile blood vessels, cardiac valvular prolapse, glaucoma
Ellis van Creveld	Facial and cardiac anomalies, small thorax
Freeman–Sheldon	"Whistling facies" with microstomia, increased muscle tone, vertebral anomalies, myotonia
Goldenhar	Laryngeal, ocular, cardiac, and renal anomalies, cervical spine fusion, hemifacial micrognathia, glaucoma, encephalocele
Holt–Oram	Cardiac, vertebral, and upper limb and shoulder girdle anomalies, hypoplasia of distal blood vessels
Hurler	Facial anomalies, macroglossia, chronic respiratory infections, growth and mental deficiencies, joint stiffness, cardiac failure, hydrocephalus
Lesch–Nyhan	Self-mutilation, airway distortion 2° to scarification, mental retardation, spasticity, choreoathetosis, seizures, contractures, hypertension, aspiration pneumonia
Marfan	Joint laxity, vertebral and ocular anomalies, mitral valve prolapse, dilation or dissection of ascending aorta with aortic valve insufficiency
Möbius	Microstomia, micrognathia, limb and brain anomalies, cranial nerve palsies
Morquio	Odontoid hypoplasia, vertebral anomalies, growth deficiency, aortic value insufficiency, joint contractures
Neurofibromatosis	Brain, vertebral, dermal, and cardiac anomalies, subcutaneous tumor with tendency to malignancy, mental deficiency, kyphoscoliosis
Noonan	Facial, vertebral, and cardiac anomalies, micrognathia, mental deficiency, pectus evacatium
Radial aplasia-thrombocytopenia (Tar)	Facial, vertebral, cardiac, and renal anomalies, micrognathia, severe thrombocytopenia, anemia, intracranial hemorrhage
Robin (Pierre–Robin)	Severe micrognathia, cleft palate, laryngeal anomalies, mandibular growth improves with age during infancy
Treacher Collins	Severe micrognathia (not improving during infancy), facial, auricular, and cardiac anomalies, choanal atresia, microstomia, airway hypoplasia
Trisomy 21 (Down)	Odontoid hypoplasia, macroglossia, cardiac defects, joint laxity, mild mental deficiency
Turner (XO)	Micrognathia, short neck, growth retardation, cardiac anomalies
VATER association	Vertebral, cardiac, renal, and limb anomalies, tracheoesophageal fistula, esophageal atresia, congenital scoliosis, imperforate anus

Source: Adapted from Benumof [132] and Katz and Stewart [133].

Supraclavicular nerve block with ultrasound guidance can be utilized after induction of general anesthesia to provide intra- and postoperative analgesia. Before performing regional anesthesia for a supracondylar humerus fracture (or other long bone fractures), a complete neurovascular examination of the upper extremity must be done, including sensation, movement of hand and fingers, assessment of radial and ulnar pulses, and perfusion to the hand (color, capillary refill). A discussion with the surgeon should also ensue. The proximity of the brachial, radial, and ulnar arteries, and ulnar, median, and radial nerves, clearly indicate the risk of injury to these structures (Fig. 33.9B). Any sign of neurovascular compromise is a contraindication to regional anesthesia. Open supracondylar fractures are uncommon, but vascular and nerve injuries are present in 12–20% of open fractures. Neurovascular compromise is less common with closed fractures. If neurovascular compromise is diagnosed or suspected, emergent reduction is indicated; in most cases the vascular compromise will improve within a few minutes – if it does not an open exploration with vascular repair is indicated. Compartment syndrome is a rare but serious complication, occurring in 1–3 per 1000 fractures. Increasing pain and anxiety, along with limb pallor, paralysis, and pulselessness, are the signs of compartment syndrome, and emergent fasciotomy is indicated. It is because of concern for compartment syndrome that some orthopedic surgeons do not agree to regional anesthesia, for fear of masking the pain that heralds this complication. See Chapter 20 for detailed discussion of supraclavicular nerve blocks.

Sports medicine procedures in teenaged athletes

The significant increase in youth sports participation for both girls and boys has given rise to the development of adolescent sports medicine, and orthopedic surgery for sports injuries in children and adolescents has increased dramatically. For example, anterior cruciate ligament (ACL) surgery in patients <20 years of age increased threefold in the USA from 1990 to 2009 [129].

A complete discussion of surgery for sports injuries is beyond the scope of this text, but because ACL surgery is the most common sports surgery in adolescents, information about this injury and the procedure for the pediatric anesthesiologist is important. Historically, non-operative treatment of skeletally immature patients was common, delaying repair until skeletal maturity. This approach may lead to meniscal and articular cartilage damage, and other problems including dropping out of sports, so early operative repair is now the standard approach. Different techniques are used before

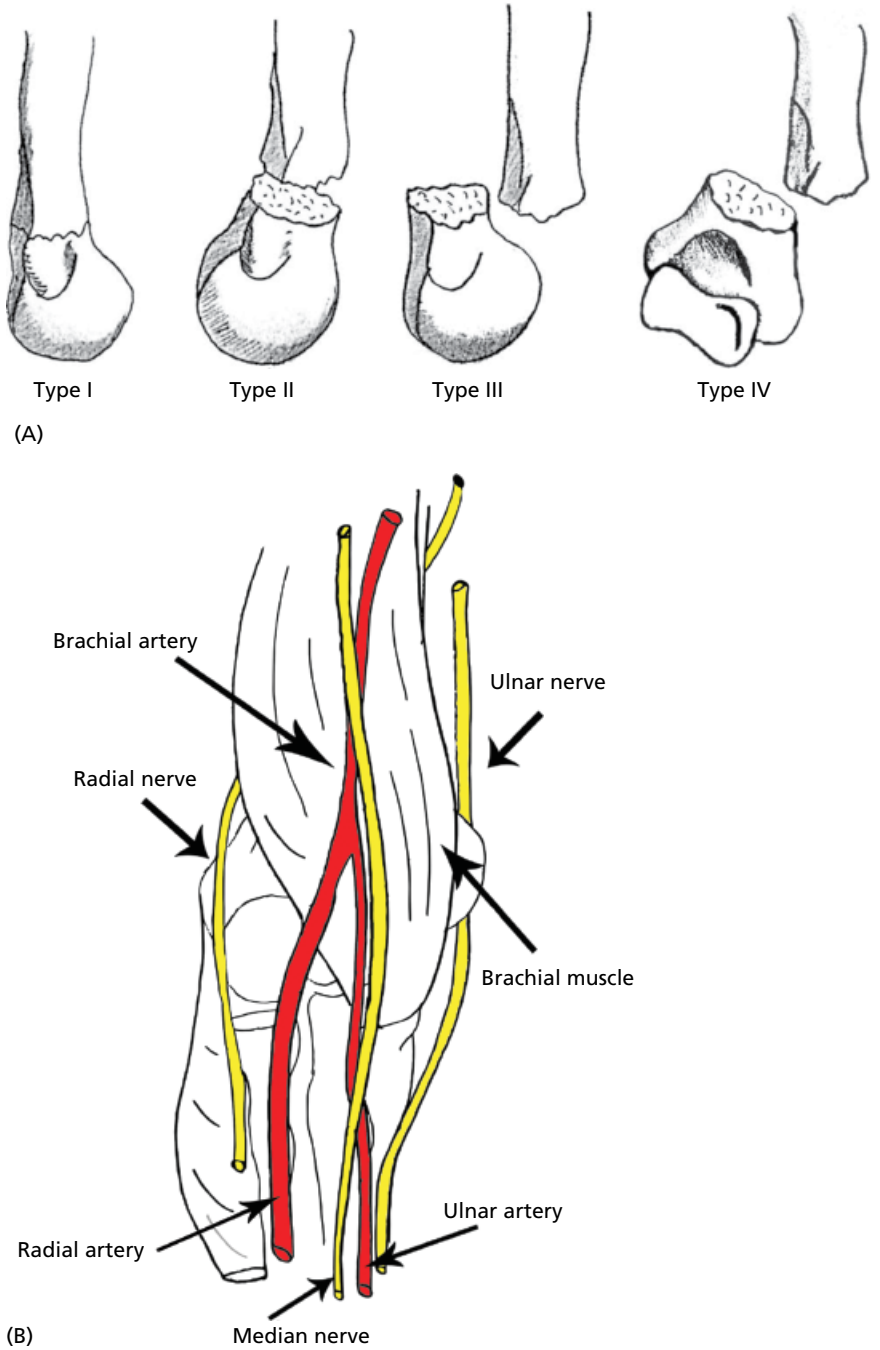

Figure 33.9 (A) Gartland classification of supracondylar humerus fractures. (B) Anatomical relationships of neurovascular bundles and supracondylar region. The brachial artery descends superficially by the anteromedial aspect of the brachial muscle, providing deep collateral arteries that run down the anterior aspect of the humerus. The median nerve descends with the brachial artery, the radial nerve runs down the lateral aspect of the humerus between brachialis and brachioradialis, and the ulnar nerve runs down the posteromedial aspect through the cubital tunnel of the medial epicondyle. *Source*: Reproduced from Zorrilla et al [127] with permission of Springer Nature.

skeletal maturity, at about 12–13 years in girls and 14 years in boys. Epidemiological studies have revealed that the overall incidence of ACL tears is greater in boys, while girls have a 2–8 times greater ACL injury rate per athletic exposure than boys.

There are a number of approaches to ACL repair, but most are arthroscopic for adolescents. Anesthesia technique may be general anesthesia or sedation combined with regional anesthesia. Local anesthetic instillation in the joint space by the surgeon can also be employed. Femoral or femoral–sciatic nerve blocks can be utilized for intra- and postoperative analgesia, and a femoral nerve catheter can be placed and local anesthetics infused via a disposable infusion pump in the patient's home after ambulatory surgery. Concern over reports of femoral nerve block leading to increased quadriceps weakness, and potentially delaying functional recovery, have limited the use of this technique in some institutions [130]. A conversation with the surgeon is clearly important before employing these techniques. A thorough presentation of nerve blocks of the lower extremity is given in Chapter 20.

CASE STUDY

A 4-year-old boy is scheduled for muscle biopsy. He has a history of walking at 20 months and is noted to walk on his toes. His parents observe that he uses his upper extremities to pull himself from the floor. He plays at the same exercise tolerance as peers but parents report that he falls down frequently. Parents are not aware of any family history of muscular dystrophy. He had an uneventful volatile anesthetic at 18 months of age for a spine MRI to evaluate his late onset of walking. The spine MRI was normal. With regard to family history of anesthesia complications, an uncle died during anesthesia for tonsillectomy as a child. He has no cardiac or respiratory problems.

On physical exam he is developmentally appropriate and has a completely normal physical exam except that his calves are hypertrophic.

Preoperative preparation includes a high suspicion for Duchenne's muscular dystrophy given his male sex, toe walking, and presence of the Gower sign (using the hands and arms to walk up one's own body to stand from a squatting position due to proximal lower extremity weakness). Furthermore, his family's anesthesia history is suspicious for hyperkalemic cardiac arrest in a male relative.

At this young age cardiac and respiratory systems are frequently unaffected; although in some cases cardiac symptoms can occur early. A cardiology consultation should be obtained preoperatively for patients with known DMD regardless of whether the patient has documented cardiac dysfunction. ACE inhibitors to treat these patients medically, even before the onset of cardiac failure, is now recommended. Thus, cardiologist involvement at an early stage of overall care is ideal. Since this child is young, asymptomatic, and does not have a DMD diagnosis confirmed, most anesthesiologists would proceed without an echocardiogram for this minor operative procedure. If DMD is diagnosed then all subsequent anesthetics should be preceded by cardiology consultation to address cardiac medications to optimize cardiac function, ECG, echocardiogram, and Holter examination if indicated. Cardiac MRI is also used extensively to evaluate both function and arrhythmia risk. If cardiac function is known to be reduced, this consultation and echocardiogram should occur close to the planned anesthetic (within 3–6 months, depending on severity). Baseline tachycardia, irrespective of cardiac function, can be present, and it is helpful to document this preoperatively. Hypotension is often present when cardiac manifestations are advanced. In the absence of respiratory symptoms a pulmonary consult would not be indicated in this case but would be a routine part of the preanesthesia evaluation for a symptomatic muscular dystrophy patient to both optimize pulmonary function preoperatively and plan for postoperative care.

Laboratory studies should be done prior to anesthetic, including a basic metabolic panel, CK (CK and potassium may be elevated in the presence of progressive muscular diseases such as muscular dystrophy), and lactate level (elevated in metabolic myopathies) since the diagnosis is unknown in this child.

Due to the high suspicion of DMD diagnosis, the anesthesiologist proceeded with a trigger-free anesthetic to avoid the risk of rhabdomyolysis and cardiac arrest. However, these patients are not at risk for malignant hyperthermia (MH). A prior exposure to MH triggers without problems does not predict the outcome with future anesthetics. Therefore, an IV catheter was placed after sedation with oral midazolam and nitrous oxide. The surgery was scheduled as a first start both to decrease exposure to volatile anesthetic and to allow adequate observation time prior to anticipated discharge home. Manufacturer recommendations vary with regard to how best to prepare the anesthesia machine for a trigger-free anesthetic. Most recommend changing the CO_2 absorbent and flushing with high fresh gas flows. Activated charcoal filters (Vapor-Clean™, Dynathetics, Salt Lake City, UT, USA) are now available for use in patients at risk for MH or rhabdomyolysis. The filters are attached to the inspiratory and expiratory limbs of the circuit to filter anesthetic gases. A total intravenous anesthetic was maintained with propofol, low-dose opioid, and nitrous oxide. Post-biopsy analgesia was provided with local anesthetic infiltration, acetaminophen, and ketorolac.

The patient was observed for 2 h postoperatively and discharged home without the need for additional opioid in the postanesthesia care unit. His muscle biopsy was consistent with DMD.

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A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 34
Otolaryngological and Dental Surgery

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Introduction

More than a million children undergo surgery every year, a third of these are performed for problems in the ear, nose, or throat (ENT) areas. In this chapter, we discuss the perioperative anesthetic considerations and management of the most common conditions requiring surgical intervention in the head and neck region. These include the following:

- Myringotomy and pressure equalization tube insertion for treatment of chronic otitis media
- Middle ear surgery
- Tonsillectomy and adenoidectomy for relief of obstructive sleep apnea or for the management of recurrent pharyngitis
- Airway surgery for evaluation of subglottic stenosis and resection of laryngeal papillomas
- Removal of foreign bodies in the airway and esophagus.

Many children scheduled to undergo head and neck surgery present with nasal discharge that may represent either allergic rhinitis or an upper respiratory tract infection (URI). Children with a URI are at increased risk for developing perioperative respiratory adverse events (PRAEs), such as episodes of breath holding, laryngospasm, bronchospasm, oxygen desaturation, and occasionally stridor [1–3]. This may be because children who have a URI also have abnormalities of the peripheral lower airways and airway hyper-reactivity. Decreased functional residual and diffusion capacity and increased closing volumes and airway resistance have been noted during a URI [4–8]. This may also explain why apneic, anesthetized children with a URI more rapidly decrease their oxygen saturation to 95% [9]. Delayed respiratory complications may occur up to 18 h postoperatively in some children [10]. Therefore, it is important to differentiate between allergic rhinitis and URIs, especially since over 90% children undergoing ENT surgery do so on an outpatient basis [11]. Tait et al described a point system to help differentiate between allergic rhinitis and actual URIs; others have noted that parental reports are just as accurate [12,13].

Approach to the child with an upper respiratory tract infection

The anesthesiologist is faced with a dilemma when deciding whether or not to anesthetize a child who has a URI. Should they anesthetize the child or should they postpone the surgery? The anesthesiologist must balance the risk for laryngospasm, bronchospasm, oxygen desaturation, and postintubation croup with the fact that these risks may not be significantly reduced without waiting 4–6 weeks or longer. By that time the child will probably have another URI [14,15]. Emergent procedures should be performed, even in the presence of significant medical problems. However, elective procedures should be undertaken cautiously in the presence of a URI. Most anesthesiologists would postpone elective surgery in a child who presents with purulent secretions and fever, but the problem is that there is no consensus on how long to postpone the procedure. The increased airway reactivity can last 4–6 weeks. Empey et al [16] demonstrated a 200% increase in airway resistance after adults who had a URI inhaled histamine. The controls had only a 30% increase. The increase persisted for as long as 6 weeks after the URI ended. Nandwani et al [17] studied the sensitivity of upper airway reflexs of non-smoking adult patients with URIs by having them inhale ammonia vapor. Airway reactivity was 2–2.5 times higher than normal in those with a URI, but had returned to baseline 2 weeks after termination of their URI.

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

Many children have at least 6–10 URIs per year, making it difficult to schedule the procedure during a period when airway reactivity is normal. Furthermore, waiting 6 weeks has not reliably been shown to decrease the incidence of respiratory complications with general anesthesia [14]. There are, however, good data to show the incidence of PRAEs is higher if URI symptoms are present or if the URI occurred less than 2 weeks before the procedure [15]. The incidence of PRAEs is higher in young children with a URI and in the presence of copious airway secretions and/or nasal congestion. Other risk factors include asthma, cystic fibrosis, bronchopulmonary dysplasia, exposure to second hand (passive) tobacco smoke, and surgery involving the airway [18,19]. These factors must be taken into consideration when deciding whether to proceed with an anesthetic or delay the procedure.

The choice of anesthetic agents and airway devices used may also influence the incidence of PRAEs. Increased rates of PRAEs are seen with inhalation induction, maintenance of anesthesia with desflurane, and airway management by trainees [15]. Children with an URI who present for minor surgery, where instrumentation of the airway is not required, are not at increased risk of complications following general anesthesia [12,20]. Both laryngeal mask airway and a tracheal tube increase PRAEs in children with a recent URI [1,21,22]. Laryngospasm is twice as common in children undergoing airway surgery if they have symptoms of a URI [23]. Tracheal intubation elicits a potent airway reflex which further decreases the changes in functional residual capacity that occurs following induction of general anesthesia [24]. A recent study by Ghareai et al [25] shows that this effect can be attenuated with intravenous lidocaine but not with topical lidocaine. The intense physical and pharmacological stimulation of the airway associated with tracheal intubation causes significant airway hyper-reactivity in patients with asthma. Administration of albutamol preinduction of anesthesia has been recommended for asthmatic children who have had a recent URI [26]. However, even patients without underlying bronchospastic disease may develop a temporary increase in airway reactivity when they have a viral infection and this increases the likelihood of laryngospasm and bronchospasm.

Laryngospasm is the most frequently reported respiratory complication associated with URIs, particularly in younger children undergoing airway surgery and in those cared for by less experienced anesthesiologists [23]. This threatening event is characterized by the midline apposition of either the true vocal cords or both the true and false vocal cords, which involuntarily close the glottis and make it difficult or impossible to breathe [27]. The primary muscles involved in laryngospasm are the lateral cricoarytenoid, the thyroartenoid muscles (adductors of the glottis), and the cricothyroid muscles, which are tensors of the vocal cords.

Laryngospasm occurs most commonly during airway manipulation (e.g. intubation or extubation of the trachea), foreign material in the larynx (e.g. secretions), or with light anesthesia in a non-intubated patient. Clinical signs of laryngospasm and partial airway obstruction start with an irregular breathing pattern or noisy airway sounds that vary in intensity and tone but usually resemble a high-pitched squeak. When this occurs, it can be managed by jaw thrust and/or application of steady positive airway pressure for 30–45 seconds. If the airway obstruction is not resolved with these measures, it may be necessary to increase the depth of anesthesia with propofol or intravenous lidocaine [28–31]. It may also be necessary to administer a rapidly acting muscle relaxant, e.g. succinylcholine, to break the laryngospasm. The lungs should be ventilated with 100% oxygen. Laryngospasm and its treatment is also discussed in Chapter 17.

Acute postobstructive pulmonary edema may occur after relief of laryngospasm-induced total airway obstruction [32,33]. Attempts by the patient to breathe against a closed glottis generate negative intrapleural pressures of approximately 30–60 cmH_2O. This, together with the immediate decrease in airway pressure that occurs with relief of the laryngospasm, induces pulmonary edema [34]. The increased negative intrapleural pressure increases venous return (i.e. increased preload) and injures the microvasculature. The combination of the increased preload and the increased vascular permeability permits fluid to move out of the vasculature and causes both interstitial and pulmonary edema. The negative intrathoracic pressure also increases left ventricular transmural pressure (i.e. afterload) [35], which affects cardiac performance. Mechanical stress at the alveolar–capillary membrane is thought to be responsible for both pulmonary edema and for frank alveolar hemorrhage. While pulmonary hemorrhage may be the result of breathing against an acute airway obstruction [36], other etiologies of pulmonary hemorrhage should be ruled out [37]. Laryngospasm-induced pulmonary edema is most effectively managed by prompt tracheal intubation and application of continuous positive airway pressure (CPAP) or positive end-expiratory pressure (PEEP) during positive-pressure ventilation. Diuretics, morphine, and sedatives may also aid in treatment of the edema. If the patient has no underlying cardiorespiratory problems, the pulmonary edema resolves quickly, allowing the trachea to be extubated within several hours.

Bronchospasm is a potentially life-threatening intraoperative event that occurs more frequently in children with a URI, whether or not they have a prior history of asthma. This increased airway reactivity is thought to represent immunological and inflammatory mediator release in response to the viral infection. Epithelial damage from viral infections may also cause airway receptor sensitization and abnormal neural responses to tachykinins, such as substance P. The contractile effects of both substance P and capsaicin were enhanced in bronchial ring segments taken from guinea pigs infected with the parainfluenza 3 virus. Pretreatment with histamine-1 and -2 (H_1, H_2), muscarinic, serotonergic, and α-adrenergic blockers did not obliterate the effect of substance P [38]. This noncholinergic bronchospasm may explain why pretreatment with albuterol failed to decrease the incidence of bronchospasm in children with URI [39]. Due to its increased vagal reactivity, acetylcholine-related bronchospasm can be inhibited by atropine [40]. Atropine blocks the smooth muscle effect of acetylcholine and decreases the release of acetylcholine from vagus nerve endings [41]. A better strategy would be to use a more selective drug to block the muscarinic M3 receptor (stimulation of which causes bronchoconstriction) but not the M2 receptor (which inhibits acetylcholine release at nerve terminals).

Viruses can produce other substances that result in airway hyper-reactivity during URI. Parainfluenza and influenza viruses contain an enzyme, neuraminidase, which cleaves

sialic acid residues from M2 muscarinic receptor agonist binding sites. Inhibition of the M2 inhibitory site increases acetylcholine release. Studies in guinea pigs have demonstrated alteration of high-affinity agonist binding (carbachol) in lung membrane preparations in response to either neuraminidase or parainfluenza virus. In addition, a neuraminidase-blocking agent inhibited viral-induced changes [42].

The use of a laryngeal mask airway (LMA) rather than a tracheal tube for children with a recent or active URI may cause less tracheal stimulation and fewer respiratory complications [22]. While some studies have shown that LMAs can be safely used in children with an active URI undergoing elective surgery, other studies have shown an association between LMA use and respiratory complications, especially in children who have an active URI or have had a URI within the past 2 weeks [43,44]. A more recent randomized controlled trial compared PRAEs after tracheal intubation with the use of an LMA in anesthetized infants. The study was terminated early because those treated with an LMA had fewer complications [45].

The choice of anesthetic can also influence the incidence of PRAEs in children with URI. While the lower blood : gas partition coefficient of desflurane (0.45) allows for rapid emergence from anesthesia, it is associated with a higher incidences of laryngospasm, breath holding, and coughing following either tracheal extubation or removal of the LMA [46,47]. The incidence of laryngospasm may be decreased during deep anesthesia, but it is not completely abolished. A recent observational study by Erb and colleagues [48] revealed that laryngospasm still occurred in children despite a high concentration of sevoflurane (4.7% ED_{95} intubation). Careful vigilance by the anesthesia provider for, and rapid management of, laryngospasm cannot be overemphasized.

In summary, children with URIs are predisposed to developing adverse respiratory events in the perioperative period. Although "URIs" are considered a single disease process, often with a common set of presenting symptoms, there may be enormous variability in the pathophysiological effects and clinical manifestation of a particular virus, depending on the stage of the illness (e.g. initial symptoms, height of symptoms, recovery phase). There are algorithms to aid in the decision of whether to proceed with an anesthetic or not, and an evidence-based management plan has also been described [49]. This includes preinduction of inhaled albutamol; use of α2-receptor agonists (clonidine or dexmedetomidine) if premedication is required; induction of anesthesia with IV agents such as propofol; maintenance of anesthesia with inhaled anesthetics such as sevoflurane (avoid desflurane); and use of the least invasive airway device consistent with the surgical procedure (preferably face mask over LMA, and LMA over tracheal intubation). The anesthesiologist should consider administering IV lidocaine or propofol before manipulating the airway and should remove the device with the child deeply anesthetized. If possible, an experienced pediatric anesthesiologist should manage the child's care [15]. Anesthesiologists must be prepared to aggressively treat bronchospasm, and to deliver supplemental oxygen to patients during transport from the operating room to the recovery room and during the recovery period. Breathing patterns and oxygen saturation should be carefully monitored in the postanesthetic care unit (PACU) to ensure adequate ventilation and oxygenation before discharging the patient home or to the ward.

KEY POINTS: ANESTHESIA IN THE CHILD WITH UPPER RESPIRATORY INFECTION

- Children with a recent URI are more prone to develop laryngospasm or bronchospasm
- The decision on whether to proceed with the surgery depends on medical need alone
- Use the least stimulating airway device possible and only during deep anesthesia
- Fewer complications occur in patients with recent URIs when anesthesia care is provided by an experienced anesthesiologist

Anesthesia for specific surgical procedures

Surgery of the head and neck involves sharing of the workspace and airway by the surgeon and anesthesiologist, making close communication between them imperative. A preoperative meeting of the operating room team is useful to determine how best to establish optimal operative conditions. The discussion should include the steps involved in the procedure, patient positioning, the need for intraoperative movement of the tracheal tube, the potential effect of neuromuscular blockade on nerve integrity monitoring, and a need for precautions to avoid airway fires.

Ear surgery

Myringotomy and insertion of pressure equalization (ventilation) tympanostomy tubes (grommets)

Otitis media is an inflammatory process of the middle ear that often accompanies viral or bacterial upper respiratory tract infections and is a common occurrence in pediatric patients. An otitis media-induced collection of thick, glue-like fluid in the middle ear may cause conductive hearing loss if left untreated. Failure of antibiotic therapy to resolve the symptoms of otitis media warrants surgical drainage of this middle ear fluid. A simple myringotomy opens the tympanic membrane and allows the accumulated fluid to drain, but this drainage path eventually heals, and the symptoms recur. Placement of a ventilating tube in the ear drum stents open the membrane and allows drainage of fluid for 6–12 months after which the tubes are often extruded spontaneously.

A myringotomy and/or placement of ventilating tubes can be usually be completed in 5–10 min and usually only requires inhalation anesthesia via a facemask. The procedure may be more surgically challenging in children with some syndromes (e.g. Down, Apert) who have narrow ear canals. For these longer procedures, it is often better to use a laryngeal mask airway (LMA) for maintenance of anesthesia. This is associated with fewer hypoxemic episodes and provides better peroperative working conditions for the surgeons [50]. Abnormalities in the cartilages and muscles surrounding the eustachian tubes frequently cause children with cleft palates to develop otitis media; procedures in these children may also last longer than routine myringotomy tube insertions, but mask ventilation usually suffices for their intraoperative airway management.

Anesthetic management for children requiring placement of myringotomy tubes usually is accomplished with brief inhalation of potent inhalation agents (commonly sevoflurane) and nitrous oxide in oxygen. Maintenance of airway patency and adequate ventilation are essential, so an oral airway is often placed to alleviate/avoid airway obstruction. Assisted ventilation may be required if the depth of anesthesia exceeds the apneic threshold. Most practitioners do not establish vascular access in healthy patients undergoing this short procedure but reserve that for children with significant underlying medical conditions. Nevertheless, an intravenous fluid set-up should be readily available in the operating room and it is important to locate a good vein for catheter insertion before induction of anesthesia. This avoids wasting time searching for venous access if a problem occurs.

A variety of management strategies exist for treatment of the mild postoperative pain associated with the placement of myringotomy tubes. Preoperative oral acetaminophen (15–20 mg/kg) or intraoperative acetaminophen suppositories (40–45 mg/kg) are often used. Intraoperative administration of ketorolac, intranasal butorphanol, or fentanyl (2 μg/kg) have been shown to reduce the need for rescue analgesics [51–53]. Since this patient population is at high risk for emergence agitation following sevoflurane anesthesia, it may be appropriate to administer intranasal fentanyl to reduce the agitation near the end of anesthesia [54]. Intramuscular morphine 0.1 mg/kg reduces postoperative pain scores and rates of emergence delirium to the same degree as IV or intranasal fentanyl [55]. A study in this patient population compared dexmedetomidine with acetaminophen and intranasal fentanyl on demand. The study was terminated early due to prolonged recovery room stays by the dexmedetomidine group [56]. In another study, patients receiving intraoperative blocks of the auricular branch of the vagus nerve had similar postoperative pain scores as patients receiving intranasal fentanyl, but those with blocks had less postoperative emesis [57].

KEY POINTS: MYRINGOTOMY TUBES

- Myringotomy tubes provide temporary (6–12 months) drainage for middle ear effusions
- Inhalation anesthesia with a facemask, and no IV catheter, is the most common approach
- Analgesia can be provided via the intranasal (fentanyl, dexmedetomidine), intramuscular (ketorolac, morphine), or rectal (acetaminophen) routes

Middle ear and mastoid surgery

Most myringotomy tubes are eventually spontaneously extruded, but some require surgical removal. While tube removal is frequently performed in the clinic, small children may require general anesthesia due to their inability to cooperate. Surgically created myringotomy openings usually heals spontaneously, but not always. When they fail to do so, they usually require the placement of a paper patch or a fat graft over the opening under anesthesia. Anesthetic management for placement of a fat graft differs slightly from anesthesia for a routine myringotomy. Nitrous oxide administration should be discontinued or limited to 50% prior to placing the tympanic membrane graft to prevent pressure-related graft displacement. Nitrous oxide diffuses into air-filled middle ear spaces faster than nitrogen moves out because nitrous oxide is 34 times more soluble in blood than nitrogen. Normal passive venting of the eustachian tube occurs at 20–30 cmH_2O pressure; nitrous oxide administration produces pressures that exceeds this level. When this occurs, the patient may complain of pain, and the graft may be displaced [58].

Repeated middle ear infections can cause mastoiditis and produce large perforations in the tympanic membrane that are difficult to repair via the auditory canal. When this occurs, additional surgery may be required via posterior auricular exposure. The skin over the outer surface of the eardrum can also grow through the perforation and into the middle ear, forming a destructive and expanding growth called a cholesteatoma. Cholesteatomas require surgical repair, occasionally in stages.

Anesthetic management for middle ear surgery typically includes inhalational agents and opioid administration. Tracheal intubation is facilitated by intravenous propofol, with or without laryngotracheal application of lidocaine. Following tracheal intubation, the operating table is usually turned 90° or 180° away from the anesthesia machine with the patient's head positioned on a soft head rest below the height of the operating table. The surgeon may request extreme lateral rotation of the operating room table to improve their view of the ear. The anesthesiologist and surgeon must ensure that nerves, muscles, and bony structures are properly padded to avoid injury during positioning. They must also prevent accidental dislodgment of the tracheal tube during positioning. The use of extra-long anesthesia circuits is required if the patient's head is positioned some distance from the anesthetic machine. Surgical drape placement should allow easy access to the patient and the tracheal tube. Careful head positioning is particularly important in children with Down syndrome and achondroplasia, as 15–31% of these children are prone to atlantoaxial (C1–2) subluxation [59,60]. The facial nerve is in close proximity to the surgical field during middle ear and mastoid surgery. Monitoring nerve integrity during surgery requires avoidance of neuromuscular blockade or demonstration of return of neuromuscular response to at least 70% of baseline by the time surgery begins.

The operative site is visualized through a microscope. Bleeding during middle ear surgery is usually minimal, partly because the surgeon injects epinephrine around the tympanic vessels to produce vasoconstriction. Close attention should be paid to the amount of epinephrine injected to avoid excessive absorption of epinephrine, arrhythmias, and wide variations in blood pressure. Relative hypotension (mean arterial pressure ≤25% below baseline) is sometimes used to decrease intraoperative bleeding.

Nitrous oxide administration during these cases may increase the volume of gas in the air-filled cavities of the middle ear and sinuses. When the nitrous oxide is subsequently discontinued, it is rapidly absorbed, causing negative pressure in the middle ear and displacement of tympanic patches. Disarticulation of the stapes bone of the middle ear can occur. When it does, hearing is impaired for up to 6 weeks postoperatively. Nitrous oxide also increases the incidence of postoperative nausea and vomiting in children undergoing middle ear surgery. Nitrous oxide reabsorption can produce sufficient

negative pressure to cause traction on the round window during recovery from anesthesia. This causes the relatively compliant walls of the eustachian tubes to collapse and prevents re-equilibration of the middle ear with atmospheric pressure [61]. Older children (more than 8 years of age) have less compliant eustachian tubes and do not suffer the effects of negative middle ear pressure or the postoperative nausea and vomiting. Children between 3 and 8 years of age seem to be affected the most [62]. Prophylactic administration of antiemetics, like dexamethasone and ondansetron, have been recommended for these patients [63]. Pre-emptive blockade of the great auricular nerve caused no greater decrease in postoperative analgesic requirements than placing the block 1 h before the end of tympanomastoid surgery [64]. It did, however, decrease postoperative opioid requirements and postoperative nausea and vomiting by approximately 66% [65].

A smooth emergence from anesthesia without coughing is preferred after middle ear surgery. Toward the end of surgery, the child is allowed to breathe spontaneously while gradually titrating opioids as tolerated to reduce postoperative pain. Administration of intravenous lidocaine 1–1.5 mg/kg in children older than 1 year of age and gentle suctioning of the oropharynx minimizes or prevents coughing following tracheal extubation.

Cochlear implant surgery

Early insertion of cochlear implants is rapidly gaining acceptance as a method for rehabilitating profoundly hearing-impaired children because it permits better development of auditory, speech, and language skills and more successful integration with normal-hearing peers. Children as young as 6 months of age have had successful cochlear implants. Placement of cochlear implants requires meticulous soft tissue dissection, hemostasis, and bone drilling; bleeding from the bone marrow can be very difficult to control. The implant stimulates the auditory nerve to enable hearing. Limits of implant stimulation are set intraoperatively with evoked stapedius reflex thresholds (ESRTs) and with evoked compound action potentials. The latter are not affected by anesthetics, but volatile anesthetics are known to abolish the stapedius reflex in more than 50% of children [66]. Anesthetics also cause a dose-dependent increase in the ESRT. This results in ESRT levels that overestimate a child's comfort level, which may lead to postoperative difficulty adjusting to the implant. Therefore, use of volatile anesthetics during this phase of the surgery is discouraged. Propofol has no effect on ESRT. Other anesthetic considerations are similar to those for middle ear surgery and appropriate communication with the surgeon ensures the successful outcome of these procedures.

KEY POINTS: MIDDLE EAR AND MASTOID SURGERY

- Care must be taken to prevent tracheal tube dislodgment during mastoid surgery
- Nitrous oxide may increase intraotic pressure and dislodge fat grafts
- Muscle paralysis should be avoided in facial surgery to prevent inadvertent damage to the facial nerve

Nasal and pharyngeal surgery

Adenoidectomy and tonsillectomy

Adenoidectomy is performed alone or in conjunction with tonsillectomy and/or myringotomy and the insertion of myringotomy tubes. The indications for adenoidectomy alone include chronic otitis media with adenoid hyperplasia-induced middle ear effusion, chronic sinusitis, and chronic or recurrent purulent adenoiditis. Severe adenoid hyperplasia results in nasopharyngeal obstruction, obligate mouth breathing, failure to thrive, and speech disorders. Long-standing nasal adenoid hyperplasia-induced obstruction may result in narrowing of the upper airway and dental abnormalities ("adenoidal facies").

Tonsillectomy, with or without adenoidectomy, is one of the most common ambulatory pediatric surgery procedures performed in the United States [67]. Two common indications for this are: (1) recurrent or chronic tonsillitis refractory to medical therapy, and (2) obstructive adenotonsillar hyperplasia and obstructive sleep apnea (OSA). Children who undergo tonsillectomy for recurrent tonsillitis are usually older and have fewer perioperative problems than those with chronic airway obstruction from hypertrophic tonsils. The latter group may present with failure to thrive, dysphagia, speech abnormalities, halitosis, cervical pharyngitis, and persistent pharyngitis. Severe airway obstruction can result in carbon dioxide retention, vasoconstriction of the pulmonary vasculature, right ventricular hypertrophy, and cardiac failure (cor pulmonale). Children less than 3 years of age presenting for adenotonsillectomy require special attention, as they have the highest perioperative respiratory morbidity [68,69].

Preoperative assessment

Habitual snoring, without alterations in gas exchange, is very common in children and may not result in sleep disruption or morbid consequences. In contrast, children with OSA have a "disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction which disrupts normal breathing and normal sleep patterns during sleep" [70]. Sleep disordered breathing and OSA are interchangeable terms. The features of OSA differ in children and adults. In children, the peak incidence of OSA occurs between 2 and 6 years of age, with an equal male/female distribution, and an excellent response to adenotonsillectomy in most children. With the increased incidence of childhood obesity, the clinical patterns of adult and pediatric OSA are begining to resemble each other [71]. Obstructive sleep apnea occurs during rapid eye movement (REM) sleep and is characterized by snoring and continuous partial upper airway obstruction during sleep. This results in paradoxical respiratory efforts, ineffective ventilation, hypercarbia, and hypoxemia [72].

Snoring, breath holding or apneic spells, failure to thrive, and repeated respiratory infections are all suggestive of OSA and indicate the need for overnight sleep polysomnography. Prior to the ubiquitous availability of mobile recording devices, definitive diagnosis of OSA was made by polysomnography; currently, not all patients undergo polysomnography preoperatively, because parents are able to provide a video or audio recording of witnessed snoring and apneic episodes on their smart phones. Respiratory events that are documented during polysomnography are outlined in Table 34.1.

Table 34.1 Respiratory events that may occur during polysomnography

Event	Definition
Central apnea	Pause in airflow with absent respiratory effort, scored when >20 s or two missed breaths and >3% decrease in oxygen saturation
Obstructive apnea	>90% reduction in airflow despite continuing respiratory effort, scored when event lasts at least two missed breaths in children
Obstructive hypopnea	>50% reduction in airflow despite continuing respiratory effort, scored when event lasts at least two missed breaths in children and >3% decrease in oxygen saturation or arousal
Mixed apnea	≥90% reduction in airflow, lasting at least two missed breaths, and containing absent respiratory effort initially (central apneic pause), followed by resumption of respiratory effort without resumption of airflow (obstructive apnea)
Obstructive hypoventilation	End-tidal CO_2 > 50 mmHg for >25% of total sleep time with paradoxical respirations, snoring, and no baseline lung disease

Source: Reproduced from Schwengel et al [225] with permission of Wolters Kluwer.

The number of hypopnea-obstructive episodes occurring during a sleep study are usually combined to give an apnea-hypopnea index (AHI), which is defined as the number of discrete obstructive events that occur per hour. Many sleep laboratories report an AHI or a respiratory disturbance index that includes the total number of respiratory events, including the number of central apnea events per hour. However, central apnea is a normal occurrence in children and is not associated with impaired respiration. True documentation of OSA in children should be based only on obstructive episodes associated with respiratory impairment [73,74]. OSA is considered to be severe if the AHI is ≥10 per hour and if the oxygen saturation nadir is ≤80%. The severity of OSA is usually based on the patient's overall clinical picture, including the frequency and severity of oxygen desaturation during the apneic episodes, duration of elevated carbon dioxide, and the number of obstructive events per hour [75–78].

Children with severe OSA are occasionally admitted to hospital preoperatively for optimization of their condition prior to undergoing adenotonsillectomy. Optimization may include oxygen administration and non-invasive nasal CPAP to stents the airway open, prevent airway collapse, and increase functional residual capacity. Bilevel positive airway pressure ventilation may also be instituted. This form of ventilation has been shown to improve pulmonary hypertension, decrease the postoperative complication rate, and may be beneficial in some pediatric patients [79,80].

KEY POINTS: ADENOIDECTOMY AND TONSILLECTOMY

- Tonsillectomy and adenoidectomy are very common surgeries performed in outpatient facilities
- The incidence of OSA is high and may be associated with CO_2 retention, hypoxemia, and pulmonary hypertension
- Parents can record their child's breathing preoperatively on their smartphone for viewing by the anesthesiologist preoperatively

Special situations in children undergoing adenotonsillectomy

A variety of special challenges may be encountered in children who present for adenotonsillectomy. These include patients with craniofacial disorders, Down syndrome, sickle cell disease, and those with known bleeding disorders. Risks of general anesthesia in these patient populations are discussed in Chapters 12 and 43. The anesthesiologist should be prepared for potential difficulty in maintaining airway patency, intubating the trachea, and maintaining ventilation, particularly in patients with craniofacial disorders. For example, patients with mucopolysaccharidosis I (Hurler syndrome) and II (Hunter syndrome) have diffuse infiltration of the upper airway and larynx with abnormal mucopolysaccharides, which predisposes them to upper airway obstruction and difficult tracheal intubation. Patients with Hurler syndrome may also have abnormal heart valves and coronary arteries at an early age. Patients with Hunter syndrome can have severe kyphoscoliosis, which may affect positioning for tracheal intubation.

Patients with trisomy 21 (Down syndrome) have midface hypoplasia that is characterized by narrow oral and nasal passages and glossoptosis. In addition, these children have hypopharngeal hypotonia that leads to hypopharyngeal collapse during induction of anesthesia. Mask ventilation may be difficult, and insertion of an oral and/or nasal airway may be necessary. Some of these patients develop hypertrophy of their lingual tonsils, which are not easily appreciated on oral examination because they are located posterior to the tongue (Fig. 34.1) [81]. Lingual tonsil hypertrophy can be responsible

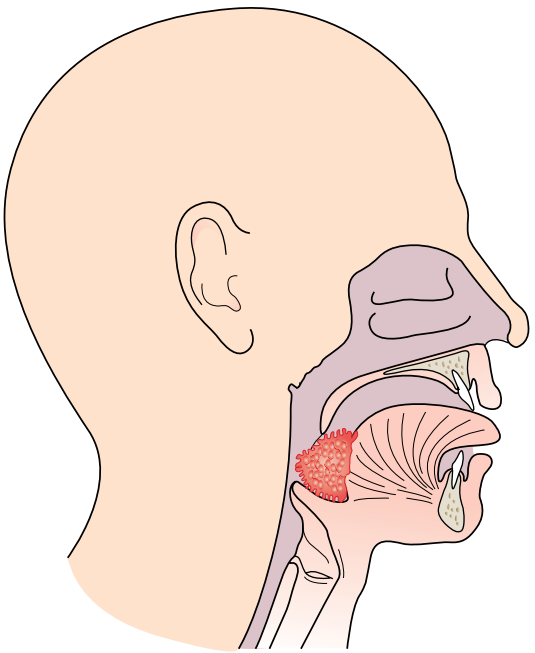

Figure 34.1 Hypertrophied lingual tonsil, which is difficult to appreciate on oral examination. *Source*: Reproduced from Olutoye et al [85] with permission of Wolters Kluwer.

for the persistence of OSA following adenotonsillectomy [82]. While the presence of hypertrophied lingual tonsils is not readily appreciated on oral examination, anesthesiologists must be aware that they are a cause of a "cannot ventilate-cannot intubate" clinical scenario [83–85].

Patients with sickle cell disease and recurrent tonsillitis are predisposed to developing sepsis. Hypoxemia in patients with OSA and sickle cell disease may have a sickling crisis. Therefore, frequent episodes of tonsillitis (>6 episodes per year) or adenoid hypertrophy resulting in upper airway obstruction are treated very aggressively in this subset of patients. Patients with sickle cell disease undergo special perioperative evaluation and management, depending on the preference of the hematologist. The main goals of these regimens is to prevent perioperative hypoxemia, maintain adequate hydration to decrease blood viscosity and subsequent concentration of sickled cells, to increase the concentration of hemoglobin to 10 g/dL via simple blood transfusion, and to decrease the concentration of hemoglobin S by blood transfusion. There are differences in opinion regarding the trigger hemoglobin value for preoperative blood transfusion in sickle cell disease patients undergoing minor surgical procedures. However, most centers have firm policies for the management of sickle cell patients undergoing routine surgery, including temperature maintenance, hydration, oxygen therapy, and pain management. The evidence that these measures are useful has not been well established [86–91]. Due to chronic pain, patients with sickle cell disease require adequate postoperative analgesic therapy [92]. Treatment of this pain may pose a challenge because even moderate doses of opioids can cause shallow breathing and hypoxemia, especially if the patient also has OSA. This makes the management of pain for these children more difficult than it is for the average patient. Preoperative consultation with the hematology service and pain service are essential before these children undergo surgery (see Chapters 12 and 37).

KEY POINTS: ADENOTONSILLETOMY IN CHILDREN WITH GENETIC SYNDROMES

- Maintenance of the airway and tracheal intubation may be difficult for patients with some syndromes
- Hypoxemia during adenotonsillectomy may result in a sickle cell crisis
- Patients with sickle cell disease must have their pain treated effectively
- Perioperative consultation with the hematology service is imperative prior to providing anesthesia for a patient with sickle cell disease

Coagulation status

Adenotonsillectomy differs from other operations in that a large, raw surface (tonsillar bed) is left open and the unopposed edges do not provide hemostasis at the end of surgery. It is, therefore, very important to obtain any history suggestive of bleeding tendencies and to discontinue medications that interfere with coagulation, such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and valproic acid, prior to surgery. However, discontinuing these medications perioperatively may cause problems managing the patient's underlying disorder. For example, discontinuing aspirin in a child with a Blalock–Tausig shunt increases the risks of clot development within the shunt. Preoperative consultation with the patient's cardiologist should be obtained to balance the risks of bleeding with the risks of a blocked shunt.

Preoperative consultation with a hematologist is indicated for children with a personal history or family history of bleeding disorders. While routine coagulation studies may not be necessary in all subjects undergoing adenotonsillectomy, they are certainly required for a history suggestive of a bleeding disorder in either the patient or the family. Appropriate laboratory tests include prothrombin time to test the extrinsic and common coagulation pathway, activated partial thromboplastin time to test the intrinsic and common pathway, and a bleeding time and studies of platelet function. Children with known inherited coagulation disorders are sometimes scheduled to undergo adenotonsillectomy. These disorders include von Willebrand disease, a hereditary disorder characterized by a deficiency of von Willebrand factor and prolonged bleeding time, and hemophilia A or B, hereditary disorders characterized by deficiency of clotting factors VIII and IX, respectively. Consultation with the hematology service to determine the dose and time for the administration of specific factors to correct the coagulation defect is indicated prior to surgery (see Chapter 12).

Intraoperative management

Adenotonsillectomy is usually completed in 15–30 min by a variety of methods, including guillotine and snare, cold and hot dissection, ultrasound coblation, and electrocautery. Many combinations of inhaled and intravenous agents have been used to provide satisfactory anesthesia for these procedures. However, it usually involves induction of anesthesia via a facemask, establishing vascular access, tracheal intubation with a preformed Ring–Adair–Elwyn (RAE) tube, and maintenance of anesthesia with volatile anesthetics. Use of an oral RAE tube allows the surgeon to easily position the self-retaining mouth gag. In addition, the shape of the tube allows the anesthesia circuit to be connected away from the surgical site (Fig. 34.2). However, some surgeons prefer to work around a regular/straight oral tracheal tube. The LMA is routinely used for adenotonsillectomy in some centers. Some anesthesiologists recommend routine use of a cuffed tracheal tube to reduce the leak of anesthetic gases and oxygen into the pharynx, which reduces the risk of airway fires. Adenotonsillectomy is a high-risk procedure for airway fires because there is an ignition source (electrocautery) in close proximity to an oxidizer-enriched environment (>21% oxygen and nitrous oxide in the pharynx), and combustible tissue, the triad necessary for an operating room fire [93]. An FiO_2 of 0.30 or less should be employed during the period of electrocautery use for adenotonsillectomy. Cuffed tracheal tubes limit the number of repeated laryngoscopy attempts, allow for use of low-flow anesthesia, and decrease the amount of detectable anesthetic gas in the operating room [94]. There is no existing randomized controlled trial that has studied the safety of LMAs versus cuffed tracheal tubes for securing the airway for this procedure.

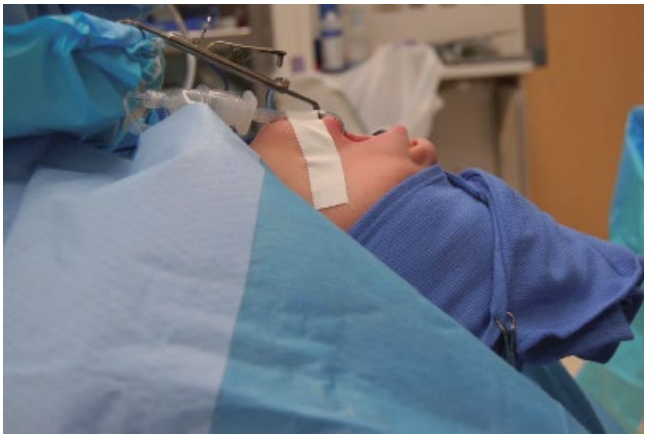

Figure 34.2 Child positioned for tonsillectomy and/or adenoidectomy. The tracheal tube is secured along the mandible away from the operative field. It is imperative to ensure that the tracheal tube is not kinked or occluded by the retractor.

At the end of surgery, the trachea can be extubated with the patient awake or during deep anesthesia, provided they are breathing comfortably without episodes of breath holding or apnea. Studies have shown that there is no difference in the incidence of oxygen desaturation, breath holding, laryngospasm, or the need for an emergency rescue airway in children extubated awake or in deep anesthesia after adenotonsillectomy [95,96]. The experience of the anesthesiologist is also a factor in reducing PRAEs [15].

The goal of the adenotonsillectomy anesthetic is to have a comfortable child without episodes of respiratory obstruction in the postoperative period. This is usually achieved by intraoperative administration of opioids. However, children with OSA may be more sensitive to the effect of opioids and reduced doses may be required to prevent postoperative respiratory depression [97]. In patients with severe OSA, small doses of opioids are titrated to effect in the PACU once the patient is awake. Acetaminophen is administered intraoperatively to provide postoperative analgesia for tonsillectomy. However, enteral administration of acetaminophen alone does not provide adequate analgesia due to delayed drug absorption and attainment of subtherapeutic plasma drug concentrations [98]. Intraoperative use of IV acetaminophen and opioids together was associated with the need for fewer rescue medications, decreased side-effects, and decreased recovery times and costs compared with single IV opioid therapy alone post tonsillectomy [99]. This was because less opioid was required.

Intraoperative infiltration of the tonsillar bed with local anesthetic is utilized by some surgeons to decrease postoperative morbidity in this population [100–102]. Different surgical techniques have also been used to determine which technique causes the least postoperative pain [103–106].

The α2-agonist dexmedetomidine was shown to reduce postoperative opioid consumption in adults undergoing major inpatient surgery [107]. This drug provides mild analgesia without respiratory depression and has increased the time to the first rescue opioid analgesic in the PACU when given in doses of 1 or 0.75 μg/kg in adenotonsillectomy patients during surgery [108]. Dexmedetomidine 0.1 μg/kg produced less respiratory depression, but provided less effective analgesia than morphine 0.1 mg/kg in children with OSA who underwent adenotonsillectomy [109].

In the United States, acetaminophen combined with codeine was formerly commonly administered for analgesia following tonsillectomy ± adenoidectomy. Codeine is converted to morphine by the highly polymorphic *CYP2D6* gene. Consequently, there are patients who are poor metabolizers (low activity variants), extensive metabolizers (high or normal activity variants), or ultra-rapid metabolizers (multiple gene copy variants). Poor metabolizers cannot convert codeine to morphine efficiently. Consequently, these patients experience no pain relief from codeine. Ultra-rapid metabolizers metabolize codeine too efficiently and can develop morphine intoxication, respiratory depression, and perioperative death. This resulted in the US Food and Drug Administration (FDA) issuing a black box warning (absolute contraindication) against the use of codeine in children in 2012 [110,111]. The decrease in narcotic use led to an increase in the use of NSAIDs, such as ibuprofen, post tonsillectomy. Prior to the FDA black box warning, the concern about the effects of NSAIDs on hemostasis had limited their use perioperatively [112]. A Cochrane systematic review of studies examining risk of bleeding with NSAIDs in post-tonsillectomy children provided inconclusive evidence one way or the other. Results of the most recent review have also failed to conclusively exclude excessive postoperative bleeding when these drugs are utilized in patients undergoing a adenotonsillectomy [113,114]. Studies have shown that the incidence of bleeding is not increased when ibuprofen with acetaminophen is administered postoperatively to treat the pain of adenotonsillectomy [115,116]. Due to these findings, and the FDA black box warning on codeine, the present practice in the United States is for some surgeons to discharge patients home post tonsillectomy and/or adenoidectomy with ibuprofen alternating with acetaminophen.

Intraoperative dexamethasone has also been used to reduce postoperative pain, edema, and to prevent nausea and vomiting after adenotonsillectomy. The minimum dose required to reduce opioid consumption was 0.5 mg/kg, however parents reported improved pain scores with 1 mg/kg of dexamethasone [117]. This report was criticized for the reported increased bleeding, the high incidence of primary hemorrhage, and the rate of need for reoperation on the day of surgery [118]. Follow-up studies and Cochrane systematic reviews have not supported an increased incidence of bleeding following use of dexamethasone during adenotonsillectomy [119]. Dexamethasone is also useful as an antiemetic. Its administration intraoperatively, in conjunction with an antiserotonin drug, such as ondansetron, is the recommended antiemetic prophylaxis for this procedure [63].

Complications

Postoperative or secondary hemorrhage and respiratory impairment are the most frequently observed complications following adenotonsillectomy. The incidences of these complications greatly depend on age of the patient and associated medical conditions. Postoperative hemorrhage is more common in children older than 10 years of age [120], while respiratory complications (supraglottic obstruction, breath holding, and need for airway rescue maneuvers) are more common in children younger than 3 years of age [75,121,122].

In many institutions, children less than 3 years of age are observed overnight in the hospital following adenotonsillectomy, particularly if they have co-morbid conditions (e.g. Down syndrome, developmental delay, OSA).

Other rare complications following adenotonsillectomy include uvular edema, uvula amputation, velopharyngeal insufficiency, and nasopharyngeal stenosis. Throat pain, otalgia, and poor oral intake are common following discharge home.

Post-tonsillectomy hemorrhage

Primary post-tonsillectomy hemorrhage is a common complication that often requires surgical re-exploration, usually within the first hour after surgery. Secondary hemorrhage presents within 2 weeks after the initial surgery, when the eschar on the surgical site is dislodged and raw mucosal surfaces are exposed. Secondary hemorrhage occurs in 0.5–2% of all tonsillectomies. Mild post-tonsillectomy bleeding can be managed conservatively, but 41% of patients with minor bleeding subsequently develop major bleeding within 24 h and require surgical exploration and cauterization of the bleeding surface.

Post-tonsillectomy hemorrhage occurs more commonly in older children. Children with bleeding tonsils usually swallow the blood before they show evidence of frank hematemesis. Therefore, they have a full stomach and must be treated accordingly during the induction of anesthesia. In rare cases, they may have significant anemia from blood loss. If there has been significant bleeding, a preoperative hemoglobin level should be obtained. If necessary, blood should be transfused. The degree of dehydration observed on clinical examination helps determine the amount of volume replacement required. Since they have a sore throat, they may not have been drinking. A severely dehydrated child has dry mucus membranes, sunken orbits, and decreased skin turgor; tachycardia and hypotension may also be present. Urine output is often decreased or absent. If the amount of bleeding and dehydration is significant, it may be difficult to obtain intravenous access. Insertion of an intraosseous needle may be required. If possible, large-bore intravenous needles should be placed because large volumes of crystalloid, with or without colloid, may be required.

Preparation for the induction of anesthesia includes having two suction catheters available, preferably of the firm Yankauer type, and medication for a rapid-sequence induction of anesthesia. Preoxygenation should be followed by rapid-sequence induction of anesthesia. The surgeon should be holding one suction and the other should be within easy reach of the anesthesiologist to quickly suction vomited blood if necessary. In situations of severe bleeding, the vocal cords may not be visible. If this occurs, an assistant should gently press on the anterior chest wall, and the anesthesiologist should aim the tip of the tracheal tube at the site where bubbles are seen during compression. Careful laryngoscopy is required because it may scrape the tonsillar bed and precipitate further bleeding. Cuffed tracheal tubes are recommended because of the full stomach. Prompt identification of the bleeding sites usually occurs during surgery. Cauterization of the tonsillectomy bed lasts only about 20 min. If signs of shock are present, blood may be transfused intraoperatively or in the recovery room. The stomach should be emptied of blood and secretions as best it can before removing the tracheal tube.

KEY POINTS: ADENOTONSILLECTOMY INTRA- AND POSTOPERATIVE MANAGEMENT

- Adenotonsillectomy is a high-risk procedure for airway fires and FiO_2 should be ≤30% during surgery
- Because they have chronic hyper-reactivity of their airways, patients are prone to laryngospasm and/or bronchospasm during tracheal tube insertion
- Postoperative respiratory complications are common in younger children while postoperative bleeding is more common in older children
- Acute postoperative bleeding from the surgical site occurs within 2 h of terminating surgery, while secondary bleeding occurs 1–2 weeks later

Endoscopic sinus surgery

Chronic sinusitis is characterized by inflammation of the sinuses and occlusion of the sinus ostia. The latter prevents the normal drainage of fluid from the sinuses into the nose. In some patients, adenoidectomy relieves the symptoms, although endoscopic sinus surgery is the mainstay for surgical treatment of chronic sinusitis that is refractory to antibiotic therapy and adenoidectomy. Direct telescopic visualization of the nasal mucus membranes allows relief of the obstruction by sharp, biting instruments or a microdebrider. This improves ventilation of the sinuses while leaving the mucous membranes intact. Children with cystic fibrosis often present for this surgery, due to impaired mucociliary function and chronic infection. The anesthesiologist should ensure that the pulmonary function of patients with cystic fibrosis has been optimized prior to surgery.

Bleeding during sinus surgery often makes visualization of the surgical field difficult. To reduce bleeding, the nasal cavity is packed with pledgets soaked in a vasoconstricting solution, usually oxymetazoline 0.025–0.05%, phenylephrine 0.25–1%, cocaine 4–10%, or lidocaine 2% with epinephrine 1:100,000 or 1:200,000. The anesthesiologist must be aware of the type and dose of vasoconstrictive agent used and ensure that the maximum allowable concentration/amount of the drug is not exceeded. Rapid absorption of these drugs from raw mucosal surfaces leads to tachycardia or bradycardia and/or hypertensive episodes in some patients [123,124]. This is especially true if intraoperative anticholinergic drugs have been administered. The intraoperative hypertension is usually transient and resolves spontaneously without aggressive treatment. The recommended maximum dose of phenylephrine in children is 20 μg/kg. Cocaine use during surgery has resulted in myocardial infarction in otherwise healthy individuals [125]. Cocaine may also block the nasociliary ganglion and cause transient postoperative anisocoria [126].

Intraoperative management for endoscopic sinus surgery requires tracheal intubation with an oral RAE tube, which is securely fixed to the mandible; this allows easy surgical access to the maxilla and sinuses. The use of cuffed tracheal tubes prevents fogging of the endoscopic equipment by excessive gas leakage from around the tube. Throat packs are almost always utilized during this surgery to prevent escape of anesthetic gases and oxygen into the surgical

environment. The surgeon and anesthesiologist must confirm the throat pack has been removed *prior* to extubation of the trachea, as a retained pack may cause airway obstruction, emergence agitation, or even death if not recognized. Intraoperative administration of intravenous corticosteroids has been used to prevent postoperative airway swelling. At the end of surgery, the surgeon often leaves stenting material in the sinuses. This may cause patient discomfort or a perception of difficult breathing during emergence from anesthesia. Therefore, the anesthetic technique should provide adequate analgesia and quick emergence from anesthesia.

A second endoscopic procedure is usually required approximately 6 weeks after the initial surgery to remove the packs (if non-absorbable packs were used) and to examine the surgical site. This second-look procedure is usually quick and the LMA is usually sufficient for airway maintenance.

Endoscopy of the larynx, trachea and bronchial tree

The major challenge during endoscopy of the respiratory tract is for the anesthesiologist to maintain adequate alveolar ventilation and oxygenation, and to provide a quiet surgical field while having a clear view of a patient who has some degree of upper or lower airway compromise. They must do this while sharing the airway with the endoscopist. Preoperative communication between the surgeons, nurses, and anesthesiologist is essential so that all members of the team are aware of the aims, steps in the procedure, equipment required, and any special precautions or requirements, e.g. need for spontaneous respiration, method of lung ventilation during the procedure, and potential fire hazards.

Lesions commonly diagnosed endoscopically include laryngomalacia or tracheomalacia, vascular anomalies that are causing tracheobronchial compression, congenital or acquired subglottic stenosis, vocal cord palsies, abnormal growths in the airway (e.g. papillomas, hemangiomas, cysts, granulomas), and foreign bodies [127,128]. Therapeutic bronchoscopy is performed to extract foreign bodies from the airway or to aspirate thick, tenacious mucus plugs from bronchi [129].

Preoperative evaluation of the airway requires a careful history of the extent of airway obstruction during sleeping, crying, or feeding. It also requires knowledge of the extent of accompanying respiratory distress (use of accessory muscles of respiration, tachypnea) and which positions or maneuvers aggravate or alleviate the symptoms. The anesthesiologist should examine any available chest radiographs, head and neck computed tomography scans, magnetic resonance imaging scans, pulmonary function tests, and arterial blood gas determinations to obtain a complete understanding of the patient's clinical situation [130,131].

Flexible fiberoptic and direct laryngoscopy and bronchoscopy

With the miniaturization of flexible endoscopic equipment, appropriately sized flexible bronchoscopes can be used to directly examine the airway of children of any age [132]. These bronchoscopes are available in sizes ranging from 2.2 to 6.3 mm outer diameter (internal channel 1.2–3.2 mm) and have been increasingly used in the smallest and sickest of children. As with any procedure, flexible airway endoscopy is performed when it is the easiest, safest, and most effective method to obtain the diagnostic information required [133]. It is often performed at the bedside of patients in the intensive care unit (ICU). In rare situations, this procedure is accomplished in infants or older children with only topical anesthesia and minimal sedation. More commonly, general anesthesia is required. Preoperative sedatives and opiates must be administered with caution to those who have airway compromise, and then only with appropriate monitoring and by persons who are skilled in advanced airway management. Some experts recommend an antisialogue to minimize secretions [134–136].

For procedures occurring in the operating room, sedation/anesthesia can be provided with midazolam, propofol, or with inhaled anesthetics, usually sevoflurane (which is less irritating to the airway than desflurane). One hundred percent oxygen is also administered. Dexmedetomidine can be used, but with caution, as the hemodynamic imbalances can be wide ranging, particularly if bolus doses of the drug are administered. The larynx and trachea may also be anesthetized by spraying local anesthetics (2–4% lidocaine 3–5 mg/kg (total dose)) on the vocal cords with an atomizer. This reduces the inhalation agent requirement and allows for maintenance of spontaneous ventilation. Spontaneous ventilation allows the surgeon to observe movement of the vocal cords with breathing. Dexmedetomidine also provides jaw relaxation and satisfactory conditions for airway endoscopy [137]. Propofol infusions 150–200 μg/kg/min plus an inhalation agent also provide adequate conditions for laryngoscopy. Others have used propofol plus remifentanil for this procedure.

A flexible bronchoscope can be inserted into the airway by one of six methods: transnasal, transoral, or via a facemask, LMA, tracheal tube, or a tracheostomy. Some devices have channels that permit easy insertion of the bronchoscope through them and are available for each route. Flexible bronchoscopy is usually performed to evaluate airway dynamics and anatomy, particularly of the upper airway. A transnasal or transoral approach provides the best views of the upper airway; an LMA or tracheal tube cannot do this.

Laryngomalacia is a common indication for using a flexible bronchoscope to assess the airway. It is used to make the diagnoses and to determine if the application of CPAP improves the airway dynamics of the affected child. This information may have a direct impact on long-term management.

Other indications for flexible bronchoscopy include cystic fibrosis, ventilator-associated pneumonia, pulmonary aspiration, bronchoalveolar lavage, and when needed (e.g. Langerhans cell histiocytosis, pulmonary alveolar microlithiasis and pulmonary alveolar proteinosis). Transbronchial biopsies can also be performed via the flexible endoscope to evaluate nodules, infiltrative disorders (e.g. after lung transplantation), infections, airway lesions, and tumors.

The American Thoracic Society has published technical standards for equipment, personnel, and competencies required to perform flexible airway endoscopy in children [133]. They have also provided extensive guidelines for the inspection, maintenance, storage, cleaning, and manual or automated reprocessing of flexible bronchoscopes for

infection control and prevention of cross-infections from patient to patient [133].

Spontaneous ventilation may be maintained throughout the whole procedure, provided the patient can effectively breathe spontaneously while anesthetized. At times, movement of the airway with breathing will interfere with accomplishing the procedure (e.g. laser therapy). If oxygen desaturation occurs during the procedure, the procedure should be stopped long enough to administer positive pressure ventilation and restore the oxygen saturation to normal. When a rigid bronchoscope is used, positive pressure ventilation can be provided throughout the procedure. Jet ventilation has been used in older children, but the potential for airway trauma has caused jet ventilation to be abandoned in younger children [134]. The goal at the end of the bronchoscopic procedure is to have the patient breathe spontaneously through their natural airway. Therefore, muscle relaxants (if used) must be utilized judiciously, and adequate reversal of neuromuscular blockade must be demonstrated before the child is awakened.

Rigid bronchoscopy

Rigid bronchoscopy may be preferred when the area of interest is the posterior larynx and cervical trachea or if the procedure requires the insertion of multiple instruments. Segmental stenosis of large airways can often be managed by bronchoscopic dilation and placement of stents. Because of the potential for trauma-related complications, these procedures must only be performed by experienced personnel in carefully selected cases.

Rigid pediatric ventilating bronchoscopes are equipped with an optical telescope and a fiberoptic light source. The optical telescope, when used with the Storz pediatric bronchoscope, provides superior resolution, magnification, and a wide-angle view [129]. Miniaturized grasping or biopsy forceps can be inserted through the channel of the instrument. An advantage of this system is that it is closed, which permits use of anesthetic gases and positive pressure ventilation while the viewing telescope is in place [129,136]. Another advantage is that it can be used to retrieve foreign bodies, which requires removal of the magnifying telescope. A sidearm port makes it possible to attach the ventilating bronchoscope to any anesthetic system to maintain anesthesia, oxygenation, and to assist or control manual ventilation (Fig. 34.3).

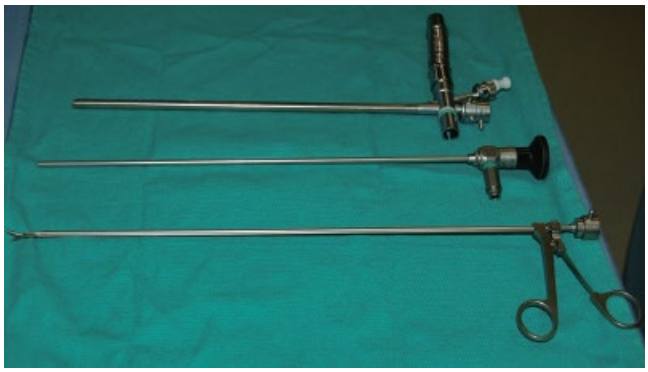

Figure 34.3 Ventilating bronchoscope, optical telescope, and foreign body forceps.

The optical telescope occupies nearly the entire internal lumen of smaller bronchoscopes, which reduces the area for gas flow, markedly increases airflow resistance, and retards passive expiration. This can potentially cause hyperinflation of the lung and hypoventilation [138]. A persistent increase in intrathoracic pressure increases the risk for barotrauma and impairment of cardiac output [138]. Maintaining adequate expiratory time is essential for complete expiration. A 2.8 mm telescope in a 3.5 mm bronchoscope permits adequate exhalation and prevents hyperinflation of the lungs, even during positive pressure ventilation [136]. When smaller bronchoscopes are used, the endoscopist can intermittently remove the telescope and occlude the orifice of the scope manually, thereby allowing the anesthesiologist to deliver brief periods of unobstructed positive pressure ventilation [138]. For bronchoscopic examinations of longer duration, intermittent determinations of $PaCO_2$ will confirm the adequacy or inadequacy of ventilation. When evaluating the airways of small infants with a 2.5 mm bronchoscope, the surgeons must remove the telescope more frequently to allow adequate ventilation and passive exhalation.

Any rapid deterioration in the patient's hemodynamic status during bronchoscopy should make one highly suspicious of a tension pneumothorax [139]. Clinical findings of a pneumothorax alone justify thoracostomy before obtaining a chest radiograph. Vocal cord movement is often evaluated by laryngoscopy while the patient awakens from anesthesia. Care must be taken during this time to avoid causing laryngospasm; many practitioners utilize topical lidocaine for this purpose.

There are competing views of the first choice of instruments (flexible or rigid bronchoscopy) for viewing the airway, depending on the indication for endoscopy. However, rigid bronchoscopy is still the first choice in children with asphyxiating foreign body aspiration (see later in this chapter) [140].

KEY POINTS: DIRECT LARYNGOSCOPY AND BRONCHOSCOPY

- Flexible fiberoptic bronchoscopy can be accomplished via facemask, LMA, endotracheal tube, or tracheostomy, or through direct nasal or oral routes
- Rigid bronchoscopy is useful for the removal of foreign bodies from the airway
- Most rigid scopes permit ventilation of the patient's lungs during the examination
- Smaller rigid scopes are more likely to cause hyperinflation of the lung and a pneumothorax
- Hyperinflation of the lung may cause hypotension and decreased cardiac output

Stridor

Stridor is noisy breathing caused by turbulent gas flow through the narrowed lumen of an airway and can occur during either inspiration or expiration. Inspiratory stridor is the result of anomalies that narrow the airway above the thoracic inlet (e.g. cysts or masses, laryngomalacia, vocal cord paralysis, hemangiomas, laryngoceles, papillomas, adenotonsillar

hypertrophy, midfacial hypoplasia, croup). Expiratory stridor is most commonly associated with airway obstruction below the thoracic inlet (e.g. cysts, hemangiomas, vascular rings, foreign bodies, bronchomalacia) [35,128]. Biphasic stridor is common and characteristic of midtracheal abnormalities caused by tracheomalacia, tracheal stenosis, or tumors. Diagnostic laryngoscopy/bronchoscopy and a variety of imaging procedures are often required to determine the etiology of stridor. These procedures usually require deep sedation or general anesthesia in young children. The anesthesiologist must understand the physiology and clinical implications of stridor.

Inspiration through a partially obstructed extrathoracic airway reduces the intraluminal airway pressure below atmospheric pressure. Because the intratracheal pressure is lower than atmospheric pressure, the extratracheal lumen narrows, increasing stridor. During expiration, the extrathoracic intraluminal pressure is positive with respect to atmospheric pressure, which dilates the lumen and decreases stridor. On the other hand, a partially obstructed intrathoracic airway dilates during inspiration due to the increased extraluminal negative pressure. During expiration, the reverse occurs, and the expiratory noise (wheezing) worsens [35,128].

A careful medical history defines the severity and duration of symptoms, age, and acuteness of onset of the symptoms, and any history of previous tracheal intubation or anesthesia. A stridulous newborn, for example, is likely to have a congenital anomaly of the airway as the etiology for stridor. A 3-year-old with sudden onset of severe stridor is more likely to have a foreign body or an infectious etiology as the cause for stridor. The stridor of a child in the PACU or ICU, whose stridor develops after tracheal extubation, is likely to have airway edema. The severity and rapidity of the progression of symptoms guides the diagnostic and treatment plan.

Approximately 45–60% of stridor is due to laryngomalacia in young infants (excluding postextubation stridor) [128,141]. Symptoms of this process are generally present from birth and must be differentiated from other congenital causes of stridor. Babies with laryngomalacia seldom have feeding difficulties. But children with glottic or oropharyngeal lesions or those with a tracheoesophageal fistula commonly have both stridor and difficulty feeding. The noise usually worsens when babies with stridor are agitated or positioned supine. The symptoms of some of these babies improve when they are placed in the prone position. Although many the infants with laryngomalacia do well and their clinical status improves with increasing age, the stridor of some children persists for 4–5 years [141].

While the incidence of upper or lower respiratory tract infections is not increased in infants and children who have laryngomalacia, their upper airway obstruction often worsens in the presence of a URI [141]. A child with laryngomalacia and URI who presents for anything but emergency surgery should be very carefully evaluated and delaying the surgery should be considered, especially if general anesthesia and tracheal intubation are required. If surgery is emergent, the anesthesiologist should maintain an audible air leak around the tracheal tube when a positive pressure of 20–25 cmH_2O is generated. A tracheal tube 0.5–1.5 mm smaller than usual may be required. These patients should be monitored postoperatively in a pediatric ICU, where prompt airway and ventilatory support are immediately available if needed.

Although uncommon, an infant with neurological abnormalities may present with stridor. Laryngeal nerve paralysis due to birth trauma, or cardiac malformations that affect the left recurrent laryngeal nerve, or postoperative complications of patent ductus arteriosus surgery may cause stridor. Frequently, the etiology of the nerve injury is unclear. Unilateral vocal cord paralysis is often the result of a peripheral nerve lesion. Infants with unilateral cord paralysis often have stridor or hoarseness and feeding difficulties. Those with bilateral vocal cord paralysis often have central nervous system problems (e.g. hydrocephalus, Arnold–Chiari malformation, Dandy Walker cyst, encephalocele, posterior fossa hematomas, or due to child abuse) [142–146]. While some authorities relate the stridor of neurological disease and vocal cord paralysis to stretching of the vagus nerve over the jugular foramen, it is often unclear what the actual cause is and why it persists after the increased intracranial pressure is normalized. Sometimes children with bilateral vocal cord paralysis and serious respiratory obstruction, or recurrent aspiration pneumonia, require a tracheostomy. As children grow, their stridor often improves.

Anesthetic considerations for children with stridor are similar, regardless of the etiology of the obstruction. Maintaining CPAP during spontaneous ventilation via a facemask often reverses the upper airway pressure gradient and decreases or eliminates the obstruction. Before the start of anesthesia, it is vital to have a wide range of tracheal tubes available for intubation, as some airway lesions, such as cricoid ring stenosis, webs, cysts, hemangiomas, epiglottitis, and croup, necessitate the use of a smaller than normal tube. Lesions such as vocal cord paralysis may cause stridor without narrowing the airway. The tracheal tube used should have a gas leak at approximately 20–25 cmH_2O airway positive pressure to prevent further tracheal injury.

Postextubation stridor is a significant problem in children after prolonged mechanical ventilation because they often have laryngeal/tracheal edema, airway narrowing, and stridor. Stridor is also common after airway surgery.

The use of high-pressure cuffed tracheal tubes in children in the past was sometimes associated with postextubation stridor. Newer low-pressure cuff tracheal tubes have not been associated with an increased incidence of stridor. Use of the newer tubes has also decreased the number of attempts for tracheal intubation with the appropriate size tube [147]. Reducing the number of attempts is important because the subglottic mucosa of children is vascular, loose areolar tissue which can fill with edema fluid with repeated trauma. In children less than 5 years old, the narrowest portion of the upper airway is the cricoid cartilage. A tight-fitting tracheal tube, burns, or other trauma causes inflammation and narrowing of the internal diameter of the cricoid ring area. This is made worse by the fact that the tracheal cartilages confine the edema to the tracheal mucosa making this area prone to edema, especially following long-term tracheal intubation.

Inhaled racemic epinephrine, heliox, and occasionally steroids are utilized to treat stridor. Racemic epinephrine (0.5 mL of 2.25% solution in 2.5 mL of normal saline) can be administered at 5 min intervals by nebulization to decrease airway edema if the heart rate remains below 200 beats/min. Oxygen saturation should be monitored during treatment. If multiple treatments are required, an arterial blood gas should be

obtained to ensure that ventilation is adequate. This is important, particularly if the child has increased work of breathing.

Heliox (usually 70% helium and 30% oxygen) facilitates ventilation in patients with stridor. The decreased density of heliox allows more laminar flow in obstructed airways and decreases the work of breathing. To avoid hypoxia, however, heliox should not be used in children whose FiO_2 requirements exceed 0.3.

Steroids are also used to manage stridor. When using them, the potential effect of these drugs on delayed wound healing should be balanced against the possible beneficial effects of steroids on the airway. When a patient cannot be weaned from mechanical ventilation for no obvious reasons, a 48 h trial of steroid therapy is warranted. This may decrease airway edema and allow successful tracheal extubation. Dexamethasone 0.25–0.5 mg/kg every 6 h is a common regimen.

KEY POINTS: STRIDOR

- Stridor has multiple causes that must be differentiated from one another
- With extrathoracic lesions, stridor is most prominent during inspiration
- With intrathoracic lesions, stridor is most prominent during expiration
- Mask CPAP may improve stridulous breathing

Supraglottitis

Acute supraglottitis (previously known as epiglottitis) is a life-threatening infection characterized by severe supraglottic edema and a risk for upper airway obstruction (Fig. 34.4). Children with this problem usually have rhinorrhea, cough, a severe sore throat, and fever. As the symptoms progress, the child constantly drools and often prefers to lean forward (tripod position) to improve their pattern of breathing. Prior to the routine immunization of children with the *Haemophilus influenza* type b (Hib) polysaccharide vaccine, many of the invasive cases of acute supraglottitis in 2–6-year-old children were the result of infection with this organism. Because of vaccination, the incidence of infection with Hib has diminished [148,149] and has been replaced by infections with group A *Streptococcus* [150], *Neiseria meningitides*, and *Candida albicans* [151,152]. The onset of supraglottitis is fulminant. The differential diagnosis of this disease includes laryngotracheobronchitis (croup) and tracheitis (Table 34.2).

Patients with suspected supraglottitis are at risk for sudden and complete airway obstruction. These patients should be managed by a multidisciplinary team from the time they present to an emergency room or clinic. The hospital or clinic should have a coordinated approach to supraglottitis that is well established. The members of this team should be immediately available. When the diagnosis of supraglottitis is made or strongly suspected, the primary goal is to quickly secure the airway. Tracheal intubation has been shown to be a safe and efficacious alternative to tracheostomy and is the preferred method for providing an airway for these patients. The following approach is consistent with those of other centers [153].

A pediatrician, an anesthesiologist skilled in pediatric airway problems, and a surgeon skilled in placing a tracheostomy in an infant or child are notified when or shortly after the child arrives in the emergency room. A thorough, rapid cardiopulmonary history and assessment is made. Examination of the airway is limited to noting respiratory rate, observing the pattern of breathing, and assessing the child's work of breathing and level of respiratory distress. At most, the heart and lungs are examined. Any maneuver likely to cause or increase agitation in the child should be reserved for the operating room; this includes manipulation or examination of the mouth and oropharynx, intravenous catheter placement, venipuncture, or arterial blood gas sampling. The child should remain sitting on a parent's (or other familiar caretaker's) lap and breath supplemental oxygen. Oxygen saturation should be monitored while the child is being closely observed by the medical team.

If the child does not have significant respiratory distress, obtaining a single lateral radiograph of the neck to confirm the diagnosis may be considered. If this is done, the child must receive supplemental oxygen while sitting up on a stretcher during transport to the radiography suite. Someone who can emergently intubate the trachea if necessary must accompany the child. If the child is in significant respiratory distress or the diagnosis is made clinically, the child should be promptly transported to the operating room while sitting up.

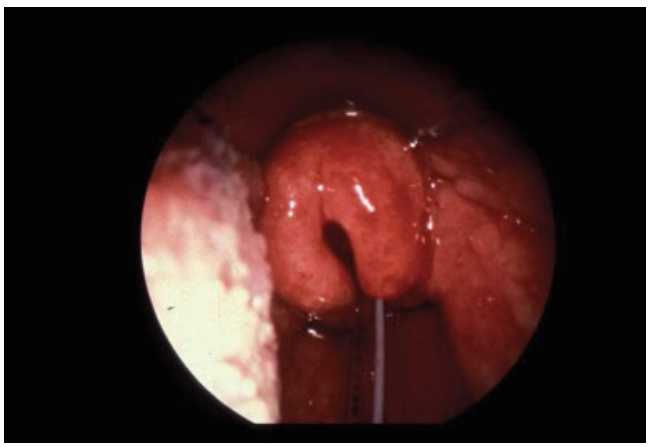

Figure 34.4 Acute edematous supraglottis. *Source*: Courtesy of Deidre Larrier MD.

Table 34.2 Features of supraglottitis, laryngotracheobronchitis, and tracheitis

	Supraglottitis	Laryngotracheobronchitis	Tracheitis
Age	2–6 years	2 months to 3 years	2–6 years
Onset	Fulminant	Gradual	Gradual
Etiology	Bacterial	Viral	Bacterial
Presentation			
Voice	Muffled	Bark	Bark
Secretions	Drooling	Drooling	None
Fever	>38.5°C	37–38°C	>38.5°C
Distress	Anxious, sitting up	Normal	Toxic appearing, sitting up

Oxygen should be administered and oxygen saturation monitored during transport. Radiological confirmation of the lesion is unnecessary and potentially dangerous in this urgent situation. Those who accompany the child during transport to the operating room must be skilled in pediatric airway management and cardiopulmonary resuscitation.

A tracheostomy tray should be open and the surgeon present when the patient arrives in the operating room. A smooth induction of anesthesia with the child sitting on the caretaker's lap and breathing sevoflurane in 100% oxygen allows for minimal airway irritation [154]. Halothane is still a viable option for the induction of anesthesia if sevoflurane is not readily available. The appropriateness of the presence of a parent or other caregiver during the induction of anesthesia must be assessed for each patient.

With the onset of anesthesia, the patient is placed in the supine or more commonly in the semi sitting position, while the jaw thrust is used and CPAP is applied via facemask to overcome upper airway obstruction. Intravenous catheter placement commences once the level of anesthesia is sufficiently deep to avoid precipitating laryngospasm with the needle insertion. Tracheal intubation is often accomplished with a tube that is 0.5–1.5 mm smaller in outer diameter than is appropriate for the patient's age and size. When everything is stable, some anesthesiologists will change the orotracheal tube to a nasotracheal tube because the child will remain intubated for several days, and a nasotracheal tube may be more secure and better tolerated by the patient.

Blood and laryngeal cultures are obtained during anesthesia, and appropriate antibiotics are administered intravenously. The selection and dose of antibiotic varies depending on the predominant organisms in the geographic area and in the patient (e.g. immunocompromised, HIV infection). If during upper airway examination, the diagnosis of supraglottitis is ruled out, and a diagnosis of tracheitis is made, the choice of antibiotic administered before cultures and sensitivities are available may differ from those chosen to treat supraglottitis. Consulting with a pediatric infectious disease specialist is appropriate and helpful. The morbidity from 24–48 h of tracheal intubation is minimal with excellent nursing care. Consequently, most otolaryngologists prefer to use a tracheal tube rather than a tracheostomy during this time. Once a gas leak (indicating resolution of the airway edema) has developed around the tube, the patient may return to the operating room for endoscopic examination of the airway.

KEY POINTS: SUPRAGLOTTITIS

- Supraglottitis is a life-threatening infection caused by several different organisms
- Successful care requires a skilled team of pediatricians, surgeons, nurses, and anesthesiologists
- Tracheal intubation should occur in the operating room emergently
- Induction of anesthesia should take place with the child sitting in a parent's lap while the child breaths sevoflurane in 100% oxygen
- Tracheal intubation often requires a tube that is 0.5–1.5 mm smaller than normal for a child of that size and age

Airway foreign bodies

Foreign body aspiration

Aspiration of foreign bodies, including food, toy parts, batteries, coins, pin caps, etc. (Fig. 34.5), is a major source of morbidity and mortality in children below the age of 5 years, with a peak incidence occurring between 1 and 2 years [155–159]. Depending on the nature and location of the aspirated object,

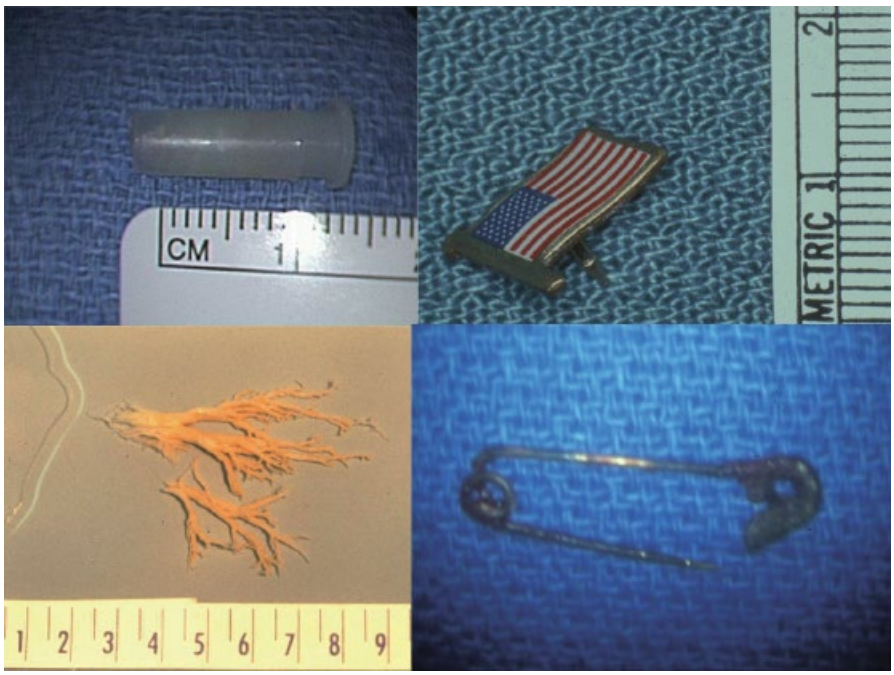

Figure 34.5 A variety of foreign bodies retrieved from the airway; clockwise from top left: plastic tube, toy flag, safety pin, and bubble gum. *Source*: Courtesy of Ellen Friedman MD.

removal can be lifesaving [160]. A detailed preoperative discussion with the anesthesia, surgery, and nursing teams allows for proper coordination and a smooth procedure.

A thorough patient history often helps establish the diagnosis of foreign body aspiration. Some parents report witnessing a choking episode, which they did not consider significant at the time because it was short lived. This often results in delayed presentation and diagnosis of the problem. The presenting symptoms of foreign body aspiration vary depending on the location, size, and duration of the aspirated object. Acutely, a child may present with hoarseness, stridor, dyspnea, and unilateral decreased air entry or wheezing [161–164]. There is often acute airway distress, especially if the object is lodged at or near the glottic inlet [160]. However, normal auscultation or physical examination does not eliminate the possibility of an aspirated foreign body because 14–45% of patients with abnormal bronchoscopic findings, including foreign bodies, have normal physical examinations preoperatively [165–167]. Objects located in the larynx or trachea are associated with as high as 45% mortality [168]. According to one study, the diagnosis of laryngotracheal foreign body aspiration was only made within 24 h of aspiration in slightly more than one-half of the patients. The diagnosis was made in the remaining patients following failure of medical management for croup or reactive airway disease, usually within 1 week of aspiration. Late diagnosed children either did not respond to medical therapy or their condition deteriorated despite appropriate medical therapy [163,169]. Partial obstruction by smaller objects may go unrecognized for weeks [168] and then present with recurrent or chronic pneumonias or bronchiectasis [170]. Some episodes of choking are not witnessed, but physicians should have a high index of suspicion for foreign body aspiration when a toddler/child presents with respiratory distress without a prior history of infection or trauma. Chronic abnormalities on chest radiography should also raise suspicion for pneumonia due to aspiration of a foreign object.

Radiopaque objects, such as coins, are easily appreciated on chest x-ray; some plastic toys now contain radiopaque markers that also makes them visible on chest x-ray. Unfortunately, the most frequently aspirated items, foodstuffs, are radiolucent and not likely to be detected by radiography. In such instances, lateral decubitus views confirm the presence of lower airway obstruction by an aspirated object. Four major patterns of airway obstruction have been described (Fig. 34.6) [171,172]:

1. *Bypass valve obstruction* involves both phases of respiration, and the chest x-ray is usually normal. Aeration is seen beyond the point of obstruction, although it is somewhat diminished.
2. *Check valve obstruction* is characterized by normal inhalation of air and impedance of exhalation, which results in hyperinflation of the ipsilateral affected lung. To appreciate this effect, inspiratory and expiratory radiographic films are required. Because expiratory films may be difficult to obtain in children, lateral decubitus films are obtained. When a foreign body has been aspirated, the mediastinum shifts toward the normal side. This is readily apparent if the gas volume between the two lungs is significantly different. When a normal child is in the left lateral decubitus position, the mediastinum and heart shift to the left; when they are on their right side, there is a shift to the right on the radiograph. A foreign body that obstructs the right main bronchus causes inflation and aeration of the ipsilateral (right) lung on a right lateral decubitus film.
3. *Ball valve obstruction* is characterized by a lesion that intermittently partially obstructs the affected bronchus. In this instance, a chest radiograph demonstrates a mediastinal shift toward the involved side due to decreased air entry, early atelectasis, and lung collapse.
4. *Stop valve obstruction* denotes a complete bronchial obstruction with impedance to air flow during both inspiration and expiration. Consolidation of the involved bronchopulmonary segment is present.

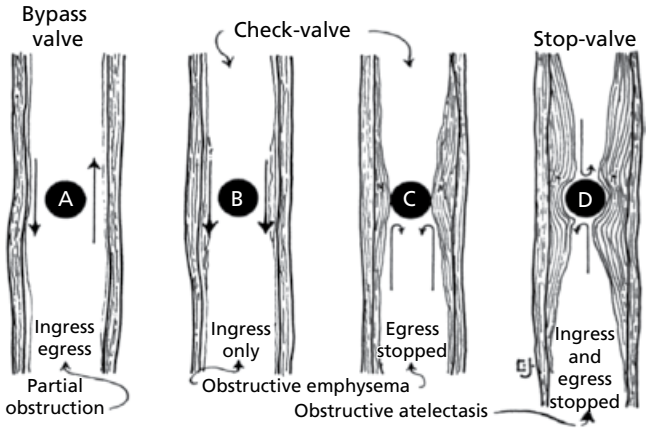

Figure 34.6 Patterns of foreign body induced airway obstruction. (A) Bypass valve. (B, C) Check valve. (D) Stop valve. *Source*: Courtesy of Ellen Friedman MD.

The urgency to proceed with anesthesia and bronchoscopic removal of a foreign body is dictated by the severity of respiratory distress and the location and nature of the aspirated material. Foreign bodies can move from one part of the airway to another and cause sudden complete airway occlusion. Ideally, the foreign body should be removed very shortly after aspiration to minimize the occurrence of pneumonia or other complications. When possible, removal of the object should occur as an urgent, not emergent, procedure in a well-prepared patient [161,173,174]. Bronchoscopic removal of a foreign object is successful 95–98% of the time, but a small number of patients may need repeated bronchoscopies because the foreign body either was not found or was incompletely removed [161,174]. In extremely rare cases, thoracotomy may be required to remove the object [174,175].

A variety of methods have been successfully utilized to anesthetize children for bronchoscopy and retrieval of a foreign body [176,177]. The anesthetic technique chosen depends on a number of factors, namely the condition of the patient, suspected location of the foreign body, and the personal preference of the anesthesiologist or surgeon. Having venous access before proceeding with surgery allows for administration of an anticholinergic agent to dry secretions, to prevent a vagal response with insertion of the bronchoscope, and to attenuate cholinergic-mediated bronchoconstriction during airway manipulation. It also allows for steroid administration to decrease airway swelling. The administration of preoperative sedatives may be controversial, as sedation can exacerbate upper airway obstruction. Parenteral presence is often as effective or more effective than drugs for calming the child.

Inhalation induction allows the anesthesiologist to avoid using positive pressure ventilation, which may dislodge the foreign body and move it. However, spontaneous ventilation does not protect against aspiration of gastric contents if the child has a "full stomach". Few anesthesiologists would advocate a rapid-sequence induction of anesthesia in infants with respiratory distress and no absolute knowledge of the current location of the foreign body. Routine fasting guidelines should apply if the patient's ventilatory status is stable.

Once anesthesia is induced, the head of the table is rotated 90° away from the anesthesiologist, and the airway is managed from the side of the table by the anesthesiologist or the head of the bed by the surgeon. The gums (in an edentulous infant) or teeth are protected from injury by moist gauze or a plastic guard. A laryngoscope is inserted into the vallecula to expose the epiglottis, arytenoids, and vocal folds, which are then inspected for mucosal abrasions or the presence of a foreign body. Next, a rigid bronchoscope is inserted to visualize the distal airway. Once the ventilating bronchoscope is in the subglottic area, the anesthesia circuit is connected to the scope to allow delivery of oxygen and positive pressure ventilation (if necessary).

For anesthesia maintenance, most anesthesiologists follow a "middle course" and allow the child to breathe oxygen and a potent inhalation anesthetic until the chest can be adequately expanded with gentle positive pressure. At that point, a decision is made about whether muscle relaxation is required. If the decision is made that muscle relaxation is unnecessary, the level of anesthesia is kept sufficiently deep to permit bronchoscopy without the patient coughing. Supplementation of anesthesia with topical anesthetic further attenuates the airway reflexes. Regardless of the method of ventilation used, the child's airway will be exposed to the atmosphere multiple times during the procedure when the surgeon removes the bronchoscope or optical eye piece. For this reason, total intravenous anesthesia may be preferred to decrease pollution from inhalational agents and to provide an uninterrupted source of anesthesia for the patient.

Ideally, spontaneous ventilation should be preserved, at least until the nature and location of the foreign body has been identified, especially if the object could not be localized radiographically. Even if the position of the foreign body was detected radiographically, its position may have changed.

Administration of nitrous oxide during this procedure is contraindicated because its use reduces the inspired oxygen concentration. Also, if there is significant gas trapping, nitrous oxide could increase the trapped gas volume and the pressure in the affected lung. On occasion, a tracheal foreign body will completely obstruct the airway; it can often be intentionally pushed distally into a mainstem bronchus. This often improves ventilation and relieves the immediate crisis. The object can then be removed under more controlled circumstances.

Occasionally, the size of the foreign body exceeds the internal diameter of the bronchoscope. When this occurs, the foreign body, forceps, and bronchoscope are withdrawn together through immobile vocal cords [173]. Administering a small dose of a short-acting non-depolarizing muscle relaxant may make it easier to do this. If the foreign body is lost during attempted removal, the pharynx should be immediately inspected. If the object is not found, the bronchoscope should be reintroduced and the larynx or trachea re-examined. If tracheal obstruction occurs and the object cannot be immediately removed, it may be necessary to push the object back to its original location to allow ventilation of the lungs. If possible, the foreign body should be returned to the affected and not to the unaffected lung because placing it in the unaffected lung could result in unreliable ventilation of both lungs. Following removal of the foreign body, the endoscopist must re-examine the airway for additional or fragmented foreign bodies and to remove secretions distal to the obstruction. It may be necessary to reinsert the bronchoscope several times before all of the foreign body and secretions are successfully removed. Doing so may cause mucosal edema and respiratory distress post bronchoscopy. Administration of steroids, humidified oxygen, nebulized racemic epinephrine and, rarely, tracheal reintubation may be required for 1 or 2 days until the edema subsides [178]. Initial doses of 0.5–1.5 mg/kg of dexamethasone (and smaller doses for 2–3 days) are often used. Racemic epinephrine (2.25%) can be administered in a 1:6 to 1:10 dilution via a nebulizer and clear plastic facemask for periods of 10 min while monitoring the electrocardiogram. This treatment is repeated every 2 h as necessary [178]. Some patients treated with racemic epinephrine develop "rebound" edema and have worse airway obstruction. Therefore, those who respond to racemic epinephrine should be monitored carefully for at least 3–4 h after each dose of the drug to detect this problem.

Aspirated vegetable matter (e.g. peanuts) are occasionally fragmented during their removal and pose a significant challenge for the bronchoscopist. Larger aspirated material may acutely occlude both mainstem bronchi, and require a thoracotomy to retrieve the material. A Fogarty no. 3 embolectomy balloon catheter may also help dislodge an impacted foreign body [129,173].

Although prompt removal of a foreign body through an open rigid bronchoscope is the mainstay of treatment for tracheal foreign body removal, diagnostic flexible bronchoscopy also may have a role [179–181]. When foreign body aspiration is not clearly evident by history, physical examinations, and radiography, some surgeons perform diagnostic flexible bronchoscopy under local anesthesia and sedation instead of rigid bronchoscopy because this is less traumatic for the patient and their airway [180]. If a foreign body is subsequently identified, the patient then undergoes rigid bronchoscopy. Flexible bronchoscopy is not usually recommended for children with respiratory distress. The decision to utilize fiberoptic bronchoscopy for diagnostic evaluation of a foreign body depends on the skills and services available at each medical center. The risks of possibly having to undergo two procedures (flexible and rigid bronchoscopy) should also be carefully considered.

KEY POINTS: FOREIGN BODY ASPIRATION

- Foreign body removal is an emergency if the child has repiratory distress
- Spontaneous ventilation should be preserved until the nature and location of the foreign body has been identified, particularly if the foreign body was not localized radiographically
- Rigid bronchoscopes allow administration of inhaled anesthetic if assisted ventilation is required

- Foreign bodies are usually best removed through a rigid bronchoscope
- Organic materials occasionally fragment during their removal
- Post bronchoscopy, edema can occur with repeated insertions of the bronchoscope and may require treatment with steroids, racemic epinephrine, or even tracheal intubation and mechanical ventilation

Esophageal foreign body aspiration

Over 100,000 children are seen annually in emergency departments after ingesting coins, buttons, beads, marbles, button batteries, can pull-tops, toys and their parts, glass, straight pins, screws, nails, and eraser heads. Ingestion of safety pins is less common today, presumably due to the advent of disposable diapers. A particularly dangerous situation occurs when button batteries get lodged and erode through the esophagus. Patients with esophageal foreign body ingestion often present with dysphagia, vomiting, abdominal pain, cough, localization or foreign body sensation, and refusal to take solids and liquids. Esophageal foreign bodies usually lodge at one of the three sites of narrowing – at the cricopharyngeal muscle (C6), at the cardioesophageal level (T4), and at the gastroesophageal junction. Lateral and anteroposterior x-rays of the chest are useful for determining if the radiopaque foreign body (e.g. a coin) is lodged in the esophagus and not the trachea [182]. Coins in the trachea are usually aligned in the sagittal plane, while those in the esophagus are aligned in the coronal plane. If the foreign body has not passed the gastroesophageal junction, it should be removed endoscopcally, often with a flexible endoscope.

Tracheal intubation and airway protection should precede extraction of a foreign body from the esophagus, as inadvertent release of an esophageal foreign body into an unprotected larynx during retrieval may be disasterous [169]. Foreign bodies can be removed endoscopically from the upper gastrointestinal inlet in More than 98% of cases [181]. An immediate "second look" should occur after removal of the foreign body to rule out trauma during the retrieval process or the presence of another foreign body or a congenital defect (e.g. pouch, esophageal stenosis). Foreign bodies that have passed through the gastric outlet into the small and large intestines usually pass through the gastrointestinal tract spontaneously; surgical intervention is rarely needed [183]. Retained esophageal foreign bodies can be treacherous because they can cause a bronchoesophageal fistula, aortoesophageal fistula, mediastinitis, esophageal diverticulum, and lobar atelectasis. In rare cases, the foreign body must be removed via thoracotomy [184].

KEY POINTS: ESOPHAGEAL FOREIGN BODY ASPIRATION

- Esophageal foreign body aspiration is common in young children
- Aspiration of button batteries may be lethal if not removed early
- Foreign bodies that pass into the small bowel are usually eliminated without the need for surgery

Laser microlaryngeal surgery

The most common indication for laser microlaryngeal surgery in children is recurrent laryngeal papillomas or juvenile laryngeal papillomatosis. Papillomatosis is a chronic, debilitating, and frequently life-threatening condition. These laryngeal tumors occur as a result of a human papillomavirus (HPV) infection acquired from the mother during pregnancy. These tumors are typically located on the vocal cords, epiglottis, and in the larynx or trachea (Fig. 34.7). They are usually symptomatic and cause aphonia, hoarseness, stridor, or respiratory distress. When a large amount of tumor is chronically present, the patient may have symptoms of right ventricular hypertrophy or cor pulmonale. Surgical excision and ablation of these lesions, the current mode of management, is accomplished with a carbon dioxide laser via an operating microscope [185]. CO_2 lasers have a fully reflective mirror at one end and a semi-reflective mirror at the other. When the material inside the resonating chamber is stimulated by an external source of energy, it emits a beam of monochromatic light that travels large distances. Light waves of the CO_2 laser are absorbed by all biological tissues and rapidly vaporize intracellular water. The resultant heat denatures protein. The laser light wave is easily focused to target tissue, including the capillaries, and vaporizes them without affecting the surrounding tissues. This provides excellent hemostasis and minimal postoperative edema and scarring. CO_2 lasers are used to treat papillomas of the nose, oral cavity, or larynx and to treat subglottic stenosis, subglottic hemangiomas, glottic webs, choanal atresia, postintubation granulomas, vocal cord nodules, and lymphangiomas, all with excellent results [186,187]. This laser has the advantage that its use allows rapid healing and preserves the quality of voice [187,188].

In a recent survey of pediatric otolaryngologists, the laryngeal microdebrider has supplanted CO_2 laser for removal of laryngeal papillomas by about 50% of practitioners [189]. A microdebrider uses suction and a rotating cold blade to more precisely excise the papillomas. It has a slightly angulated tip that suctions mobile papilloma tissue into the cutting blade and leaves firmer underlying native tissue intact. A prospective comparison of the microdebrider and the CO_2 laser revealed that the microdebrider and laser cause equivalent postoperative pain, but the microdebrider is associatesd with

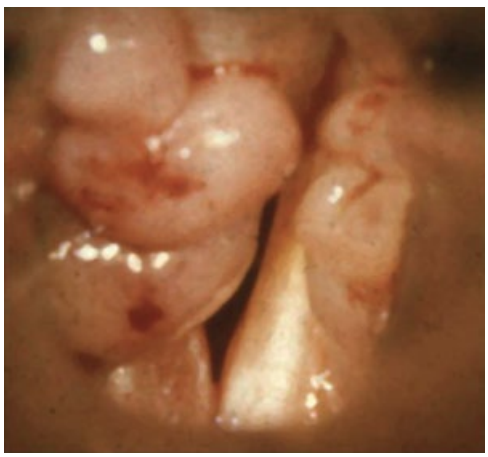

Figure 34.7 Papillomas on the vocal cord. *Source*: Courtesy of Deidre Larrier MD.

greater improvements in voice quality, shorter procedure times, and overall lower cost [190]. Microdebrider use has reduced the need for laser treatment of these lesions [189].

Adjuvant medical therapy for laryngeal papillomas is also on the rise. Cidofovir and interferon have proven to be beneficial in some children. Cidofovir is, however, reserved for patients requiring four or more surgical treatments per year because it has carcinogenic potential, and because there are not good supportive data for its use [191]. There are some reports of HPV vaccine resulting in a reduction or resolution of laryngeal papillomatosis in children [192]. The recommendation in 2006 that girls in the USA should receive HPV vaccine may reduce the future incidence of laryngeal papillomatosis in children [193].

Use of either the CO_2 laser or the laryngeal microdebrider requires suspension laryngoscopy, hyperextension of the neck, and a motionless surgical field (i.e. relaxed vocal cords) to prevent injury to the surrounding healthy tissue. Prompt recovery of consciousness and protective airway reflexes are necessary at the conclusion of surgery.

KEY POINTS: LASER MICROLARYNGEAL SURGERY

- The virus causing airway polyps can be transmitted from mother to fetus
- Lasers and microdebridors are commonly used to treat airway polyps
- Patients must be still during the procedure to avoid injury to normal tissue
- Children with papillomatosis often require multiple surgical procedures and may be quite fearful. Administration of preoperative medications to allay their anxiety may worsen the degree of airway obstruction

Anesthesia for laser microlaryngeal surgery

Children with recurrent laryngeal papillomas often present for treatment of recurrent tumors. The only effective way to keep their airway "tumor free" is by repeated endoscopic and laser excision of the papillomas until puberty, when the tumors tend to regress [194]. Perioperative anxiety is, therefore, fairly common in affected children due to the need for repeated surgeries. The judicious use of sedatives and, most importantly, a reassuring preoperative visit by the anesthesiologist, helps allay their fears. A child with significant airway obstruction should only receive preoperative sedation while being monitored and then only when oxygen, positive pressure ventilation, suction, and an anesthesiologist or surgeon skilled in advanced airway intervention is immediately available. Pedunculated papillomas can cause ball-valve obstruction of the airway in certain positions, which a good history will elucidate. It is usually prudent to avoid administering muscle relaxants and to maintain spontaneous ventilation until the surgeon has examined the airway and determined the location and extent of the lesions. Induction of anesthesia is similar to that for any child with anticipated severe airway obstruction: a slow inhalation induction with sevoflurane in 100% oxygen and avoidance of agitation and worsening the airway obstruction. It is often helpful to maintain 5–10 cm of PEEP in the anesthetic system to distend the hypopharynx, improve the airway, and facilitate mask ventilation. Muscle relaxants are administered when necessary, but only after demonstrating an ability to ventilate the child's lungs with positive pressure.

Laser surgery can be performed with spontaneous ventilation or with apnea. Jet ventilation and laser-safe tracheal tubes were mainstays of this type of surgery but have fallen out of favor. Only 10% of otolaryngologists now use laser-safe tracheal tubes to secure the airway [189]. This is in part due to the fact that laser-safe tubes do not completely prevent an airway fire if there is an inadvertent laser strike against the tracheal tube, even when lower oxygen concentrations are being used [195].

Spontaneous ventilation without tracheal intubation allows the surgeon to work without interruption. Otherwise, they must intermittently remove and place the tracheal tube to allow positive pressure ventilation. A deep anesthetic plane can be achieved with total intravenous anesthesia using propofol 200–300 μg/kg/min plus intermittent opioid administration morphine 0.5 mg/kg, fentanyl 2–3 μg/kg, or remifentanil infusion 0.1–0.25 μg/kg/min. Aerosolized lidocaine reduces airway irritability. Intravenous dexamethasone administration reduces postoperative swelling. Periods of hypoxemia can be treated with intermittent mask ventilation or by the surgeon reintubating the trachea to allow brief periods of manual ventilation. Jet ventilation with intermittent apnea provides ventilation and a quiet surgical field, but concerns that jet ventilation might force papillomas into the tracheobronchial tree and might cause barotrauma, plus the inability to monitor expired carbon dioxide tensions, has decreased its use for airway surgery.

If spontaneous ventilation was maintained via a natural airway during surgery, a tracheal tube can be inserted and secured until the child is completely awake. Alternatively, the inhalation agents can be discontinued and the patient transported to the recovery room breathing blow-by oxygen until completely recovered from anesthesia. Patients occasionally develop postoperative stridor, which can usually be managed with racemic epinephrine.

KEY POINTS: INTRAOPERATIVE MANAGEMENT OF MICROLARYNGEAL SURGERY

- Children with papillomatosis require multiple procedures to remove the lesions
- In some children with complete airway obstruction, CPAP is required during the induction of anesthesia to maintain a patent airway
- Surgery may be performed either during spontaneous breathing or during periods of apnea
- Jet ventilation is seldom used any more for fear of forcing tumor into the distal airways

Safety precautions during laser surgery

The major risks of laser therapy are fires and injury to operating room personnel by overshoot of the laser beam or reflection of the beam off of a polished instrument. Red rubber tracheal tubes wrapped with metallic tape will deflect the beam and prevent a fire. However, it is not possible to tape the part of the tube located beyond the vocal cords, making that portion of the tube vulnerable to the beam and to vaporization. Some tracheal tubes (non-latex) are manufactured specifically for laser surgery. However, they are more expensive and have larger outer diameters than regular polyvinyl chloride tubes, especially in the smaller sizes. As a result, they are not useful for small children or for those with an airway markedly narrowed by papillomas.

Laser radiation increases the temperature of the material it strikes, which can cause a fire. Therefore, flammable material (e.g. surgical drapes) must be kept out of the laser beam path. Use of surgical drapes should be kept to a minimum during laser surgery for this reason. Burning surgical drapes not only burn the patient, they also produce a significant amount of smoke that poses a hazard to both the patient and the operating room staff [196]. As a preventive measure, the face, neck, and shoulder surfaces of the patient should be covered with wet towels to absorb stray laser energy and prevent fires.

The CO_2 laser beam does not penetrate the cornea, but operating room personnel should wear glasses (regular eyewear will suffice) or protective goggles and place moist gauze pads over the eyes of patients as a precaution when using this type of laser. The primary uses of argon and neodymium:yttrium-aluminum garnet (Nd:YAG) lasers are for ophthalmological surgery and for excision of endobronchial lesions and treatment of gastrointestinal bleeding. The beam from Nd:YAG lasers can penetrate the cornea and damage the retina. It can also penetrate glass, which necessitates covering glass windows in the operating room with appropriate material. Special protective eyewear is mandatory when using these lasers.

As stated, the shaft of a tracheal tube can be covered with protective material to reduce the chance of a fire. Tracheal tube cuffs should be filled with saline rather than air. Placement of saline-soaked pledgets above the tracheal tube cuff during laser surgery offers some protection. Care must be taken to remove the pledgets before removing the tracheal tube to prevent aspiration of the pledget and obstruction of the airway.

The mixture of gases used during airway surgery affects the combustion risk. The use of more than 30% oxygen or of nitrous oxide sustains combustion, and their effects are additive [198]. Helium impedes combustion; and the differences between nitrogen and helium are not clinically significant [197].

The different methods available for airway management during laser surgery attempt to prevent airway fires, but this is not always possible. If, despite all precautions, a fire occurs, the flow of oxygen should be discontinued immediately and the tracheal tube disconnected from the gas source and removed. Tracheal tubes do not readily burn in air, which is why it is best to use air as the carrier gas whenever possible [188]. The anesthesiologist must check that the entire tube has been removed. A chest radiograph should be obtained and bronchoscopy performed to determine the extent of lung and tracheal burn injury, smoke inhalation, and possible retention of a foreign body. Complications are treated, based on the severity of the injury. Treatment may include steroids, humidification of inspired gases, tracheostomy, and assisted ventilation. Tracheal stenosis may occur later [188].

KEY POINTS: LASER MICROSUGERY FIRE PREVENTION AND TREATMENT

- Airway fires can occur during laser treatment of airway papillomas
- The inspired gas used during laser surgery should be as close to room air as possible to prevent ignition of the tracheal tube if there is a laser strike
- The use of oxygen and nitrous oxide together poses a greater risk of airway fire

Subglottic stenosis and tracheal reconstructive surgery

Endoscopic assessment of the airway is the gold standard for diagnosis of subglottic stenosis, which is defined as any narrowing of the airway from just below the vocal folds to the lower border of the cricoid cartilage. The narrowing may be either congenital or acquired. Some congenital subglottic stenosis is associated with chromosome 22q11 deletion, Down syndrome, and CHARGE syndrome (*C*, coloboma, *H*, heart defect, *A*, atresia of choanae, *R*, retarded growth and development, *G*, genital hypoplasia, *E*, ear anomalies/deafness) [199,200]. Neonatal congenital subglottic stenosis presents with biphasic stridor, chest wall retractions, and a barking cough that is somewhat similar to the cough of laryngotracheobronchitis. Airway inflammation associated with a URI often worsens these symptoms. Persistent croup that is refractory to treatment should raise a high index of suspicion for subglottic stenosis. Fortunately, congenital subglottic stenosis frequently resolves as children mature. Acquired subglottic stenosis, on the other hand, persists until definitive therapy occurs. Acquired subglottic stenosis is commonly the result of prolonged tracheal intubation but may also be the due to blunt or penetrating injury of the larynx. In these instances, symptoms such as progressive hoarseness, dyspnea, stridor, or feeding difficulties can occur 2–4 weeks following injury. Children with subglottic stenosis/injury are prone to frequent URIs. The exact location of the injury is usually identified by careful endoscopic evaluation of the airway [201].

The Myer–Cotton grading system classifies subglottic stenosis. It is based on the degree of stenosis: grade 1: <50% lumen obstruction; grade 2: 51–70% lumen obstruction; grade 3: 71–99% luminal obstruction; and grade 4: complete luminal obstruction [202]. The degree of stenosis is determined by inserting various size tracheal tubes and determining the largest tube that can be easily inserted while still being able to maintain a gas leak below 20 cmH_2O with positive pressure. Grades 1 and 2 can be managed endoscopically, but grades 3 and 4 require open surgery.

About 50% of patients with congenital subglottic stenosis require a tracheostomy. An even higher percentage of those with severe acquired subglottic stenosis require tracheostomy (see Chapter 16) [203]. With time many children "outgrow" the need for ventilatory support. Tracheostomy significantly

changes the quality of the child's life. Although a tracheostomy is often life saving, it can be associated with significant morbidity and mortality. The risk of death from complications of tracheostomy is 1–2% per year [204].

Periodic endoscopic airway evaluations are performed to assess whether there has been interim resolution of the stenosis. This procedure is performed during deep general anesthesia using suspension laryngoscopy. The child breathes spontaneously throughout the procedure. By redetermining the size of tracheal tube that can most easily be inserted and still allow an audible gas leak, physicians can determine if there is less narrowing and if it might be possible to remove the tracheostomy. If attempted decannulation fails or if the airway obstruction exceeds 50% of the normal lumen size, further intervention is required. This can include endoscopic balloon dilation or CO_2 laser endoscopic scar excision, with or without mitomycin application to prevent reapposition of the raw submucosal edges [205]. Children with firm mature scars, cartilaginous narrowing, and structural defects in the airway exoskeleton are likely to fail balloon dilation of the airway and require open reconstructive procedures, such as splitting the anterior cricoid cartilage or laryngeal reconstruction.

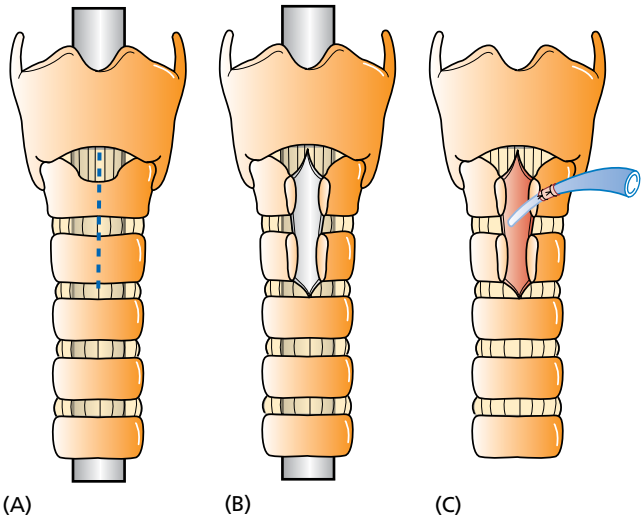

Figure 34.8 Cricoid split procedure. (A) A midline vertical cartilaginous incision is made 2 mm from the thyroid notch inferiorly through the second tracheal ring. (B) The largest possible tracheal tube is inserted. (C) Stay sutures are placed through the cricoid ring, and the skin incision is closed. *Source*: Reproduced from Zalza and Cotton [206] with permission of Elsevier.

KEY POINTS: SUBGLOTTIC STENOSIS

- Children with subglottic stenosis are prone to frequent respiratory tract infections
- Balloon dilation of the stenotic area improves symptoms in some patients
- Tracheostomy is necessary in some patients until they "outgrow their stenosis" or have definitive surgery to correct the lesion

Anterior cricoid split procedure

The goal of the cricoid split procedure is to decompress the subglottic space by opening the cricoid ring, the only complete cartilaginous ring of the airway. Cricoid spit surgery is performed over the largest nasotracheal tube possible. A midline vertical cartilaginous incision is made 2 mm from the thyroid notch inferiorly through the second tracheal ring, and a tracheal tube inserted (Fig. 34.8) [206]. Stay sutures are placed through the cricoid ring, as for tracheostomy, and the skin incision is closed. It may be necessary to leave the tracheal tube in place for up to 2 weeks to temporarily stent the incision open to allow fibrous ingrowth in the cricoid ring and to prevent airway obliteration by granulation tissue. This also allows time for the mucosal swelling to subside and for the split cricoid to heal. Tracheal extubation is then attempted after treatment with steroids.

Laryngeal reconstruction

Laryngeal reconstruction is performed when the subglottic stenosis is refractory to endoscopic balloon dilation or when the stenosis is severe (grade 3 or 4). This surgery is successful about 90% of the time when anterior costal cartilage or thyroid ala cartilage are used for the reconstruction [207]. A shoulder roll is placed and the head is hyperextended. Induction and maintenance of anesthesia can be accomplished with inhalation or intravenous anesthesia or both. During surgery, the tracheostomy is replaced with a tracheal tube inserted through the tracheostomy stoma and anchored in place with sutures. It may be necessary to shorten the oral RAE tube to prevent endobronchial intubation in some patients. Laryngeal reconstruction or laryngotracheoplasty is performed through a horizontal skin incision with midline dissection from the cartilage of the thyroid notch superiorly to the third or fourth tracheal rings inferiorly (Fig. 34.9) [203]. A vertical median anterior incision is made into the stenotic lumen. Posterior subglottic or posterior commissure stenosis may require a midline posterior cartilaginous incision to increase the diameter of the posterior lumen. Sculpted segments of harvested costal cartilage are then sutured into the midline incision to increase the airway lumen. A solid stent, when necessary, provides support during the postoperative period. This stent is sometimes wired to the tracheostomy tube. After allowing an appropriate period for healing of the grafts, the stent may be removed and the intraluminal granulation tissue excised. Alternatively, if a solid stent is not required, towards the end of surgery the oral RAE tube is replaced by a nasotracheal RAE tube. Further operative procedures may be required to remove granulation tissue and to allow the epithelium to cover the grafts and operative sites. Tracheal extubation occur when the airway lumen is deemed adequate; often prolonged intubation of up to 2 weeks is required after laryngeal reconstruction.

Both total intravenous and inhalation anesthesia have been used successfully for this surgery. The anesthesiologists are challenged during this procedure to provide a quiet surgical field while sharing the airway with the surgeon. The most important requirement for perioperative management is constant effective communication between the surgeon and anesthesiologist, particularly at times when the airway is removed to allow surgical access and stent placement. Knowledge of the critical points and the required precautions during this surgery are paramount. These include: (1) tracheal incision and the risk of coughing, damage to the tracheal tube cuff, or extravasation of air into the mediastinum; (2) risk of pneumothorax or pneumopericardium;

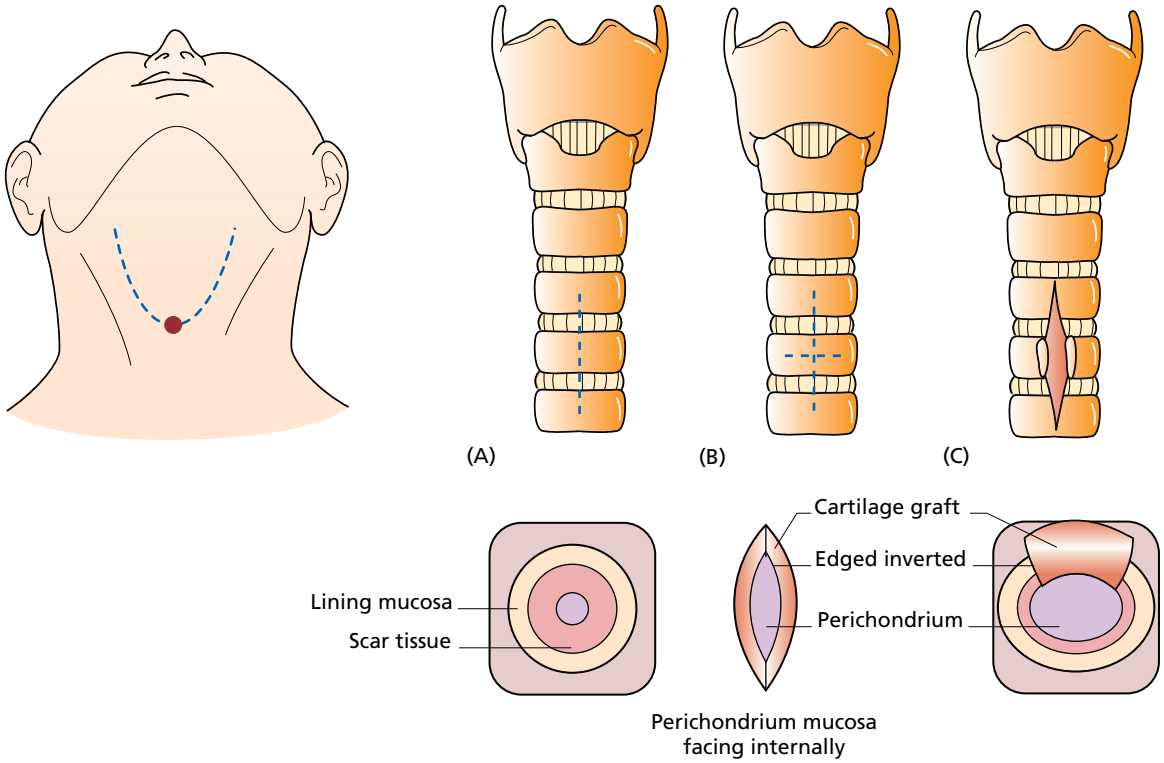

Figure 34.9 Laryngotracheoplasty. (A) A horizontal skin incision is made incorporating the superior aspect of the stoma. A vertical incision is made in the thyroid cartilage from a point immediately below the anterior commissure through the upper tracheal rings with care to remain in the midline. (B) The intraluminal scar and lining mucosa are incised along the length of the stenotic segment. (C) The costal cartilage graft is then shaped into an ellipse and placed in position with the lining perichondrium facing internally. *Source*: Reproduced from Cotton and Myers [203] with permission of Elsevier.

(3) replacement of an oral tracheal tube with a nasotracheal tube and possible loss of the airway; (4) hemorrhage from injury to thymic, innominate, or thyroid vessels; (5) mainstem bronchus intubation with the initial intubation through the tracheostomy site; (6) occlusion of the tracheal tube with blood or mucus or tracheal tube kinking and impaired ventilation due to high resistance; and (7) replacement of an oral or nasotracheal tube with possible trauma to the surgical site [208]. Precautions must be taken throughout the procedure to avoid surgical fires.

Adequate postoperative sedation and relaxation are mandatory to avoid excessive coughing and movement of the tracheal tube. Both can interfere with healing.

KEY POINTS: CRICOID SPLIT AND LARYNGOTRACHEAL RECONSTRUCTION

- An anterior cricoid split is performed to open a narrowed subglottic space and is followed by postoperative tracheal intubation for at least a couple of weeks
- Laryngotracheal reconstruction is performed for severe subglottic stenosis or stenosis that is refractory to balloon dilation
- Vigilance is required throughout the surgery because the surgeon may have to remove the tracheal tube for short periods of time to accomplish the surgery
- Knowledge of the critical points of the surgery is mandatory for safe, effective accomplishment of this surgery
- Prolonged tracheal intubation is often required

Dental procedures

Pediatric dental procedures are routinely performed in a dentist's office with local anesthesia, with or without sedation. Children with behavioral disturbances, such as severe autism or developmental delay, children with multiple medical problems, and those requiring extensive dental restoration often require general anesthesia to facilitate their surgery. General anesthesia allows the dentist to complete dental restoration in a timely fashion without administering excessive amounts of local anesthetic or approaching the maximum limits of sedation with which they are comfortable in their dental office.

Sedation versus anesthesia

Pediatric dental sedation is occasionally complicated by serious morbidity and mortality. Most serious adverse events are respiratory [209]and are the result of opioid administration as part of the sedative regimen [210,211] or as a result of the administration of higher than usual doses of local anesthetics, sedatives, or analgesics, in particular. These adverse events are also more common when monitoring is inadequate or the personnel is insufficiently skilled [212]. The increased prevalence of childhood obesity also poses a challenge for pediatric dentists. If the sedative doses are based on the patient's total body weight, oversedation and airway obstruction may occur. If they are based on lean body mass, the patient may be undersedated with a shorter duration of the sedative effects [213]. An increase in adverse events with sedation [214,215] and the increased mortality associated with office-based procedures [216] strengthens the case for improved monitoring

during sedation for outpatient procedures in general [217]. A revised recommendation by the Committee on Drugs, Section on Anesthesiology of the American Academy of Pediatrics, [218] states that:

1. Appropriate documentation, including informed consent prior to procedure, must be obtained.
2. The patient must undergo a documented presedation medical evaluation to rule out underlying medical and surgical conditions that may place the child at increased risk from sedative medications. This should also include a focused airway examination for large tonsils or airway abnormalities that may increase the potential for airway obstruction.
3. There should be an appropriate interval of fasting before sedation.
4. A balance must be sought between the depth of sedation and risk for children who are unable to fast because of the urgent nature of the procedure.
5. There should be a clear understanding of the pharmacokinetic and pharmacodynamic drug effects and drug interactions of the medications being used for sedation.
6. Appropriate sedative medications and reversal agents should be available.
7. Sedative and anxiolytic medications should only be administered by or in the presence of individuals skilled in airway management and cardiopulmonary resuscitation and the use of emergency checklists is recommended.
8. Age- and size-appropriate equipment for airway management and venous access should be checked beforehand and be immediately available.
9. Appropriate physiologic monitoring should be employed during and after the procedure.
10. Sufficient number of staff to both perform the procedure and monitor the patient afterwards should be available for deeply sedated patients; that individual should have no other responsibilities and should record vital signs at least every 5 minutes.
11. Specific discharge criteria to responsible party accompanying patient is required.

Unfortunately, there is no exact definition of conscious sedation in outpatient settings. Customarily it is defined as a state of sedation that "permits appropriate response by the patient to physical stimulation or verbal command, e.g. 'open your eyes'." This implies that the patient retains their ability to interact with the medical care team. Purely reflexive activity, such as the gag reflex, simple withdrawal from pain, or making inarticulate noises are not appropriate responses for the purpose of this definition. A sedated child who displays only reflex activity of this sort is in a state of deep sedation, not conscious sedation. The Committee on Drugs states that the term "conscious sedation" should be replaced with "moderate sedation" [219].

Considerations for dental surgery

Existing co-morbidities must be considered when planning anesthetic management for this group of children. Many of them have underlying cardiac anomalies and require systemic bacterial endocarditis prophylaxis (see Chapter 27). The facial and airway structures of some patients make direct laryngoscopy challenging and may require special intubation equipment. Patients with developmental delay or serious behavioral disturbances can pose difficulties because they have poor motor control and involuntary movements, spasticity, and aggressive behavior (screaming, biting, kicking), particularly when they are frightened by a strange environment. This behavior may make it difficult to place and secure an intravenous catheter or to perform inhalational induction of anesthesia. Intramuscular ketamine 3–5 mg/kg mixed with atropine 10–20 μg/kg and midazolam 0.1 mg/kg is useful for inducing anesthesia in noncooperative patients [220,221]. Sedation or a "catatonic state" are induced by this combination of drugs, which allows easy movement of the patient, obtaining intravenous access, inducing general anesthesia, tracheal intubation, and maintenance of anesthesia with the technique of choice. If the patient has a seizure disorders, they should take their anticonvulsant medications on the day of surgery. Ketamine does not increase the incidence of seizures in patients with seizure disorders.

Dental anesthesia

Extensive dental restoration is best managed with nasotracheal rather than orotracheal intubation. The tube is secured around the patient's head with a fabric tube holder. In some patients, however, nasotracheal intubation is not practical, including patients with previous cleft palate repair or epidermolysis bullosa. In these patients, an oral RAE tube is placed. When it is, constant vigilance is required to prevent accidental dislodgment of the tube. Oral tubes are secured to one side of the mouth initially and moved to the other side when required to facilitate the procedure.

Prior to nasotracheal intubation, oxymetazoline drops are applied to both nares to induce mucosal vasoconstriction and decrease bleeding during insertion of the tracheal tube. Graduated sizes of well-lubricated nasopharyngeal airways are commonly used to dilate the nares in preparation for nasotracheal intubation. Placing the tube in warm water for a few minutes decreases its stiffness, which decreases the incidence of epistaxis following nasotracheal intubation. Cuffed tracheal tubes should be used when possible. Limiting the number of attempts at nasotracheal intubation reduces the incidence of epistaxis. Epistaxis complicates nasotracheal intubation because it makes visualization of the larynx more difficult.

Following inhalation induction of anesthesia and 2–3 mg/kg of intravenous propofol, a tracheal tube can be inserted under direct vision without difficulty. Once the vocal cords are visualized, a RAE tube can be inserted through the nares and passed through the vocal cords, with or without the use of Magill forceps. Nasal RAE tubes are commonly used for dental surgery because they allow the use of a rubber dam when required [222]. The preformed, fixed bend in the tube helps stabilize the tube, decreases the likelihood of kinking, reduces the likelihood of injury to the nares, and allows a low profile for maximum surgical convenience. The problem with tubes with a preformed bend is that they have a fixed distance from the bend to the distal end of the tube. For most children this places the tip of the tube in the midtrachea. In others, the tube is too long and causes bronchial intubation. For some, the tube is too short, which places the tip of the tube barely

below the vocal cords. The bend also makes tracheal suctioning difficult. It is important to remember that flexing the head on the chest moves the tip of the tube deeper into the trachea and that extension of the head moves it towards the vocal cords.

A gauze throat pack is usually inserted before initiating surgery to prevent aspiration of blood or extracted teeth. Confirmation of the removal of the pack must occur at the end of surgery because retention of a pack after tracheal extubation can be disastrous. Either spontaneous or mechanical ventilation is acceptable.

The postoperative period is often characterized by emergence delirium, with or without postoperative nausea and vomiting. Occurrence of these events should be managed accordingly.

KEY POINTS: DENTAL SEDATION AND ANESTHESIA

- When dental anesthesia is provided in a dentist's office, suction, oxygen, monitoring equipment, sedative medications as well as the drugs and equipment needed for resuscitation must be available
- Vasoconstrictive drugs should be placed in the nose before insertion of a tracheal tube to minimize bleeding
- Many children undergoing dental surgery have co-morbid diseases that must be fully understood before undertaking sedation and anesthesia, especially in non-hospital settings
- Gauze throat packs must be removed prior to tracheal extubation to prevent airway obstruction

CASE STUDY

A 13-year-old obese male who resides in a home for children with special needs was admitted for outpatient dental restoration for severe dental caries. His history includes severe developmental delay and occasional violent behavior. Other pertinent medical history includes obstructive sleep apnea, for which his pediatrician has prescribed a CPAP machine. The caregiver accompanying the patient states the patient has not been compliant with using his CPAP machine.

Preoperative considerations

The patient is considered to have moderate to severe OSA (Table 34.3). This information was important in planning his anesthetic. One question was whether he should receive intraoperative opioids. The immediate challenge, however, was how to separate this child from his caretaker and take the child to the operating room. He was unlikely go willingly with only the anesthesia care provider. It was decided that a staff member of the resident home, with whom he has a special rapport, would accompany him to the operating room and remain with him during the induction of anesthesia. This is usually the preferred approach.

An alternative method of managing his separation anxiety would be the administration of IM ketamine (4 mg/kg), midazolam (0.1 mg/kg), and glycopyrrolate (0.01 mg/kg). The latter two medications are given to counteract any ketamine-induced hallucinations and to prevent excessive airway secretions. While it is possible that midazolam 0.5–1 mg/kg could be given orally, it was thought that this patient's history of combative behavior would make it difficult to get him to swallow oral medication. Some practitioners would reduce the PO dose of midazolam to 0.25 mg/kg due to the patient's history of OSA. The administration of IM ketamine IM would be a good option.

Table 34.3 Severity ranking system of obstructive sleep apnea (OSA) based on polysomnography*

	Apnea-hypopnea index	Oxygen saturation nadir
Normal	0–1	>92%
Mild OSA	2–4	
Moderate OSA	5–9	
Severe OSA	>10	<80%

* Peak end-tidal CO_2 ($ETCO_2$) and duration of time spent with $ETCO_2$ >50 mmHG should be considered when assessing severity of OSA.
Source: Reproduced from Schwengel et al [225] with permission of Wolters Kluwer.

Intraoperative considerations

Because of the patient's obesity and sleep apnea, tracheal intubation was the best option for assuring an effective airway. This also provided the dentist with good operative conditions, especially because a nasotracheal tracheal tube was utilized. Following inhalation induction of anesthesia, a short-acting muscle relaxant was administered intravenously. Muscle paralysis was provided because the surgeon planned to do extensive dental work, and muscle paralysis would improve operating conditions for the dentist. Nasotracheal intubation was accomplished with a sedative-hypnotic agent alone. Desflurane was used for maintenance of anesthesia because its low blood gas solubility would not lead to significant absorption of the agent into fat. This would shorten the time to awakening from anesthesia, which was preferred in this child. Despite the fact that desflurane is associated with airway irritability, it was felt to be the best choice for this patient. Because no dental extractions were planned, intraoperative opioids were not administered. If teeth had been extracted, intraoperative opioids could be carefully titrated once the patient resumed spontaneous ventilation to maintain a spontaneous respiratory rate of 16–20 breaths/min. For this patient with significant OSA, it was decided to administer opioids after tracheal extubation, when the patient was awake. Small amounts of dexmedetomidine 0.25 μg/kg could also have been administered intraoperatively to reduce the possibility of having him awaken in a pain-induced agitated state. Additional analgesics were administered following tracheal extubation as needed.

Intraoperatively, the heart rate gradually decreased from 110 to 60 beats/min. Despite the decrease in heart rate, the patient remained normotensive. Some practitioners would have administered IV glycopyrrolate at the beginning of the dental restoration procedures for both heart rate control and control of oral secretions. This was not done in this case. Aliquots of IV glycopyrrolate 5–10 μg/kg would have been administered if hypotension had developed. It must be remembered that giving IV glycopyrolate for dexmedetomidine-induced bradycardia may produce an exaggerated hypertensive response [223]. At the conclusion of surgery, the patient's neuromuscular blockade was fully reversed, and his trachea was extubated when he was fully awake.

Postoperative considerations

This patient was placed in a semi-upright, lateral (non-supine) position throughout recovery to decrease the incidence of airway obstruction, to improve breathing, and to allow drainage of blood or oral secretions.

Despite awake tracheal extubation, it was not possible to wean him from oxygen. His oxygen saturations intermittently decreased to 85–88% for approximately 10 s. An oral airway (which he tolerated) and shoulder roll were placed to prevent flexion of the head and obstruction of the airway, but this only partially resolved the problem. Mask CPAP was applied, which decreased his bradycardia and hypoxemic episodes and improved his breathing. Fortunately, he was receptive to using this device. Over about 6 h, he was able to maintain his oxygen saturation in a normal range, and CPAP was applied when he slept.

While most dental restoration procedures are performed on an outpatient basis, because of this patient's co-morbidities, he remained in the hospital overnight in a stepdown unit. Part of that decision was based on the fact that it was unclear if suitable care (availability of a nurse on site and the degree of supervision/care needed) could be provided in the residential home. Fortunately, one of the staff from the residential home was able to remain in the hospital with the patient overnight, which was calming for the patient.

Since the patient was admitted to the hospital, a prolonged PACU stay was unnecessary, but would have occurred if he were going "home" after surgery – as the American Society of Anesthesiology suggests for patients who have OSA [224,225]. The recovery of patients with OSA also depends on the amount of opioids they have received. To reduce potential problems, NSAIDs or NSAIDs combined with smaller doses of opioids, e.g. acetaminophen/hydrocodone, are considered when additional drugs are required in the recovery room or on the floor. Often the presence of a familiar caregiver in the recovery room and hospital prevents or decreases postanesthetic agitation and the need for sedation and opoids.

There is no consensus regarding postoperative disposition of patients with OSA within the hospital after surgery, i.e. the intensive care unit versus a stepdown unit. There is agreement, however, that these patients should be observed in a monitored postoperative setting with pulse oximetry monitoring [222].

Twenty-four hours after surgery, the patient was fully awake and had returned to his preoperative state. He was discharged back to his care facility.

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 35

Anesthesia for Ophthalmological Surgery

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Introduction

Pediatric ophthalmological surgeries are among the more common procedures in pediatric anesthesia practice. The patients range from healthy outpatients undergoing relatively simple procedures such as strabismus correction, to more complicated patients with syndromes requiring cataract removal, to premature infants requiring laser photocoagulation for retinopathy of prematurity. This chapter starts with a review of extraocular conditions, including nasolacrimal duct obstruction and strabismus. Then intraocular conditions will be discussed, including glaucoma, open globe injuries, cataracts, retinoblastoma, and retinopathy of prematurity. Finally, a case study of a retinoblastoma patient will be presented which synthesizes many of the concepts in the chapter into a real-life scenario.

Anesthetic effects of commonly used ophthalmic drugs

Several medical problems are associated with congenital and acquired eye anomalies and pathology. The anesthesiologist must have a good understanding of the associated medical entities as well as the different anesthetic drugs and procedures that profoundly affect ocular physiology. A basic understanding of intraocular pressure and its control, along with the pharmacology of drugs used by the ophthalmologist, and the potential for drug interactions with anesthetic agents is necessary to provide adequate anesthetic care for pediatric patients during eye surgery (Table 35.1).

Extraocular conditions

Nasolacrimal duct obstruction

Up to 6% of healthy neonates have congenital nasolacrimal duct obstruction, presenting with epiphora or continuous tearing. In the absence of infection, a conservative approach is appropriate for a few months to see if the tear duct opens with time. However, if nasolacrimal duct stenosis persists, a series of procedures with increasing invasiveness are performed. Initial intervention involves probing and irrigation of the nasolacrimal duct. Nasolacrimal duct probing can be performed in an office setting or in an operating room with a general anesthetic depending on the age of the patient as well as surgeon preference. In the later scenario, a standard mask induction and maintenance of anesthesia with inhalational agents can provide satisfactory operative conditions. Some anesthesiologists place a laryngeal mask airway (LMA) to secure the airway. If simple probing and irrigation does not resolve the condition, the child may require balloon dilation and/or silicone tube placement, either following the initial probing or on a subsequent operating room visit.

In a very small percentage of patients the obstruction may persist and could result in infections of the tear sac. This would require a more invasive and longer procedure such as dacryocystorhinostomy which involves creation of a communication between the lacrimal sac and the nasal cavity. The anesthetic management for this procedure should include securing the airway with an endotracheal tube, as access to the airway will be limited during the operation. Analgesic drugs should also be administered. All procedures described are performed on an outpatient basis unless the child has other concomitant medical conditions that warrant postoperative observation.

Strabismus

Strabismus correction is one of the most common surgical procedures in ophthalmology. It is characterized by a misalignment of the visual axes and may be congenital or acquired. It occurs in 2–7% of children. The congenital form may occur as a result of abnormal innervation while the acquired form may occur following traumatic nerve palsies.

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

Table 35.1 Anesthetic effects of commonly used ophthalmological drugs

Drug	Dose (mg/drop)	Ophthalmological effect	Anesthetic implication
Atropine (1%)	0.5	Mydriasis, cycloplegia	Tachycardia, flushing
Cocaine (1%)	0.5	Vasoconstriction	Hypertension, dysrhythmia, hyperthermia
Cyclopentolate (0.5%)	0.25	Mydriasis, cycloplegia	Convulsions (not common)
Cyclopentolate (1%)	0.5		
Echothiophate (0.25%)	0.1	Antiglaucoma	Anticholinesterase (long acting)
Epinephrine (0.25%)	0.1	Antiglaucoma	Hypertension, dysrhythmias
Phenylephrine (2.5%)	1.2	Mydriasis, vasoconstriction, decongestion	Hypertension
Scopolamine (0.25%)	0.1	Mydriasis, cycloplegia	Central nervous system excitement
Timolol (0.25%)	0.1	Antiglaucoma	β-blockade, non-selective
Timolol (0.5%)	0.25		
Tropicamide (0.5%)	0.25	Mydriasis, cycloplegia	Tachycardia
Tropicamide (1%)	0.5		

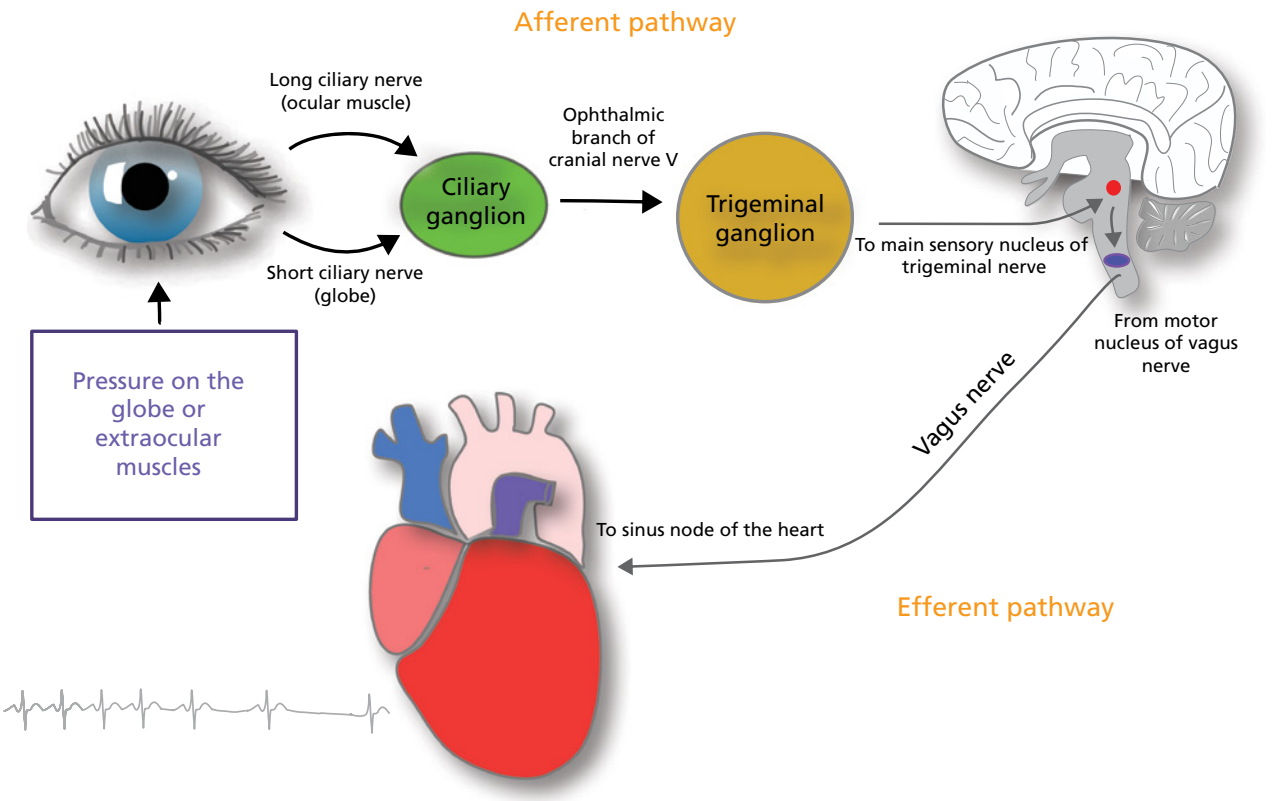

Figure 35.1 Oculocardiac reflex pathway. *Source*: Diagram by Mark Mazziotti MD.

Strabismus may present in healthy children but can also occur in association with congenital syndromes and neurological disorders. The outcome of the surgical correction for this surgery is excellent when performed early in life. The primary considerations for anesthesiologists caring for children having strabismus surgery include the cardiovascular effects of the required preoperative eye drops, the oculocardiac reflex, and postoperative nausea and vomiting.

Ophthalmic drugs

Phenylephrine drops may be placed in the eye(s) prior to strabismus repair in order to facilitate mydriasis and hemostasis. However, absorption of ophthalmic phenylephrine can cause profound systemic vasoconstriction and hypertension. A recommendation to prevent systemic hypertension following phenylephrine eye drops (2.5%) is the instillation of one drop in each eye [1,2]. Other agents (0.5% cyclopentolate, 0.5% tropicamide) may be used to induce mydriasis without causing hypertension.

Oculocardiac reflex

Traction on the extraocular muscles, which inevitably occurs during strabismus surgery, produces vagal stimulation via the trigeminal-vagal reflex, also referred to as the oculocardiac reflex (Fig. 35.1). The afferent pathway of this reflex involves the ophthalmic division of the trigeminal nerve, while the efferent pathway involves the vagus nerve. The oculocardiac reflex may be triggered during any surgery in which there is traction on the extraocular muscles or eyelid. Some studies suggest that the oculocardiac reflex occurs more frequently when the medial rectus is stimulated, however other studies report no difference in the potential to trigger the

reflex between the different extraocular muscles [3,4]. A gentle surgical technique can prevent the oculocardiac reflex. If the reflex does occur, alerting the surgeons and the subsequent alleviation of traction on the rectus muscles or pressure on the eye usually dissipates symptoms. Other situations that may trigger this reflex include placement of a retrobulbar block, enucleation, and maxillofacial or endoscopic sinus surgeries. Pressure on the eye or empty globe may also elicit this reflex. The oculocardiac reflex can result in a variety of dysrhythmias including sinus or junctional bradycardia, atrioventricular block, bigeminy, multifocal premature ventricular contractions, ventricular tachycardia, or sinoatrial arrest [5].

These changes in rhythm may decrease as surgery progresses, as the reflex may fatigue, or it may diminish with continued intermittent traction. Medical therapy (i.e. administration of anticholinergic agents) may be necessary. Prophylactic administration of glycopyrrolate or atropine may help decrease the frequency, intensity, and duration of this reflex. However, this practice remains controversial as dysrhythmias have been associated with the administration of anticholinergic agents and the reflex may still occur regardless of pretreatment [6]. A retrobulbar block may trigger the oculocardiac reflex if moderate pressure is applied to the eye but when the block takes effect, it can prevent the oculocardiac reflex by blocking the afferent limb of the reflex.

The LMA provides an effective alternative to endotracheal intubation in otherwise healthy children undergoing elective strabismus surgery [7]. In the absence of gastroesophageal reflux, the LMA provides an excellent airway for patients who can sustain spontaneous ventilation for the duration of eye muscle surgery. Hypercarbia may exacerbate the oculocardiac reflex [8], therefore in order to treat or prevent hypercarbia during anesthesia with a LMA, the anesthesiologist may consider mechanical ventilation with positive inspiratory pressures not exceeding 20–25 mmHg or pressure support ventilation.

Postoperative nausea and vomiting

Nausea and vomiting occurs in 50–80% of patients in the postoperative period following strabismus surgery and may delay discharge from the hospital. A recent review revealed postoperative nausea and vomiting (PONV) as the reason for 50% of unplanned overnight hospital admissions following strabismus surgery [9].

The exact mechanism of the observed increased predisposition to nausea and vomiting following strabismus surgery is not known but may be related to altered visual perception and a different afferent input postoperatively or it may be secondary to an oculoemetic reflex, which is analogous to the oculocardiac reflex. It is worthy of note, however, that prevention of the oculocardiac reflex during strabismus surgery by prophylactic treatment with anticholinergic agents (atropine or glycopyrrolate) has not been found to reduce the incidence of nausea and/or vomiting [10]. A large number of studies have examined the management of postoperative nausea and vomiting in general. Prophylactic treatment using more than one drug is clearly indicated according to the consensus statement of the Society for Ambulatory Anestheia [11]. However, no single agent, combination of agents, or anesthetic technique has completely eliminated this problem.

Despite persistence of this problem, propofol has contributed to the decline in the incidence of PONV [12] and studies have shown that it offers some protective effect against PONV following strabismus surgery [13–16]. Droperidol and metoclopramide, both antidopaminergic drugs, reduce nausea and vomiting by their action on dopaminergic sites [17,18]. Droperidol is, however, now rarely used in the United States due to the Food and Drug Administration (FDA) black box warning (strong contraindication) against its use. This warning cites serious cardiac arrhythmias due to prolongation of the QTc interval and recommends 12 lead electrocardiogram (ECG) monitoring 1 h before surgery and 2–3 h postoperatively if droperidol is administered to a patient [19,20]. Droperidol had been favored in the past as an antiemetic as it was cheaper than its counterpart serotonin antagonist agents. However, its use was also associated with occasional prolonged periods of sedation. Metoclopramide has also been used for many years to treat PONV. When compared with ondansetron, a serotonin antagonist also utilized in the management of PONV, metoclopramide decreased nausea and vomiting to a much lesser degree than ondansetron in patients following strabismus surgery [21,22].

Strategies to decrease PONV in strabismus patients currently revolve around serotonin antagonists. Dexamethasone is often used in conjunction with this class of drugs. When administered at a dose of 50 μg/kg, dexamethasone was found to be just as effective as higher doses of 250 μg/kg [23]. Nitrous oxide and the use of opioids have been implicated in the development of PONV. Therefore, avoidance of nitrous oxide as a maintenance agent and administration of non-steroidal agents such as ketorolac will help decrease the incidence of PONV following strabismus surgery. High-risk patients such as those undergoing strabismus correction surgery have been found to benefit from combination antiemetic therapy [24–26].

Malignant hyperthermia considerations

In the past patients with strabismus were thought to be susceptible to malignant hyperthermia as most patients with malignant hyperthermia had associated musculoskeletal disorders including strabismus and ptosis. A subsequent review of 2500 patients tested for malignant hyperthermia susceptibility did not show any association with strabismus surgery. Malignant hyperthermia is no longer considered to be a risk for children with strabismus and these children are now routinely anesthetized with inhalational anesthetics without an observed increase in the incidence of malignant hyperthermia [27,28]. Masseter muscle spasm has also been associated with strabismus surgery, particularly in patients who received halothane and succinylcholine [5], although another study contradicted this finding [29]. The increase in jaw tension that may be observed initially following succinylcholine administration, together with an inability to displace the mandible from the maxilla to facilitate insertion of an oral airway, is now thought to represent a normal clinical state following succinylcholine administration [27,28]. Succinylcholine has a black box warning from the US FDA against its use for elective airway management in children and so this problem should not be clinically relevant for contemporary anesthetic practice.

In summary, it does not appear there is an association between strabismus and malignant hyperthermia [30]; however, if masseter muscle spasm is suspected in a patient,

particularly a young or preadolescent child, it is important to recognize that the patient may be susceptible to developing malignant hyperthermia [27,31,32]. The importance of a detailed anesthetic family history also cannot be overemphasized.

KEY POINTS: EXTRAOCULAR CONDITIONS

- Nasolacrimal duct obstruction surgery can involve simple probing, balloon dilation with or without tube placement, or dacryocystorhinostomy; airway management techniques range from facemask, to LMA, to endotracheal intubation
- Strabismus surgery drug interactions such as hypertension from absorption of 2.5% phenylephrine instilled in the eye can be prevented by limiting the dose to one drop in each eye
- The oculocardiac reflex is produced by traction on the extraocular muscles or pressure on the globe, and is mediated by the ophthalmic division of the trigeminal nerve (afferent) and the vagus nerve (efferent). It can be prevented by gentle surgical technique and pretreatment with an anticholinergic agent, and fatigues with repeated stimulation
- Postoperative nausea and vomiting is very common after strabismus correction; multimodal antiemetic therapy with ondansetron, dexamethasone, and avoidance of nitrous oxide and opioids, are effective

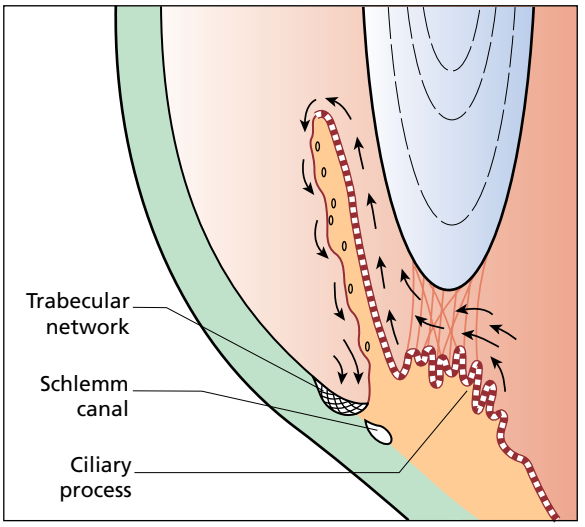

Figure 35.2 Magnified view of ciliary body showing aqueous humor production and flow pattern.

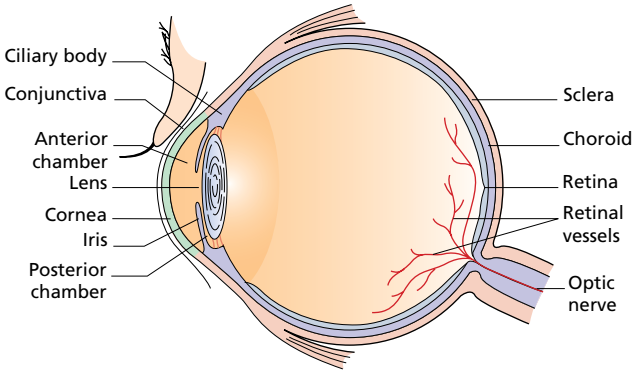

Figure 35.3 Anatomy of the anterior chamber of the eye.

Intraocular conditions

Prior to an in-depth discussion of the intraocular conditions, it is imperative to understand the production and regulation of aqueous humor in the eye as well as intraocular pressure and how it may be impacted by different anesthetics.

Control of intraocular pressure

Aqueous humor is present in both the anterior and posterior chambers of the eye. The majority of the aqueous humor is produced in the posterior chamber by active secretion, filtration, and diffusion from the blood supply to the ciliary body (Fig. 35.2). Aqueous humor passes from the posterior chamber, through the ciliary body behind the iris to the front of the lens, then through the pupil into the anterior chamber (Fig. 35.3). The most lateral portion of the anterior chamber, called the angle, contains a meshwork of tissue that filters the aqueous humor before it reaches the canal of Schlemm and eventually drains into the episcleral veins. This fluid contains no blood cells and only 1% of the concentration of protein found in plasma. Thus, the aqueous humor is clear and allows transmission of light to the retina [33].

Normal intraocular pressure (IOP) is maintained between 10 and 21 mmHg by a balance between the production and drainage of aqueous humor, choroidal blood volume, extraocular muscle pressure, and vitreous humor volume [34]. Sudden increases in IOP may result in acute glaucoma. If this occurs in the presence of an open globe, prolapse of the iris or lens and/or hemorrhage from blood vessels may occur. Therefore, it is imperative that the anesthesiologist maintains normal IOP during eye surgery. Laryngoscopy and intubation of the trachea, coughing, vomiting, or straining during induction or emergence from anesthesia can all dramatically increase IOP to values as high as 40 mmHg [35]. Although the effect of laryngoscopy is transient and of no serious consequence in the patient with normal intraocular physiology, this increase in pressure may be very significant for patients with glaucoma or other eye pathology. Administration of intravenous lidocaine prior to intubation has been found to prevent an increase in IOP [36–38]. IOP changes with LMA insertion are less than those following tracheal intubation [39].

Coughing causes venous hypertension which increases the intraocular blood volume and has a dramatic effect on IOP. Several metabolic or acid–base derangements may occur during general anesthesia and can also impact IOP. Hypoxia and hypercarbia cause retinal venodilation and an increase in IOP [40]. Both mild hypo- or hypercarbia produce clinically insignificant effects [41]. Hypothermia decreases IOP by decreasing the rate of aqueous humor production. Arterial pressure changes have little effect on IOP [34].

Effect of anesthetics on intraocular pressure

In general, sedative–hypnotic agents, inhalational agents, and opioids tend to decrease IOP with the exception of ketamine [34,42]. Earlier reports on the use of ketamine and IOP measured by Schiotz tonometry, which measures corneal compressibility, indicated that ketamine resulted in an elevation of IOP [43]. Currently, IOP is routinely measured with applanation tonometry, a method believed to more accurately measure IOP. While ketamine does not lower IOP, the IOP measured following ketamine administration may be more reflective of the awake measurement rather than an elevated value. The use of ketamine may actually be preferable to other agents when an accurate measurement of IOP is necessary, as is the case of children with suspected glaucoma in whom accurate measurements of the IOP can only be obtained under anesthesia [44,45]. Nystagmus and blepharospasm associated with ketamine administration may preclude its use in children with an open globe injury.

Non-depolarizing muscle relaxants decrease pressure on the globe and may decrease intraocular pressure [34]. Succinylcholine, a depolarizing muscle relaxant, increases IOP by inducing tonic extraocular muscle contracture, choroidal vascular dilation, and relaxation of orbital smooth muscle. In normal eyes, an increase in IOP of about 7 mmHg has been observed following succinylcholine use [46]. This modest increase is transient and of little consequence in a patient with normal IOP. However, if a patient has a high baseline IOP, the increase in IOP induced by succinylcholine administration may be greater and any rise may be significant in that setting. In the case of an open globe, an increase in pressure could result in the loss of vitreous humor. Despite reports to the contrary, no one method has been shown to prevent the intraocular hypertension observed with the administration of intravenous succinylcholine [47–49]. While some reports state there are no adverse events following the use of succinylcholine for anesthesia in a child with an open globe injury [50], caution should be exercised using this drug in the presence of such an injury. High-dose rocuronium provides a viable option for modified rapid-sequence induction without the concern of associated elevation of IOP in this subset of children who present for emergency surgery. In addition, the availability of sugammadex for the reversal of dense neuromuscular blockade after a short procedure should render succinylcholine use even less necessary in this scenario [51].

KEY POINTS: INTRAOCULAR PRESSURE

- Intraocular pressure is dramatically increased by laryngoscopy and intubation, coughing, vomiting, or straining; all should be minimized in patients with elevated IOP
- Sedative–hypnotic agents, inhalational agents, and opioids all decrease IOP, except ketamine, which maintains baseline IOP
- Non-depolarizing muscle relaxants decrease IOP; succinylcholine increases IOP and should be avoided in patients with elevated IOP or an open globe

Glaucoma

If outflow of aqueous humor is obstructed for any reason, IOP increases and can lead to glaucoma. Primary congenital glaucoma includes neonatal and infantile glaucoma, which presents at birth or within the first 2 years of life, respectively. Juvenile glaucoma presents in late childhood without corneal enlargement (buphthalmos), and often in children of families with a strong history of open-angle glaucoma. Secondary glaucoma develops in association with an underlying ocular or systemic condition (e.g. Sturge–Weber syndrome, neurofibromatosis, mesodermal dysgenesis) [52].

Successful surgical treatment of primary congenital glaucoma requires early recognition of the problem. Confirming the diagnosis in infants who present with a history of excessive tearing, photophobia, irritability, and buphthalmos usually requires measuring the IOP during an exam under general anesthesia. The eye examination and pressure measurement can be followed by surgery if the diagnosis is confirmed. The initial surgical procedures for pediatric glaucoma include goniotomy or trabeculotomy to create a route for the exit of aqueous humor via the Schlemm canal. If unsuccessful, other surgical options include trabeculectomy, placement of a glaucoma drainage device, or cyclodestructive therapy to destroy the ciliary body and decrease aqueous humor production [53].

Anesthetic considerations for patients during glaucoma surgery include awareness and management of associated medical problems as indicated; especially if glaucoma exists as part of a syndrome, as well as use of appropriate medications and methods/drugs to prevent further increase in IOP (see section “Control of intraocular pressure”).

Open globe injuries in a patient with a “full stomach”

Traumatic eye injuries are common in children. Surgical exploration of the eye wound, removal of any existing foreign material, and closure of the laceration within several hours of the injury offer the best chance of salvaging the eye following traumatic injury. After penetrating trauma, the pressure inside the eye is atmospheric. External pressure on the eye or an increase in internal pressure can prolapse the lens, iris, or vitreous and markedly reduce the chance of recovery of vision. The goal preoperatively and during the induction of anesthesia is to prevent coughing, crying, and vomiting because these activities increase intraocular venous blood volume. Increased intraocular venous blood volume and IOP may cause extrusion of the ocular contents.

Preventing an increase in IOP is important, but difficult to accomplish. Preoperatively, the child should remain flat and quiet, and the eyes should be patched to minimize eye movements (this can be scary and confusing to young children). Sedating the child before patching the eyes is essential if the child is too young to cooperate and cannot understand a careful, gentle explanation of the procedure. Giving a young child midazolam (0.5–0.75 mg/kg PO) or diazepam (0.2 mg/kg PO) will provide adequate sedation. Intranasal midazolam may cause crying and agitation and should therefore be avoided in the setting of an open globe injury. The α2-agonist, dexmedetomidine, is an effective premedication when administered intranasally and it has an advantage over intranasal midazolam as it is not associated with pain when administered via

this route [54–57]. Administration of dexmedetomidine has also been found to attenuate the increase in IOP associated with succinylcholine administration [58].

In a calm, sedated child, application of EMLA (eutectic mixture of local anesthetics) cream may provide adequate topical anesthesia to allow for insertion of an intravenous catheter. The EMLA cream should be applied to several sites where veins are visible (or likely to be present) and covered with a clear occlusive dressing. Forty-five to 60 min later, the skin should be anesthetized to allow painless insertion of an IV catheter. Once vascular access has been achieved, subsequent doses of sedatives can be titrated to effect, and a rapid-sequence induction of anesthesia can be easily accomplished. The anesthesiologist should assume that all children who present with a penetrating eye injury have a full stomach. After trauma, gastric emptying time is quite erratic and unpredictable such that delaying surgery for 6–8 h does not reliably decrease the risk of aspirating gastric contents.

In the presence of an open eye injury, the anesthesiologist must preoxygenate the patient, being careful not to exert pressure on the injured eye with the mask. Preoxygenation is followed by injection of a sedative–hypnotic anesthetic agent and a muscle relaxant into an injection port of a rapidly flowing IV catheter. Options to minimize the effects of laryngoscopy and intubation on IOP include: intravenous administration of lidocaine (2 mg/kg), fentanyl (2–3 μg/kg), or morphine sulfate (0.05–0.1 mg/kg) prior to the administration of either propofol (2 mg/kg) or thiopental (4–6 mg/kg). Administration of the sedative–hypnotic agent should be followed immediately by a dose of succinylcholine (2 mg/kg) or high-dose rocuronium (1–1.2 mg/kg) to facilitate rapid-sequence induction. High-dose rocuronium offers advantages over succinylcholine because rocuronium provides rapid onset of neuromuscular blockade without impacting IOP. Tracheal intubation should only be attempted after the muscle relaxant has taken effect. This will prevent coughing during laryngoscopy and the detrimental effect on IOP.

Cricoid pressure, which is traditionally applied during induction of anesthesia to occlude the esophagus and prevent passive regurgitation of stomach contents into the lungs, should be maintained until the airway is secured. In situations where intubation is not achieved on first attempt and/or there is accompanying desaturation, the application of cricoid pressure may also decrease the likelihood of stomach dilation if gentle manual positive pressure ventilation is required prior to endotracheal intubation. While utilization of cricoid pressure may be under some debate, it remains the traditional approach to securing the airway in a patient with a potential full stomach [59].

Securing intravenous access for the induction of anesthesia may be challenging in a child. For the normal, chubby toddler who has no visible veins, the risk of crying, struggling, and raising IOP while venous access is being secured, may pose a greater risk than aspiration during induction of anesthesia with inhaled anesthetics and cricoid pressure.

Cataracts

Cataracts in children may be congenital or acquired. Congenital cataracts are of two types: idiopathic and those associated with syndromes. Several syndromes (e.g. Stickler, Hallermann–Streiff, Laurence–Moon–Biedl, Lowe, cerebrotendinous xanthomatosis, and Marfan) are associated with a high incidence of cataracts (see Chapter 43 for further discussion of these syndromes). Metabolic disease states such as galactosemia, and chromosomal abnormalities, such as trisomy 21, are also associated with the presence of cataracts. Cataracts may also be associated with systemic disease, steroid induced, or acquired as a complication of radiotherapy.

Cataract surgery in otherwise healthy children or in those with minimal associated medical co-morbidities, is performed as an outpatient procedure. While this surgical procedure is routinely performed under general anesthesia with supplemental opioid analgesia in children, one study has shown that general anesthesia supplemented with a regional block (sub-Tenon block) resulted in less postoperative pain and fewer requirements for postoperative rescue medication [60]. As with other surgical procedures, associated co-morbidities or medical conditions must be taken into account when administering anesthesia for cataract surgery. A deep plane of anesthesia is required during surgery for all patients to minimize the chance of coughing or straining and loss of vitreous humor or other intraocular contents once an incision has been made on the globe. If a patient's cardiovascular system cannot tolerate a deep plane of anesthesia, neuromuscular-blocking agents should be administered to supplement general anesthesia. Succinylcholine should not be administered after the globe is incised, because the ensuing contraction of the extraocular muscles which may occur for up to 15–20 min can potentially increase IOP sufficiently to extrude the ocular contents through the surgical incision.

Ideally, the patient who has had cataract surgery should not cry excessively or struggle postoperatively. Extubation of the trachea or LMA removal while the patient is still deeply anesthetized will help achieve this goal.

KEY POINTS: GLAUCOMA, OPEN GLOBE INJURIES, AND CATARACTS

- Glaucoma involves the obstruction of outflow of aqueous humor; an eye exam under anesthesia may reveal increased IOP and may be followed by goniotomy or trabeculotomy as surgical interventions
- Avoiding increases in IOP is critical in open globe injuries; an inhaled induction with a full stomach may be preferable to multiple IV attempts in a crying child; and succinylcholine should be avoided if possible.
- Cataract surgery patients often have genetic syndromes; a deep plane of anesthesia is required to prevent movement, straining, or coughing

Retinoblastoma

Retinoblastoma, a malignancy of the retina, is the most common primary intraocular malignancy of childhood [61]. However, of all pediatric malignancies, retinoblastoma is rare and comprises only 3–4% of all pediatric cancers [62]. Decreased vision, eyes gazing in different directions (lazy

eye), and abnormal pupillary light reflex or leukocoria (white pupils) are the presenting symptoms. This condition is usually picked up during a routine eye examination by the pediatrician or by parents who may notice different color pupils during flash photography. Leukocoria is commonly associated with retinoblastoma (Fig. 35.4).

The management of retinoblastoma continues to evolve. The treatment is currently determined by tumor classification at diagnosis and can involve focal therapy (laser photocoagulation or cryotherapy) used alone or in combination with systemic intravenous chemotherapy, intra-arterial chemotherapy, and/or intravitreal chemotherapy [63]. Systemic intravenous chemotherapy is associated with unique toxicities including alopecia, hearing loss following carboplatin therapy, or secondary malignancies that can occur with etoposide. Chemotherapy in various forms including intra-arterial therapy can also be associated with myelosuppression [64]. Additional treatment options for retinoblastoma such as radiotherapy, radioactive plaque therapy, and enucleation are reserved for specific situations [63]. Although external beam therapy has been utilized in the management of retinoblastoma, it is associated with secondary malignancies and is rarely used today in current management. Children with retinoblastoma frequent the operating room for examinations under anesthesia to monitor tumor growth or resolution, as well as for surgical therapy. Smooth inhalational induction of anesthesia with insertion of a LMA provides adequate anesthesia for brief examinations; analgesic drugs may be warranted if surgical therapy is planned. The oculocardiac reflex may be triggered during surgery and should be adequately managed (see earlier in this chapter).

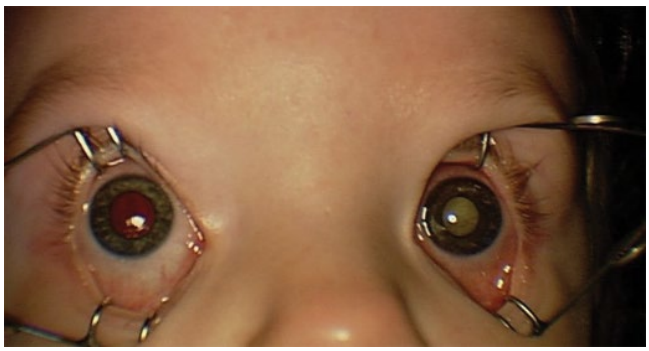

Figure 35.4 Child with leucokoria in the left eye. *Source*: Courtesy of Dan Gombos MD.

Intra-arterial chemotherapy, also referred to as ophthalmic artery chemosurgery, is a localized treatment for retinoblastoma that involves catheterization of the ophthalmic artery, a branch of the internal carotid artery, via a transfemoral approach, in order to allow for direct delivery of chemotherapy to the eye under fluoroscopic guidance (Fig. 35.5) [65]. There are limited published data on the long-term side-effects with this treatment. Thus far, experts have not reported any significant complications such as secondary neoplasms that may occur with intravenous chemotherapy or facial bony defects that can result following radiotherapy. This procedure, which is typically performed in the interventional radiology suite with the patient under general endotracheal anesthesia, is gaining popularity as it offers an alternative treatment to enucleation of the eye, thereby preserving vision (Fig. 35.6). It is also associated with a 70% 5-year survival rate [63,66,67]. Preoperative considerations include premedication for anxiolysis as these patients may have undergone several different procedures in the course of tumor management, and replacement therapy for low cell counts (neutropenia) as a result of systemic chemotherapy. While this procedure has not been associated with long-term complications thus far, it is frequently associated with adverse respiratory and hemodynamic events during the procedure. Respiratory events typically present as an acute decrease in lung compliance characterized by a decrease in tidal volumes and occasional desaturation. This may occur prior to injection of any substance into the eye, i.e. prior to injection of saline, contrast, or chemotherapeutic agent [68]. It also may occur when the microcatheter is between the internal carotid artery and ophthalmic artery [69].

Utilization of pressure control ventilation is helpful intraoperatively as a decrease of as little as 10 mL in the tidal volume can herald an impending respiratory event. This mode of ventilation will also prevent a steep increase in thoracic pressure that may accompany the decreased lung compliance and

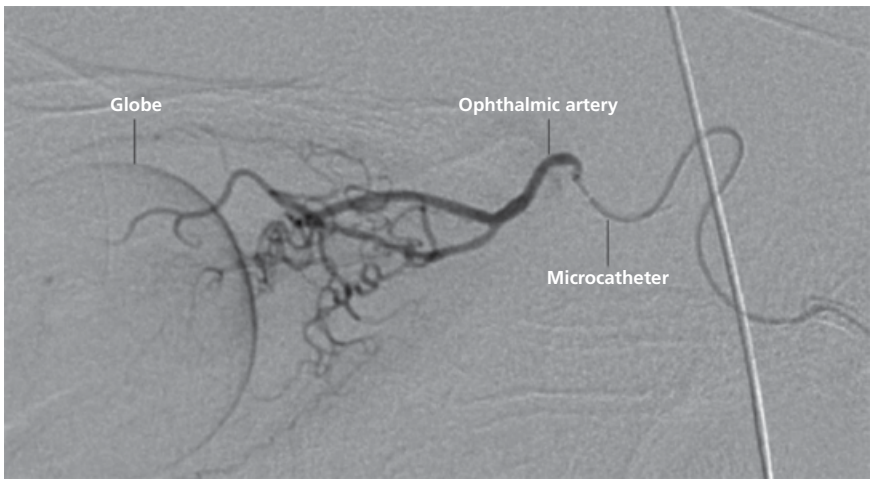

Figure 35.5 Superselective injection of the ophthalmic artery showing the ocular vessels prior to chemotherapy delivery. *Source*: Reproduced from Jabbour et al [65] with permission of Journal of Neurosurgery.

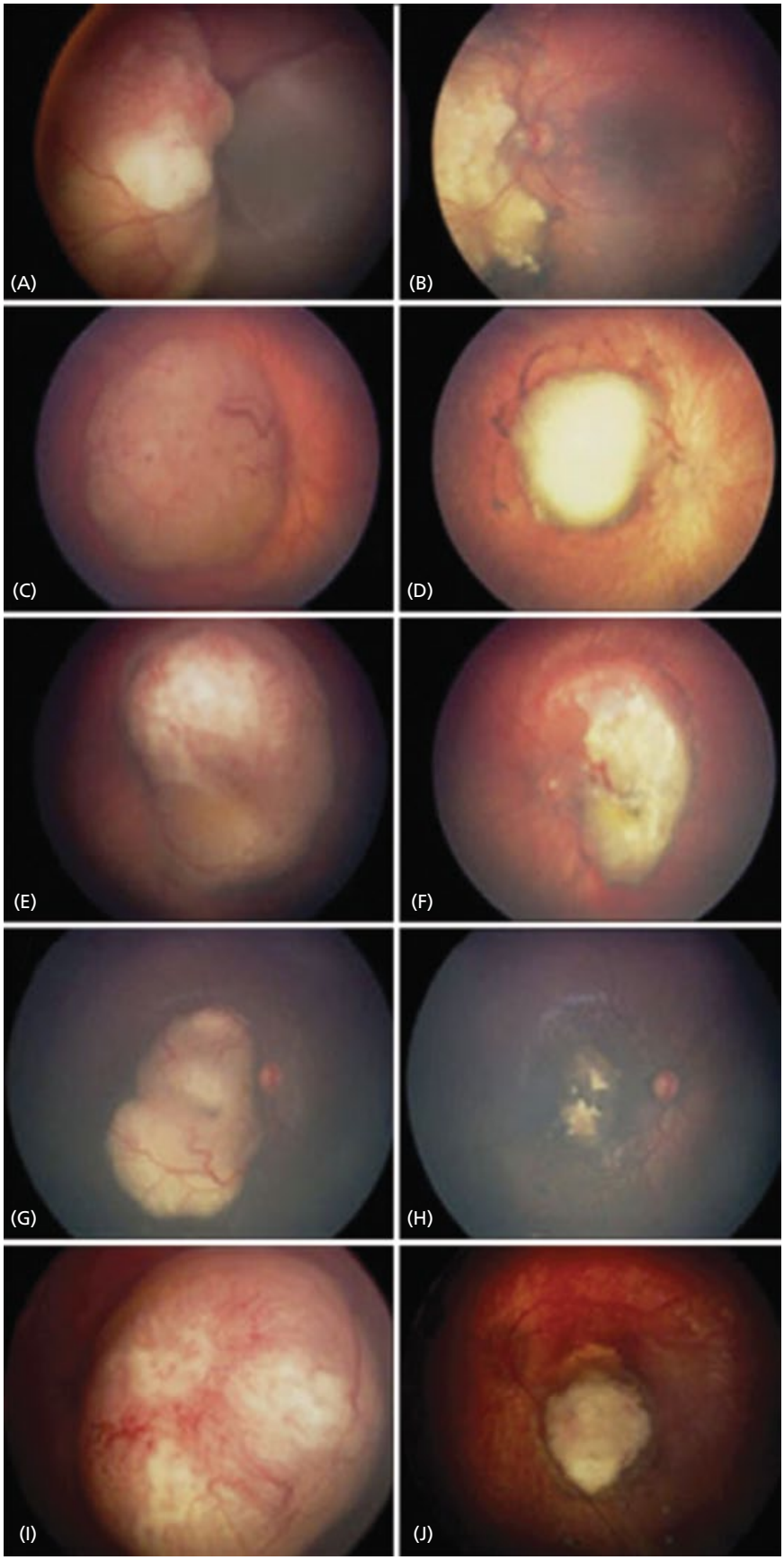

Figure 35.6 Images obtained in five cases showing the response of a solid retinoblastoma before (A, C, E, G, I) and after (B, D, F, H, J) treatment with intra-arterial chemotherapy. *Source*: Reproduced from Jabbour et al [65] with permission of Journal of Neurosurgery.

subsequent limited venous return to the heart [68]. The occurrence of this acute decompensation in respiratory mechanics has not been found to be related to the frequency of the procedure; it may occur during the first intra-arterial chemotherapy treatment or during subsequent therapies. The exact etiology of this acute respiratory decompensation is also not well defined. It can occur despite complete muscle relaxation, is not associated with wheezing, and has not been observed to have a recurring pattern. Acute respiratory decompensation is successfully resolved with the administration of intravenous epinephrine administration at bolus doses of 0.5–1 μg/kg when this is administered at the onset of the event. Hemodynamic changes that may occur during this procedure include bradycardia and hypotension. Bradycardia has been described during injection of the chemotherapeutic agent melphalan, as well as during balloon-assisted procedures [70–72]. Hemodynamic changes typically occur following the respiratory events described above [72] but may not be observed if epinephrine has been administered to treat the acute respiratory event. Epinephrine may also be used to treat the hemodynamic event if it occurs *de novo*. Since these two events often occur together during this procedure, the diving reflex has been proposed as the underlying mechanism triggering both the acute changes in respiration and hemodynamics [68]. This reflex is mediated by the ophthalmic branch of the trigeminal nerve via the anterior ethmoidal nerve. Stimulation of the anterior ethmoidal nerve results in bradycardia, hypotension, and apnea in animals [73]. It is believed that manipulation of the catheter in the ophthalmic or internal carotid artery may stimulate trigeminal afferents in the blood vessel, resulting in a reflex similar to the diving reflex in the pulmonary and cardiovascular systems and mediated, in part, by the vagus nerve.

KEY POINTS: RETINOBLASTOMA

- Retinoblastoma is the most common intraocular malignancy of childhood
- Initial treatment may involve laser photocoagulation or cryotherapy, systemic intravenous chemotherapy, intra-arterial chemotherapy, and/or intravitreal chemotherapy
- Radiotherapy, radioactive plaque therapy, and enucleation are reserved for specific situations
- Intra-arterial chemotherapy involves catheterization of the ophthalmic artery, and direct delivery of chemotherapy to the eye under fluoroscopic guidance. Acute decrease in respiratory compliance without bronchospasm, bradycardia, and hypotension may occur; treatment is with IV epinephrine

Retinopathy of prematurity

Retinopathy of prematurity (ROP), formerly known as retrolental fibroplasia, is a vasoproliferative disorder of premature infants that may result in blindness. The first phase of this disease is characterized by suppression of vascular endothelial growth factor by hyperoxia, resulting in an arrest of normal retinal vascularization. The second phase is characterized by vascular proliferation induced by hypoxia-triggered stimulation of the vascular endothelial growth factor. Hence both hyperoxia and hypoxia play a role in the pathogenesis of ROP [74,75]. Multiple risk factors for ROP have been described and these include low gestational age (strongest risk factor), low birth weight, postnatal weight gain, hyperglycemia, insulin therapy, and neonatal co-morbidities [75,76].

Oxygen supplementation and fluctuations in oxygen concentration have also been associated with ROP. Optimal oxygen saturation targets in preterm infants remain an ongoing topic of controversy and study. Multiple recent studies have compared low (85–89%) and high (91–95%) target oxygen saturations in preterm infants less than 28 weeks of gestational age to outcome measures such as death, severe ROP, bronchopulmonary dysplasia, necrotizing enterocolitis, neurodevelopmental impairment, and hearing loss [77,78]. Although a higher target oxygen saturation range of 91–95% has been associated with increased severity of ROP, this range is often recommended as the lower oxygen saturation target groups of 85–89% have been associated with an increased risk of death at discharge and at 18–24 months corrected age [79]. Nevertheless, the controversy continues, with practitioners maintaining oxygen saturations anywhere from the mid–high 80s to the low 90s range.

Retinopathy of prematurity can be classified based on disease extent, severity, and location of disease. The stages are illustrated in Figure 35.7 [80]. Severe disease can lead to retinal detachment and visual loss or blindness, therefore early intervention is advocated. Laser therapy has been found to result in better visual acuity compared with cryotherapy and is a widely accepted treatment modality for ROP [81,82]. Laser photocoagulation converts the relatively hypoxic retina into anoxic retina, reducing the stimulus for new vessel formation and disease progression. The drawback of this therapy is that it destroys retina, which can lead to significant loss of visual field. This is why antivascular endothelial growth factor treatments, with intravitreal injections of these agents, have emerged as an effective treatment for ROP. However, the safety and long-term effects of these agents remain a topic of ongoing investigation [83,84]. For late-stage ROP in which retinal detachment has already occurred, scleral buckling or vitrectomy is performed but these procedures usually fail to provide useful vision [85].

Patients with ROP have increased susceptibility to develop strabismus, cataracts, and glaucoma and should have scheduled follow-up examinations to help prevent and treat these conditions.

The anesthetic management of this patient population is challenging as multiple medical co-morbidities are usually present, including apnea of prematurity, congenital cardiac anomalies, and bronchopulmonary dysplasia, which may be associated with oxygen requirements. In addition, when ROP or its progression are diagnosed by ocular examination, laser photocoagulation is often an urgent case scheduled as soon as possible after the examination, in order to retard the progression of the disease by intervening as soon as possible. There can be institutional variation regarding the location where surgical interventions for ROP occurs. The goal is to

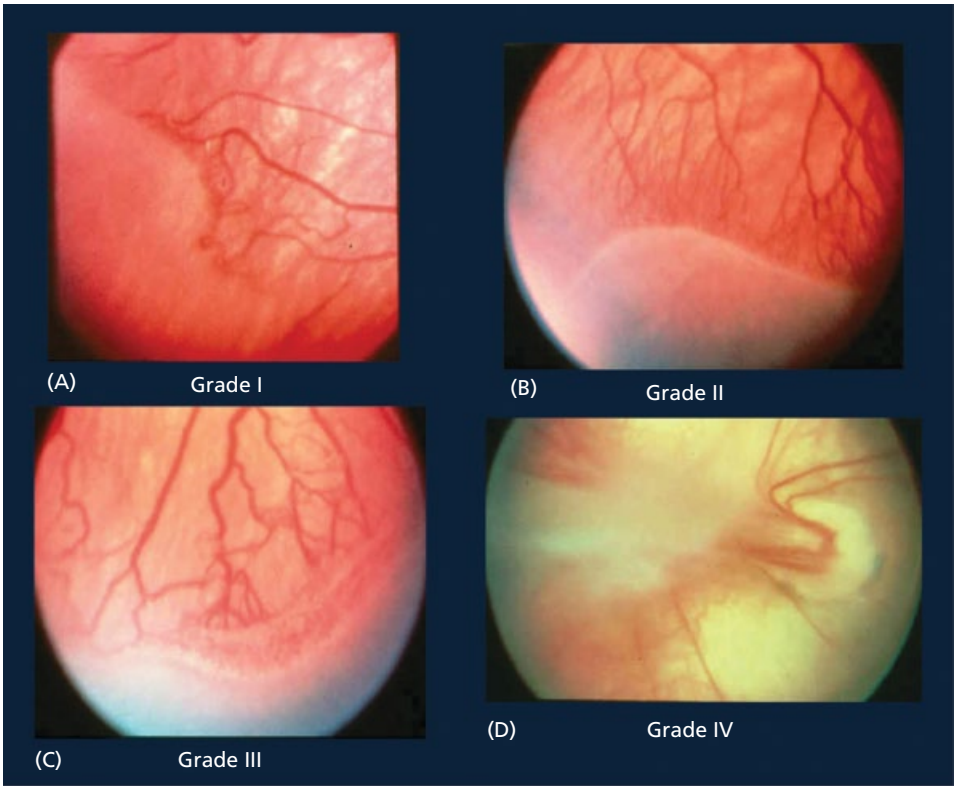

Figure 35.7 Retinopathy of prematurity stages. (A) Grade I: a demarcation line is seen between the vascular and avascular retina. It is a thin structure that lies in the plane of the retina. (B) Grade II: the demarcation line grows to occupy a volume and has a height and width to form a ridge above the plane of retina. (C) Grade III: in this stage extraretinal fibrovascular tissue is seen arising from the ridge into the vitreous. It may be continuous or non-continuous and is posterior to the ridge. (D) Grade IV: a partial detachment of the retina is seen which may be exudative or tractional. Grade V (not shown): here a total retinal detachment is seen as the child usually presents with leukocoria (white pupillary reflex). *Source*: Adapted from Vision Research Ropard Foundation, www.ropard.org. Descriptions from Shah et al [80].

provide a comfortable patient with minimal cardiorespiratory compromise and a quiet surgical field. Laser surgery may be performed in the operating room if the pulmonary status of the neonate will allow for transportation to the operating room. A general anesthetic may provide improved procedural conditions and pain management. A properly seated LMA is a viable alternative to endotracheal intubation in the occasional premature infant with mild to moderate lung disease who has not previously required tracheal intubation. In some institutions, these operations are performed in the intensive care unit which allows for seamless postintervention monitoring [86] and also avoids any interruption in respiratory support if the patient requires supplemental or mechanical respiratory support at the time of surgical intervention. Intravenous sedatives, analgesics, and topical anesthesia have been utilized in neonates who are either ventilated mechanically or are breathing spontaneously [87–89]. Retinal examinations and surgical interventions for ROP can be painful, and non-pharmacological treatments may not be effective for pain management. Nevertheless, pharmacological treatments must be cautiously administered if pain is suspected during the procedure, particularly if postoperative extubation is planned [90,91].

Prevention of ROP or its progression are important considerations when anesthetizing the premature infant for other procedures. As noted, the optimal oxygen saturation range for prevention is controversial, but these infants must not receive unnecessarily high FiO_2; it is prudent to reduce the inspired oxygen, when possible, to achieve SpO_{2in} the mid-90s percent range. The patient who is not intubated before ROP surgery and requires tracheal intubation can be extubated immediately after the procedure, but the risk of postanesthetic apnea is significant in many of these neonates, and careful monitoring in the neonatal intensive care unit setting is warranted. See Chapters 22 and 23 for further discussion of postanesthetic apnea.

KEY POINTS: RETINOPATHY OF PREMATURITY

- ROP risk factors include prematurity, hyperoxia, hypoxia, and neonatal co-morbidities
- The stages of ROP start with vascular proliferation which can increase, and lead to, partial or full retinal detachment and blindness if not treated
- Laser photocoagulation stops progression of the disease and is often performed as an urgent procedure under general endotracheal anesthesia at the bedside or in the operating room

CASE STUDY

A 2-year-old child with unilateral retinoblastoma is scheduled for intra-arterial chemotherapy. The patient was previously healthy and recently presented with unilateral strabismus and leukocoria. An ophthalmic examination under anesthesia was performed which demonstrated unilateral multifocal tumors with subretinal seeding. The patient presents from home on the day of the procedure to the interventional radiology suite. The preoperative evaluation and examination are unremarkable. The parents note that the patient is extremely anxious.

Preoperative considerations

Patients with retinoblastoma frequent the operating room for examinations under anesthesia and surgical treatment, and also non-operating room locations for diagnostic imaging and treatment. This patient may be at risk for separation anxiety due to age and repeated anesthetic encounters. Following the preoperative evaluation, the anesthesiologist should have a discussion with the family regarding possible behavioral and/or pharmacological interventions available for preoperative anxiety. Child Life personnel, may help decrease the child's anxiety if the child can be adequately engaged preoperatively. Alternatively, as this patient presents from home with no intravenous access, oral, nasal, or less commonly, intramuscular routes of medication administration should be considered. If there are no significant respiratory concerns or concerns for obstructive sleep apnea, oral midazolam 0.5–1 mg/kg is a reasonable choice for premedication. If the patient does not tolerate oral medication, intranasal dexmedetomidine 1–2 μg/kg can be considered. This has an advantage over intranasal midazolam which is associated with pain on administration. The median onset time of 1 μg/kg intranasal dexmedetomidine is slower than that of oral midazolam, however it does provide effective anxiolysis with minimal respiratory depression within 25 min of administration.

As patients with retinoblastoma often have repeated anesthetic encounters, a review of past anesthetic records is important. Some patients with retinoblastoma may have received prior systemic chemotherapy, and pertinent systemic toxicities and laboratory work should be reviewed.

Intraoperative considerations

Anesthesia provided in the interventional radiology suite should meet the same requirements as anesthesia provided in the operating room, including standardization of both anesthesia and emergency equipment (airway and code cart). The anesthesia provider should be familiar with the surroundings, equipment, and support services available in this non-operating room location. Intra-arterial chemotherapy is performed in an interventional radiology suite capable of biplane angiography under general endotracheal anesthesia. Exact medications for induction and maintenance of anesthesia are provider and patient dependent. Pressure control ventilation is the recommended mode of ventilation in order to adequately monitor respiratory mechanics as respiratory events commonly occur during this procedure. Following induction of anesthesia and prepping and draping of the patient, the femoral artery is cannulated and intravenous heparin is administered. A microcatheter is then directed under fluoroscopy to the origin of the ophthalmic artery.

Intraoperatively, an abrupt decrease in tidal volume is noted during manipulation of the microcatheter. The oxygen saturation also decreases to 88%, while the capnogram remains unchanged. The patient remains hemodynamically stable. Bilateral auscultation of the lungs reveals clear breath sounds with no wheezing.

Respiratory events typically occur when the microcatheter is advanced between the internal carotid artery and ophthalmic artery. A neural diving reflex-type mechanism has been proposed as a possible cause. A decrease in lung compliance presenting as a decrease in tidal volumes is observed and hypoxia can occur. Treatment includes hand ventilation with 100% oxygen and increased inspiratory pressure, notifying the interventional neuroradiologist to cease catheter manipulation, and administration of 0.5–1 μg/kg intravenous epinephrine. Although the event may appear similar to bronchospasm, wheezing is rarely appreciated on auscultation, and the capnogram is not typical of an obstructive pattern. Pretreatment with antihistamines, steroids, or inhaled bronchodilators are not effective. Hemodynamic issues such as bradycardia and hypotension have also been reported during this procedure. Bradycardia has been described during balloon-assisted procedures and during injection of the chemotherapeutic agent. Treatment includes an intravenous bolus of 0.5–1 μg/kg epinephrine.

Following resolution of the respiratory event, the procedure can typically resume, as recurrence of respiratory events related to catheter manipulation are rare. The anesthesia provider should also rule out other causes of respiratory and hemodynamic events such as severe bronchospasm, pulmonary edema, and anaphylactoid reactions. After catheter position is confirmed, injection of chemotherapeutic agent(s) such as melphalan, topotecan, and/or carboplatin occurs. Following femoral catheter removal and manual compression to achieve groin hemostasis, the trachea can be extubated. A smooth emergence should be prioritized. Prophylactic antiemetics should be administered during the procedure as postoperative nausea and vomiting is commonly associated with this procedure.

Postoperative considerations

The patient should remain flat for a prolonged period in the recovery area as rebleeding from the groin site is possible. Recurrence of respiratory events related to the intraoperative manipulation in the recovery area are uncommon. Periorbital and lid edema or redness may occur following the intra-arterial chemotherapy procedure but this is typically transient. Serious ocular, neurological, and femoral catheterization complications are rare. Patients are typically observed in the recovery area for a prolonged period of time and overnight admission is institutionally and patient dependent.

Multiple cycles of intra-arterial chemotherapy may be required for retinoblastoma patients. Occurrence of a respiratory event related to catheter position with subsequent procedures is unrelated to occurrence during the initial procedure. Therefore, the anesthesiologist should maintain vigilance during all intra-arterial chemotherapy procedures.

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A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 36

Anesthesia for Plastic and Craniofacial Surgery

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Introduction

General anesthesia has allowed surgeons to correct disfiguring lesions in infants and children since the introduction of anesthesia in the middle of the 19th century. Cleft lip and palate reconstruction was among the earliest surgical procedures for which general anesthesia was used for pediatric patients [1]. John Snow published the first report of giving an ether anesthetic to a 7-year-old boy for cleft lip reconstruction in *The Lancet* in 1847. He subsequently administered chloroform for lip reconstruction 147 times between 1847 and 1858, mostly to infants between 3 and 6 weeks of age. Cleft lip and palate repairs have also been an impetus for other innovations in anesthesia care for infants. This includes Ivan Magill's first use of endotracheal anesthesia for an infant in 1924 and Philip Ayre's introduction of the T-piece circuit in 1937 [2]. Modern developments in anesthesia and plastic surgery have permitted increasingly complex reconstruction of disfigured infants and children. The past decade has seen major advances in the understanding of anomalous development and the evolution of diagnostic and therapeutic technology. This chapter focuses on the anesthetic challenges encountered in major craniofacial reconstruction, including cleft lip and palate repair.

Craniofacial embryology

Normal development

The basic structures of the fetus are formed during the embryonic period of gestation, i.e. between postconceptual weeks 2 and 8. The skeleton of the head is composed of the neurocranium (calvaria or cranial vault), the viscerocranium (facial skeleton), and the cranial base. These structures are highly integrated, and their formation and development are closely interwoven. The cranial base is the foundation of the skull, and its formation and development greatly influence the morphology of the other components. Embryologically, the cranial base and facial complex are derived from neural crest tissues; the neurocranium arises from mesoderm [3,4].

The neural tube closes by the 3rd week of gestation. Its dorsal crests are composed of multipotent tissue that migrates widely into adjacent mesenchyme between the diencephalon and the cardiac swelling. Translocated neural crest cells undergo differentiation into a wide variety of cell types and form cartilage, bone, ligaments, muscles, and arteries of the cranial base and facial regions.

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

Cranial base

The cranial base extends from the foramen magnum to the frontonasal junction and consists of the sphenoid, petrous portion of the temporal bone, and cranial surfaces of the ethmoid bones. The pars basilaris of the clivus and the occipital bone are also part of the base. Phylogenetically, it is the oldest portion of the skull, and its development appears to be genetically determined. The bony structure is preceded by a cartilaginous structure, the chondrocranium, which first appears in the 6th week of gestation. Before chondrification, blood vessels, cranial nerves, and the spinal cord are established between the brain and extracranial sites. Centers of ossification appear during the 8th week of gestation. In contrast to the largely intramembranous bone of the cranial vault, which originates by direct ossification of mesenchyme, the osteogenic membrane, the cranial base is endochondral bone and formed from a cartilaginous prototype. Its sutures are cartilaginous joints (synchondroses), which grow by chondrocyte mitosis. The spheno-occipital synchondrosis is the principal site of growth in the cranial base during childhood.

The cranial base is an important shared junction between the cranial vault and face. Its inner surface relates to the brain and its outer surface relates to the nasopharynx and facial complex. Its shape and size strongly influence final calvarial morphology. The primary stimulus for growth of the cranial base is growth of the brain. The ventral parts of the frontal and temporal lobes determine the size and alignment of the floor of the cranial base, namely the anterior and middle cranial fossae [5]. The cranial base is, in turn, the template on which the upper face develops. Various junctures between the cranial base and facial bones, especially in the nasomaxillary complex, determine the influence of the cranial base on facial growth. The anterior cranial fossa is spatially related to the nasomaxillary complex. The middle cranial fossa is also related to the pharyngeal space and airway. The interposition of three sets of space-occupying sense organs complicates the attachment of these two skull components to each other and influences the growth of the facial skeleton in particular. These interactions become obvious in most craniofacial pathologies, e.g. in hyper- or hypotelorism, are associated with cranial vault or cranial base malformations or plagiocephaly with unilateral coronal synostosis with facial scoliosis.

Cranial vault

The cranial vault consists of the frontal, parietal, temporal, and occipital bones. The mesenchyme that precedes the cranial vault or neurocranium is derived from paraxial mesoderm and is at first arranged as a capsular membrane around the developing brain. Ossification of intramembranous calvarial bones requires the presence of the brain. According to the functional matrix concept, bone growth occurs in response to functional demands. The sutures of the calvaria can be considered interosseous ligaments that connect opposing bone surfaces. The bones of the calvaria are displaced outward by the expanding brain and deposit new bone at the contact edges of the sutures [5]. The ultimate size and shape of the cranial vault are therefore determined by internal hydrostatic pressures that the expanding brain and cerebrospinal fluid (CSF) pulsation waves exert on the cranial sutures. This stimulates compensatory sutural bone growth.

The face

Development of the head and face occurs between the 4th and 10th weeks of gestation by fusion of five facial swellings: the single frontal prominence and paired maxillary and mandibular prominences (Fig. 36.1). This depends upon the inductive activities of the prosencephalic and rhombencepahlic organizing centers, which are regulated by the expression of the sonic hedgehog gene as a signaling protein in the neural floor plate cells [6,7]. The rostral prosencephalic center induces the visual and inner ear apparatus, the upper third of the face, and the neurocranium. The caudal rhombencephalic center is responsible for the viscerofacial skeleton (i.e. middle and lower thirds of the face). Gradients of chemical and physical properties emanating from the organizing centers regulate the process of craniofacial formation [8]. The five facial swellings surround a central depression, which is the stomodeum or future mouth.

The frontal prominence encloses the forebrain from which pairs of thickened ectodermal surface placodes (nasal and optic) are derived. The nasal placodes invaginate to form the nasal passages. The surface ridges or nasomedial and nasolateral processes give rise to the nose, the philtrum of the upper lip, and the primary palate. The nasal complex is formed when the frontal prominence merges with the nasal capsule, which is part of the cranial base. The nasal capsule surrounds the olfactory organs and forms the cartilages of the nostrils and the nasal septum. Septal cartilage intervenes between the cranial base above and the palate below and plays a major role in subsequent growth of the midface. The optic placodes, which ultimately develop into eyes, are induced by lateral optic diverticula from the forebrain. Expansion of the cerebral hemispheres produces medial migration to a frontal position.

The maxillary and mandibular prominences are derived from the first branchial arch. The branchial arches are five segmented bilateral swellings of the pharyngeal foregut, consisting of a mesodermal core surrounded by neural crest tissue. The arches are separated by branchial grooves externally and pharyngeal pouches internally. The cartilaginous skeleton of the first arch, Meckel's cartilage, provides a template for development of the mandible. The ear and auditory apparatus are derived from the first and second arches and from the first groove and pouch. The external ear components migrate from an initial cervical location. The internal ear components arise from the otic placode, which is induced by the vestibulocochlear nerve. The rest of the branchial arches, grooves, and pouches form various parts of the pharynx and laryngeal apparatus.

The facial prominences and their skeletal cartilage, mesenchyme, and neurovascular bundles undergo cell proliferation, swelling, migration, and fusion in a critically timed series of events. Fusion of the paired mandibular prominences in the midline provides continuity of the lower jaw and lip. Fusion of the maxillary and mandible prominences laterally creates the commissures of the mouth. Fusion of the nasomedial processes and maxillary prominences provides continuity of the upper jaw and lip and separation of the stomodeal chamber into separate oral and nasal cavities. Fusion of the nasomedial processes in the midline forms the central upper lip, the tip of the nose, and the primary palate (Fig. 36.1).

During the 6th week of development, the secondary palate is formed from palatine shelves that initially grow inferiorly

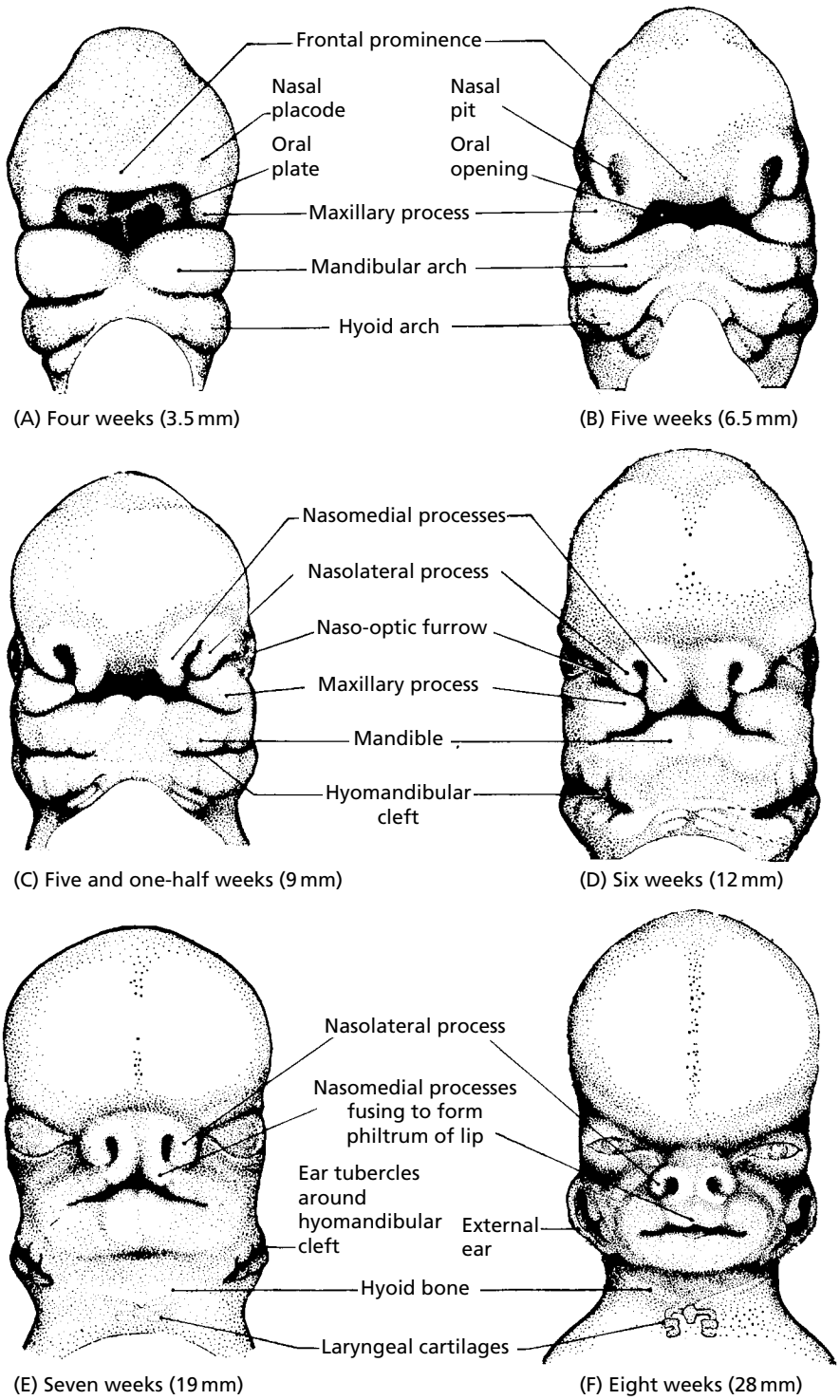


Figure 36.1 Stages in the embryonic development of the face. The median and paramedian structures from the upper lip to the forehead derive from the frontal prominence. The maxillary and mandibular regions, the ear, and the pharyngeal and laryngeal structures, derive from the branchial arches. *Source*: Reproduced from Patten [182] with permission of McGraw-Hill Companies.

from the maxillary prominences downward into the stomodeum and lateral to the tongue. Initially, these palatal shelves are widely separated from the primary palate owing to their vertical orientation on either side of the tongue. During the 7th and 8th weeks of gestation, coincident with longitudinal growth and straightening of the embryo and withdrawal of the tongue from between the shelves, the lateral palatal shelves rotate to a horizontal position and fuse with each other. The palatal mesenchyme then differentiates into bony and muscular elements that correlate with the position of the hard and soft palate, respectively. In addition to fusing in the midline, the secondary palate fuses with the primary palate and the nasal septum. These fusion processes are complete by the 10th week of embryogenesis; development of the mammalian secondary palate thereby divides the oronasal space into separate oral and nasal cavities, allowing mastication and

respiration to take place simultaneously [9]. The nature of the "intrinsic shelf force" responsible for this reorientation is unknown, although mouth-opening reflexes, which involve withdrawal of the face from against the heart prominence, have been implicated in the withdrawal of the tongue from between the vertical palatal shelves.

The neural crest tissue gives rise to the facial skeleton, and the mesoderm will form the facial muscles. Current studies demonstrate the influence of the cranial base as it adjusts to its broader structural context and provides added support for the developmental and structural integration of the cranial base with both the cranial vault and face [10]. During facial development, cells are monitored by genetically determined pathways and adjust their rates of accumulation, apoptosis, and hyperplasia to produce organs of predetermined size [11]. Forward growth of the mandible relocates the tongue more anteriorly. Successful fusion of the components of the palate by the 12th week requires a complicated synchronization of shelf movements with withdrawal of the tongue and growth of the mandible. By this time, the face takes on a human appearance.

KEY POINTS: CRANIOFACIAL EMBRYOLOGY

- The cranial base is an important junction between the cranial vault and face. Its inner surface relates to the brain and its outer surface relates to the nasopharynx and facial complex
- The ultimate size and shape of the cranial vault are determined by internal hydrostatic pressures that the expanding brain and CSF pulsation waves exert on the cranial sutures
- Septal cartilage intervenes between the cranial base above and the palate below and plays a major role in subsequent growth of the midface

Anomalous development

Various genetic and environmental factors cause anomalous craniofacial development [12]. The etiology of craniofacial syndromes and craniosynostosis is heterogeneous and multifactorial. Genetically based malformations may be caused by single-gene deficiencies or by chromosomal aberrations. Genes for several autosomal dominant craniofacial malformations have recently been defined: mutations in genes regulating fibrous growth factor receptors (FGFR-1, -2, -3, -4) and transforming growth factors (TGF-1, -2, -3) as well as *MSX2* and *TWIST* genes [13–15]. The identified gene loci associated with cleft lip and palate include regions on chromosomes 1, 2, 4, 6, 14, 17, 19, and X (*MHFR*, *TGFA*, *D4S175*, *F13A1*, *TGFB3*, *D17S250*); gene products (e.g. TGFA, TGFβ3, MSX1, IRF6, TBX22, GSTM1) also often act as growth factors [16,17]. Currently, there are no specific tests available for genetic susceptibility to orofacial clefts. Environmental factors include congenital infections, irradiation, and exposure to chemical teratogens, such as phenytoin, vitamin A analogs, and alcohol. For many malformations, the etiology is unknown.

Maldevelopment can occur through several mechanisms. Malformations that develop during the embryonic period are distinct from deformations that occur later in the fetal period and may be self-correcting with postnatal catch-up growth [6]. Fetal or postnatal head restraint can also cause premature fusion of cranial sutures [15]. Malformations can originate in anomalies of neural crest cells that may be deficient in number, may not complete migration, or may fail to cytodifferentiate. Neural crest tissues also form much of the cardiac conotruncal septum, and there is an association between craniofacial and cardiovascular malformations in syndromes in which neural crest defects play a role [18,19]. Examples include retinoic acid syndrome, DiGeorge syndrome, the CHARGE association (*C*, coloboma of the eye/central nervous system anomalies, *H*, heart defects, *A*, atresia of the choanae, *R*, retardation of growth and/or development, *G*, genital and/or urinary defects, *E*, ear anomalies and/or deafnes), and some variants of hemifacial microsomia. Malformations can also be caused by intrauterine compression of the embryo early in gestation. For example, in the amnion rupture sequence, early rupture of the amnion leads to defective morphogenesis secondary to compression of the embryo. In addition, adherence of amniotic bands to developing embryonic structures may interfere with normal development and result in simple to bizarre malformations that are not associated with embryological lines of fusion.

Malformations may result from intrauterine vascular accidents. For example, a shift in the blood supply of the face from the internal to the external carotid artery occurs during the 7th week of gestation when the normal stapedial artery atrophies. This shift occurs at a critical time of midface and palate development and has the potential to cause deficient blood supply and defects of the midface, upper lip, and palate. Malformations can also be secondary to defects in brain development because all components of the skull depend on the brain development [12–15,20,21]. Several syndromes are described below.

KEY POINTS: ANOMALOUS DEVELOPMENT OF CRANIOFACIAL STRUCTURES

- Successful fusion of the components of the palate by the 12th week requires a complicated synchronization of shelf movements with withdrawal of the tongue and growth of the mandible. By this time the face takes on a human appearance
- Genetically based malformations may be caused by single-gene deficiencies or by chromosomal aberrations
- Neural crest tissues also form much of the cardiac conotruncal septum, and there is an association between craniofacial and cardiovascular malformations in syndromes in which neural crest defects play a role like the DiGeorge syndrome and CHARGE association
- Malformations may result from intrauterine vascular accidents. For example, a shift in the blood supply of the face from the internal to the external carotid artery occurs during the 7th week of gestation. Deficient blood supply may cause defects of the midface, upper lip, and palate

Table 36.1 Nomenclature of craniosynostosis

Affected suture	Traditional name	Literal translation
Sagittal	Scaphocephaly	Boat skull
Metopic	Trigonocephaly	Triangle skull
Unilateral coronal	Plagiocephaly*	Oblique skull
Bicoronal	Brachycephaly	Short skull
Multiple sutures	Acrocephaly†	Topmost skull
	Turricephaly†	Tower skull
	Oxycephaly	Sharp skull
	Kleeblattschadel	Cloverleaf skull

* Plagiocephaly is not necessarily synonymous with unilateral coronal synostosis.
† Some authors use acrocephaly and/or turricephaly synonymously with brachycephaly to indicate bicoronal synostosis.
Source: Reproduced from Marsh [181] with permission from Elsevier.

Box 36.1: Exogenous causes and predisposing conditions in craniosynostoses

- Congenital infections
- Radiation exposition
- Pre-/postnatal pressure-induced skull restriction
- Chemical teratogens:
  - Phenytoin
  - Vitamin A
  - Alcohol
- Mucopolysaccharidoses (Hurler, Morquio)
- Metabolic diseases:
  - Rickets
  - Hyperthyroidism
  - Hypophosphatasia
- Hematological diseases:
  - Polycythemia vera
  - Thalassemia

Source: Reproduced from Messing-Jünger and Martini [26] with permission of Springer Nature.

Craniosynostosis

Precocious brain development is reflected by rapid head enlargement, beginning in early gestation and continuing through the first postnatal year. Craniosynostosis, or premature closure of the cranial sutures, restricts skull growth in the affected region. Single suture synostosis leads to characteristic skull deformities as growth is inhibited in the synostotic suture and compensated by increased skull expansion in non-affected areas (Table 36.1). The degree of skull deformity depends on the number of sutures involved and the time at which premature fusion begins. The earlier the synostosis, the greater the deformity, which may result in a reduced intracranial volume. If the expanding cerebral structures find a restricted intracranial volume, intracranial hypertension may result. Several different mechanisms are responsible for craniosynostosis [12–15].

The causes can be multifactorial. Multiple pregnancies and other fetal head-constraining conditions are possible causes for non-syndromic craniosynostes, but also metabolic, storage or hematological disorders as well as genetic defects (Box 36.1). More than 180 syndromes with associated craniosynostosis have been described and up to 57 involved genes identified.

Table 36.2 Craniosynostosis syndromes

Syndrome	Chromosome localization	Gene
Apert syndrome	10q25.3-q26	*FGFR2*
Crouzon syndrome	10q25.3-q26	*FGFR2*
Jackson–Weiss syndrome	10q25.3-q26	*FGFR2*
Beare–Stevenson cutis gyrata syndrome	10q25.3-q26	*FGFR2*
Pfeiffer syndrome	10q25.3-q26	*FGFR2*
	8p11.2-p12	*FGFR1*
Thanatophoric dysplasia	4pl6	*FGFR3*
Crouzonodermoskeletal syndrome	4pl6	*FGFR3*
Muenke craniosynostosis	4pl6	*FGFR3*
Craniosynostosis, Boston type	5qter	*MSX2*
Saethre–Chotzen syndrome	7p21-p22	*TWIST*

Source: Courtesy of M. M. Cohen, Jr.

Box 36.2: Secondary craniosynostosis

Storage disorders
- Hurler
- Morquio

Metabolic disorders
- Rickets
- Hyperthyrioidism

Hematological disorders
- Polycythemia vera
- Thalassemia

In 85% a monogenetic background is found, mainly as multiple mutations in single genes. Only 15% of craniosynostotic conditions are caused by chromosomal aberrations. They can either be numeric chromosomal aberrations or deletions and duplications. The *FGFR2* gene is most often affected in 56.3% followed by the *FGFR3* gene (24.4%). Non-syndromic craniosynostosis may also be partially induced by genetic alterations. Genome-wide association studies may identify chromosomal susceptibility loci [22–24].

Typical craniosynostosis syndromes follow Mendelian genetic patterns and the involved genes and chromosomal localizations are well known (Table 36.2). Crouzon, Apert, Pfeiffer, and Jackson–Weiss syndromes, once thought to be separate but overlapping entities, are known to result from different mutations of the same genes [25]. In syndromic families, some members have normal phenotypes but different sutures can be affected in different individuals. Secondary craniosynostosis due to microcephaly and early CSF shunting in preterm babies are also well known conditions, as well as the influence of teratogens like diphenylhydantoin, aminopterin, methotrexate, retinoid acid, oxymetalzoline, and valproic acid (Box 36.2) [26].

Craniosynostosis may be an isolated deformation or part of a malformation syndrome. Isolated non-syndromic craniosynostosis occurs in six in every 10,000 births [12]. Sagittal synostosis is most common in more than 50%, followed by metopic synostosis and uni- or bilateral coronal synostosis. Lambdoid synostoses are very rare. Recently, a significant increase of trigonocephaly has been observed, without

knowing the underlying cause yet [27]. In single-suture craniosynostosis only deformation of the skull is obvious, although slight changes in cerebral architecture also have been described recently. Syndromic craniosynostoses most often also involve cranial base and facial structures and other parts of the skeleton.

Single suture craniosynostosis

The typical skull deformities following single-suture craniosynostosis are the result of compensatory growth (Fig. 36.2). The cephalic index (maximum biparietal diameter multiplied with 100 divided by maximum anteroposterior diameter) was introduced by the Swedish anatomist Anders Retzius and is used to measure the extent of deformity as well as for follow-up of later head development. Not all premature craniosynostoses lead to an obvious skull deformity. Typical anthropomorphic skull types are dolichocephalic (long headed), brachycephalic (broad headed), and mesocephalic (moderate head form).

Sagittal craniosynostosis

This is the most frequent form of craniosynostosis and presents the typical scaphocephalic form of skull with an elongated anteroposterior diameter and a narrowed biparietal diameter. The fused sagittal suture often forms a bony ridge and resembles the keel of a boat. The biparietal region is particularly narrow and sometimes lowered (Fig. 36.3). Frontal and/or occipital bossing can be very prominent and result from compensatory skull growth. The head circumference is generally increased, and the head is dolichocephalic. In 11% of cases, additional morphological brain changes were found on magnetic resonance imaging (MRI) studies.

Unicoronal craniosynostosis

The unilateral supraorbital ridge is retruded and the contralateral side sometimes compensates for the lack of growth and protrudes. In most cases, there is facial scoliosis that is caused by unilateral midface involvement. The deformity is described as anterior plagiocephaly. Patients may squint and have a compensatory head tilt (Fig. 36.4).

Bicoronal craniosynostosis

This entity can be syndromic and a genetic work-up is indicated. The head circumference is decreased, due mainly to a marked flattening of the forehead (Fig. 36.5). The orbits and both temporal squamae protrude. Additional turricephalic compensation

Figure 36.3 Scaphocephalic child with typical biparietal narrowing and resulting flattened head.

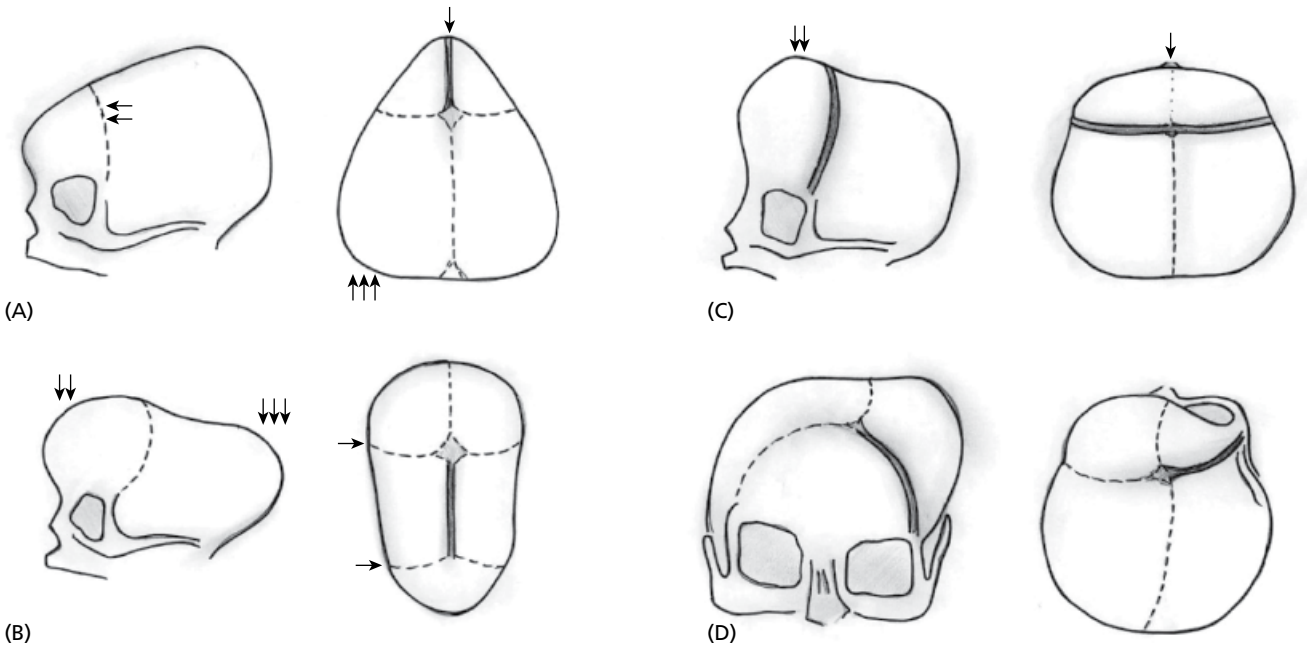


Figure 36.2 Single-suture craniosynostosis results in specific cranial deformities. (A) Trigonocephaly is the result of premature closure of the metopic suture and typical features are a frontal keel (↑), anterior displacement of the coronal sutures (↑↑), and compensatory bulging of the parietal squamae (↑↑↑). (B) Scaphocephaly is characterized by bitemporal or biparietal narrowing (↑) and frontal (↑↑) and occipital (↑↑↑) compensatory bossing. The shape of the skull resembles the keel of a boat or a saddle. (C) Brachycephaly means short skull and is the result of bicoronal craniosynostosis. The frontal region is flattened (↑) and some cases show early compensatory oxycephalic deformity (↑↑). (D) Anterior plagiocephaly results from unilateral coronal synostosis and causes asymmetrical and rotational deformity of the fronto-orbital region with additional midface and skull deformities.

Figure 36.4 Facial scoliosis in a child with anterior plagiocephaly.

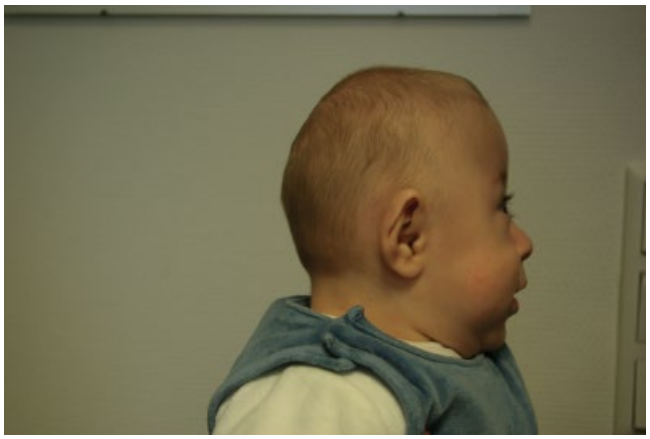


Figure 36.5 Brachycephalic head caused by bicoronal craniosynostosis.

Figure 36.6 (A) Hypotelorism in metopic synostosis. (B) Frontal keel.

can occur. This is the typical picture of a brachycephalic head. Early surgery is sometimes necessary to treat elevated intracranial pressure. The midface is often also involved.

Metopic craniosynostosis

The skull deformity with metopic craniosynostosis varies from a frontal ridge to severe trigonocephaly with narrowing of the frontal region and a keel-shaped forehead with hypotelorism and epicanthal folds (Fig. 36.6). It can be associated with genetic syndromes such as Opitz C syndrome or trisomy 11. The head circumference is usually decreased.

Lambdoidal craniosynostosis

Isolated lambdoidal craniosynostis is rare and accounts for only 3% of all premature synostoses. Most of the clinical forms of posterior plagiocephaly are positional deformities and do not require surgical correction. In true lambdoidal craniosynostosis, the contralateral forehead bulges forward. In cases that are caused by position, there is ipsilateral bossing.

Syndromic craniosynostosis

Craniosynostosis syndromes that are also associated with hand and feet abnormalities are described as acrocephalosyndactylies.

Apert syndrome

Apert syndrome is the most severe of several craniosynostosis syndromes that involves all the craniofacial structures: calvaria, cranial base, and face. Apert syndrome occurs in approximately one per 55,000 births due to mutations in the *FGFR2* gene on chromosome 10 [22]. Although the mode of transmission can be autosomal dominant, most cases are sporadic. Apert syndrome is characterized by craniosynostosis, midface hypoplasia, and retrusion plus symmetrical syndactyly of the hands and feet (Fig. 36.7). The dysmorphic features are listed in Box 36.3.

In Apert syndrome the craniosynostosis involves multiple cranial sutures, but most commonly involves the coronal sutures and causes brachycephaly. The occiput is usually flattened. The cranial base has a broad, flat, short contour with premature synostosis. The anterior cranial fossa is markedly shortened, which constrains development of the nasomaxillary complex. The nasal cavity, palate, and maxilla are shortened, narrowed, and retropositioned. The midface hypoplasia and brachycephaly result in proptosis because the orbits are too shallow to house the globe. The middle cranial fossa is rotated to a more vertical position than normal, which secondarily diminishes the dimensions of the pharynx. The interorbital space is always large, and the orbits may be misaligned. The shortened cranial base results in a vaulted cranium and a deep forehead. Platybasia, Chiari malformation, and hydrocephalus are relatively common. Severe dental malocclusion is typical. Lateral skull base deformities are responsible for a

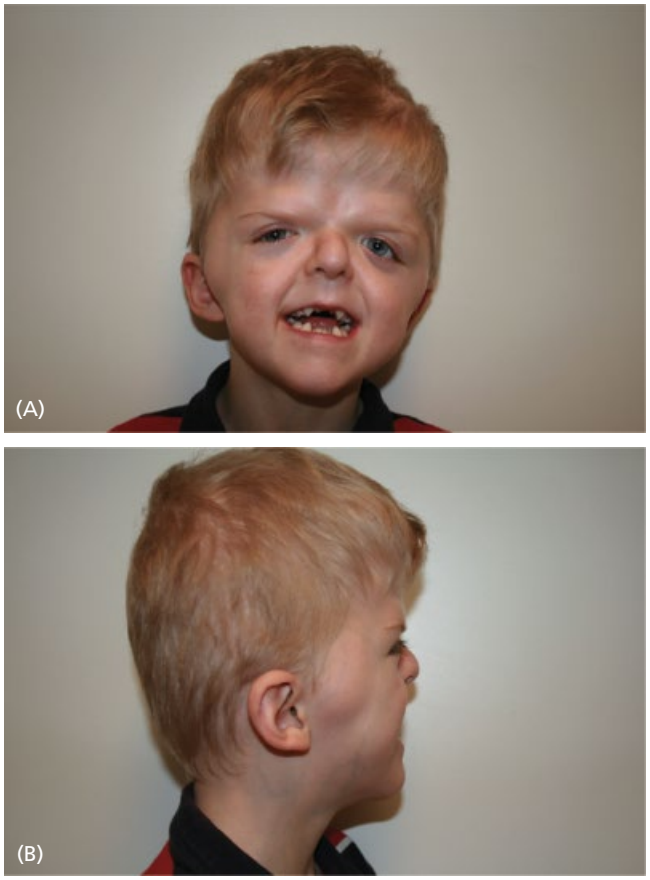


Figure 36.7 Six-year-old boy with typical features of Apert syndrome. (A) Down-slanting palpebral fissures, depressed nasal bridge, and dental malocclusion. (B) Flat facies due to midface hypoplasia.

high rate of hearing disorders. A significant number of patients are mentally retarded; most of the children have IQs below 80.

Saethre–Chotzen syndrome

Phenotypically variable, the relatively common Saethre–Chotzen syndrome is often misdiagnosed. Because mild forms may not be recognized, the true incidence is unclear. Typical features are brachy- and acrocephalic deformities, mostly due to bicoronal abnormalities and plagiocephaly (Fig. 36.8). The hairline is low and the facial appearance broad, flat, and asymmetrical. The nose is beaked, and there may be ptosis of the eyelids. The inheritance pattern is autosomal dominant.

Pfeiffer syndrome

The clinical phenotype of Pfeiffer syndrome is variable. Patients typically show a turribrachycephalic deformity that is mostly due to abnormal bicoronal sutures. Cloverleaf heads have also been reported. Hypertelorism, proptosis, maxillary hypoplasia, mandibular prognathism, and malocclusion occur as well. Ankylotic joints are typical skeletal findings. Severe skull base anomalies are associated with platybasia and Chiari malformation and also with spinal malformations and vertebral fusion. The incidence of this syndrome is about one in 210,000; its inheritance is autosomal dominant. Early surgical correction of the constraining skull structures can lead to normal neurocognitive development if brain growth is not impaired.

Crouzon syndrome

The phenotype of this syndrome is characterized by brachycephaly caused by bicoronal synostosis, maxillary hypoplasia, and shallow orbits that lead to ocular proptosis and a beaked nose. Besides coronal synostosis, scaphocephaly, trigonocephaly, and cloverleaf skull may also exist. Skull base abnormalities with platybasia and Chiari malformations are also found. Due to the midfacial deformities, nasopharyngeal airway obstruction is common and may lead to sleep apnea and impaired nose breathing. This may be a problem if the mouth is closed during a mask induction. The prevalence of Crouzon syndrome is one per 25,000 livebirths, with about two-thirds of cases being familial (autosomal dominant) and one-third sporadic. Neurocognitive development is rarely affected.

Cloverleaf skull (Kleeblattschädel)

The cloverleaf skull deformity is the most severe form of craniostenosis and is most often associated with Pfeiffer syndrome. All major sutures and the skull base are involved which produces marked constriction of intracranial structures, including the rapidly developing brain and its vessels, especially important venous structures. Early surgery is mandatory to protect the brain. Chiari malformation and hydrocephalus are common accompaniments of this lesion and need to be treated early as well. Other deformities are hypertelorism, orbital proptosis with visual impairment, and a hypoplastic skull base and midface structures that produce upper airway problems.

Other relatively common craniofacial syndromes are the Jackson–Weiss and Carpenter or Antler–Bixler syndromes.

Facial anomalies

Branchial arch malformations

Branchial arch anomalies are symptom complexes caused by deficient development of the branchial arches. They are etiologically and pathogenetically heterogeneous [12] with wide variability in expression. External ear deficiencies, auricular tags, and persistent branchial clefts or cysts are common branchial arch anomalies. Micro- or macrostomia results from abnormal merging of the maxillary and mandibular prominences. These abnormalities are examples of severe first arch anomalies. Micrognathia, also a first arch anomaly, is the result of retarded mandibular development by any mechanism; it may be an intrinsic malformation or a deformation by the chin being compressed against the chest late in gestation.

Treacher Collins syndrome (mandibulofacial dysostosis)

Treacher Collins syndrome occurs with an incidence of one in 50,000 livebirths and involves structures derived from the first and second branchial arches [12]. The major facial features include midface hypoplasia, micrognathia, microtia, conductive hearing loss, and a cleft palate that is caused by deficiencies of the maxillary and branchial arch mesenchyme (Fig. 36.9). The syndrome can be an autosomal dominant disorder with variable expressivity, but over 50% of cases are new mutations. The gene responsible for this syndrome has

Box 36.3: Features of Apert syndrome

Craniofacial dysmorphology

- Craniosynostosis:
  - Coronal synostosis most common
  - Steep full forehead (frontal bossing)
  - Flat occiput
  - ± Hydrocephalus
- Maxillary retrusion (midface hypoplasia):
  - Flat facies
- Shallow orbits:
  - Exorbitism or proptosis
- Relative mandibular prognathism
- Variable facial asymmetry
- Supraorbital horizontal groove
- Hypertelorism
- Down-slanting palpebral fissures
- Strabismus
- Parrot-beaked nose
- Depressed nasal bridge
- Cleft palate or bifid uvula
- Trapeziodal-shaped (cupid's) lips
- High arched palate
- V-shaped maxillary dental arch
- Severe tooth crowding
- Dental malocclusion
- Reduced nasopharyneal dimensions

Limb dysmorphology

- Syndactyly:
  - Osseous and/or cutaneous
  - Fingers and toes
  - Digits 2, 3, and 4 always
  - Symmetrical
- Thumb and great toe malformations

Occasional abnormalities

- Cardiovascular:
  - Atrial septal defect
  - Over-riding aorta
  - Ventricular septal defect
  - Pulmonic stenosis
  - Coarctation of aorta
  - Endocardial fibroelastosis
  - Pulmonary artery atrophy
- Skeletal:
  - Aplasia or ankylosis of joints
  - Synostosis of radius and humerus
  - Short humerus
  - Cervical spine fusion
- Pulmonary:
  - Pulmonary aplasia
  - Cartilaginous anomalies
  - Tracheoesophageal fistula
- Gastrointestinal:
  - Pyloric stenosis
  - Ectopic anus
- Renal:
  - Polycystic kidney
  - Hydronephrosis
- CNS:
  - Mental retardation
  - Hearing deficit

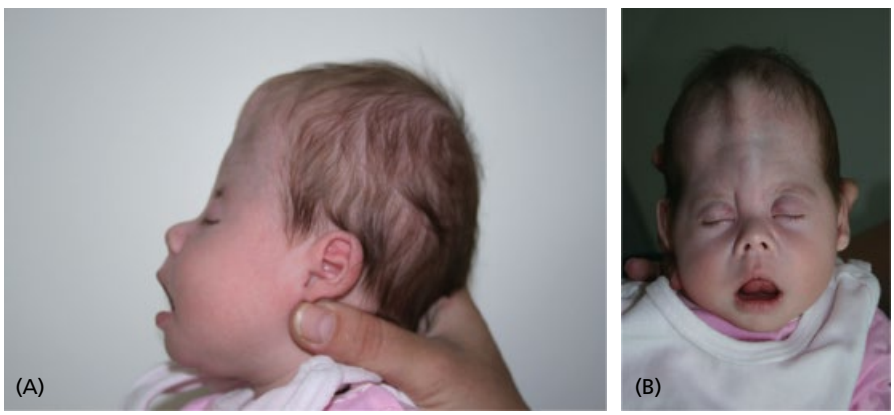


Figure 36.8 Infant with Saethre–Chotzen syndrome. (A) Brachycephaly. (B) Metopic ridge due to premature synostosis and turricephaly.

been mapped to chromosome 5q31.3-32. The mutation causes aberrant expression of a nucleolar protein named treacle. The abnormalities are bilateral, usually symmetrical, and confined to the craniofacial complex (Box 36.4). Besides the facial features, the patients often have choanal atresia, microphthalmia, absence of the parotid gland(s), and congenital heart disease. Mental deficiency is not common.

The characteristic facial appearance is the product of an abnormal cranial base and a dysmorphic mandible and maxillary–malar complex [28]. The face is narrow, with downsloping palpebral fissures, depressed cheekbones, and a large down-turned mouth. The cranial base angle (nasion-sella-basion angle) is reduced, which positions the posterior pharynx forward. The pharyngeal dimensions are reduced in all dimensions by several hypoplastic skeletal elements [28–31]. Some patients also exhibit a discrete area of constriction near the base of the tongue, such as occurred in an 11-year-old patient whose pharyngeal lumen was 5 mm wide [29]. Little correlation exists between the degree of pharyngeal hypoplasia and the severity of the facial deformity. The malar (cheek) bone is hypoplastic and the orbital wall is deficient. The mandible is disfigured in all dimensions.

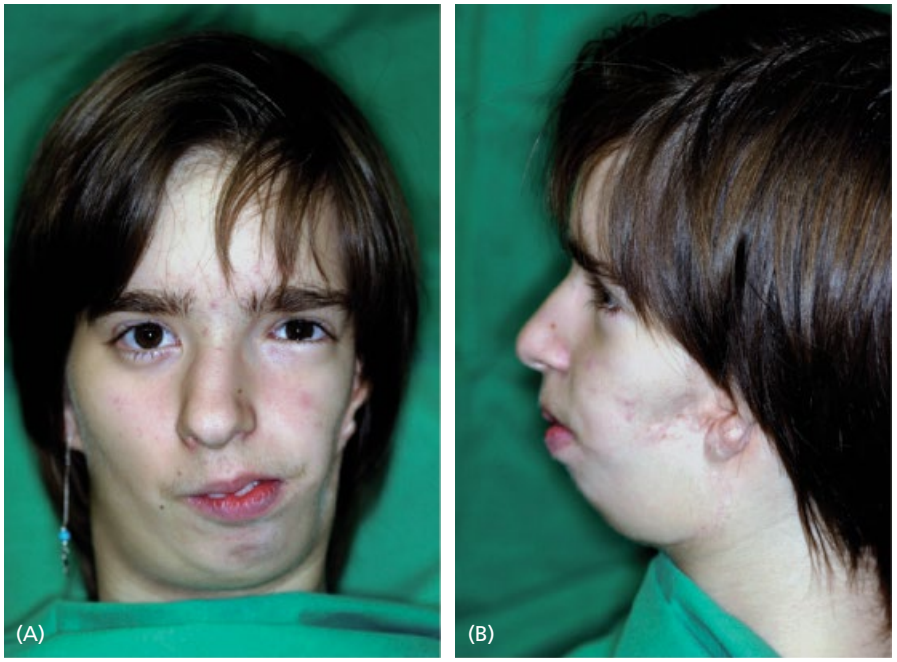


Figure 36.9 Fifteen-year-old girl with mandibulofacial dysostosis. She has no mental deficiencies but has malar deficiencies, auricle malformation, microtia, and a retrognathic mandible.

Box 36.4: Features of Treacher Collins syndrome

Facial dysmorphia

- Skeletal hypoplasia/aplasia:
  - Malar and zygomatic bones
  - Supraorbital ridges
  - Mandible
- Facial muscle hypoplasia/hypotonia
- Eye:
  - Lower lid coloboma or notching
  - Partial absence of lower eyelashes
  - Antimongoloid slant to palpebral fissures
- Ears:
  - Auricle malformation, misplacement
  - Ear canal defects, conductive deafness
  - Inner ear malformations
  - Non-pneumatized mastoid
- Pharyngeal hypoplasia
- Dental malocclusion
- High arched palate
- Projection of scalp hair onto lateral cheek
- Bind fistulas, dimples, or tags between the ears and angle of the mouth

Occasional abnormalities

- Macrostomia
- Microstomia
- Cleft palate
- Velopharyngeal incompetence
- Upper eyelid coloboma
- Choanal atresia
- Microphthalmia
- Absence of parotid gland
- Congenital heart disease
- Mental deficiency not common

Nager and Miller syndromes are characterized by facial features that are similar to those of Treacher Collins plus limb deformities.

Robin sequence

The Pierre Robin sequence (PRS – MIM 261800) is a well-defined subgroup of the cleft lip and/or palate population with an unknown etiology of the branchial arch. PRS is characterized by cleft palate, micrognathia, and respiratory difficulties (due to glossoptosis) in the early neonatal period, and is often observed as a part of other Mendelian syndromes such as Stickler syndrome, velocardiofacial syndrome, and Marshall syndrome or fetal alcohol syndromes [32,33]. PRS is also a part of campomelic dysplasia (MIM 114290), consisting of bowing of the long bones, malformation of the pelvis and spine, rib anomalies, club feet, hypoplastic scapulae, micrognathia, and cleft palate [34]. In a "sequence," some anomalies are secondary to a primary anomaly, whereas in a syndrome, multiple anomalies have a single pathogenesis. The PRS may be the result of deregulation of *SOX9* and *KCNJ2* [35]. The pathogenesis of the Robin sequence is diverse, but the common feature is failure of mandibular development and secondary failure of the tongue to descend from between the palatal shelves. When this is an isolated finding, the deformity may be due to intrauterine mandibular constraint. The mandible is intrinsically normal and will undergo catch-up growth postnatally [6]. If the Robin sequence is associated with a syndrome that includes intrinsic mandibular hypoplasia, the mandible remains small.

Oculo-auriculovertebral spectrum: Goldenhar syndrome and hemifacial microsomia

The oculo-auriculovertebral spectrum (OAVS) is also known as the first and second branchial arch syndrome, hemifacial microsomia, Goldenhar syndrome, or facio-auriculovertebral

syndrome. This condition is caused by maldevelopment of the first and second branchial arches and is complex and heterogeneous. There is defective facial development involving the ear, eye, zygomatic bone, mandible, parotid gland, tongue, and facial muscles. Maldevelopment is not limited to facial structures: cardiac (tetralogy of Fallot, ventricular septal defect), pulmonary (hypoplasia or aplasia of lung), renal, skeletal (vertebral anomalies, commonly cervical), central structures (cranial nerve anomalies), and other anomalies, including laryngeal anomalies, also occur. The abnormalities present in various combinations, tend to be asymmetrical and are unilateral in 70% of cases [20]. Malformations of the external ear or microtia are mandatory features of the OAVS and occur as an isolated malformation (population frequency of 0.03%), or in association with other anomalies such as mandible hypoplasia, epibulbar dermoids, and spinal vertebral defects. The constellation of anomalies suggests that they originate at approximately 30–45 days of gestation.

It has been suggested that disturbances in the branchial arches or in the neural crest cells impede development of adjacent tissues. A vascular pathogenesis caused by hematoma formation at the time the stapedial artery system develops has been demonstrated in animals [36]. In this model, focal hemorrhage and an expanding hematoma destroy tissues in the ear and jaw areas. Three unrelated children have been reported with similar unilateral craniofacial defects and other structural abnormalities that had a known disruptive vascular pathogenesis [37]. The frequency of occurrence is estimated to be one in 3000–5000 births. The condition is usually sporadic, although familial instances have been reported. Several chromosomal anomalies have been associated with this condition, and it has occurred in infants born to mothers who had taken thalidomide, primidone, or retinoic acid. It is usually discordant in monozygotic twins.

Maxillary, mandibular, and auricular hypoplasia is the primary feature of this syndrome. Macrostomia is the result of a lateral facial cleft from the commissure of the mouth. Mandibular condyle deformities, present in all patients, range from slight hypoplasia to complete absence of the condyle with agenesis of the ascending ramus. When accompanied by epibulbar dermoid and vertebral anomalies it is called the Goldenhar syndrome, and when it occurs predominantly unilaterally it is called hemifacial microsomia. Most of these patients have normal intelligence.

KEY POINTS: CRANIOSYNOSTOSIS AND BRANCHIAL ARCH MALFORMATIONS

- Sagittal craniosynostosis is the most frequent form and presents the typical scaphocephalic skull with elongated anteroposterior diameter and narrowed biparietal diameter
- Apert syndrome is the most severe of several craniosynostosis syndromes involving all of the craniofacial structures: calvaria, cranial base, and face. A difficult airway is common.
- The large group of facial anomalies, including Pierre Robin sequence, and the Goldenhar, Treacher Collins, Crouzon, and Apert syndromes could make it extremely difficult to intubate the trachea due to disfigured mandibles in all dimensions, often associated with retrognathia

Hypertelorism and orbital malposition

Orbital malposition may occur in any direction and may involve different directions in each orbit. The bones and sutures making up the walls of the orbits may be primarily involved. The malposition may also be the result of craniosynostosis or craniofacial clefting. It may be associated with encephalocele, tumor, or other cranio-orbital malformations. Other cranio-orbital malformations include encephaloceles that involve craniofacial structures; with frontoethmoidal or sincipital and basal subtypes (nasofrontal, nasoethmoidal, naso-orbital, and transethmoidal) [38]. These malformations lead to significant naso-orbital deformities (Figs 36.10 and 36.11). One of the most disfiguring tumors of the orbital region is the plexiform neurofibroma that is associated with neurofibromatosis type 1. Isolated orbital hypertelorism is a skeletal deformity that consists of lateralization of the bony orbit and enlarged ethmoid sinuses. The nose may be slightly involved or severely distorted, and the nasal deformity may be difficult to correct. Dysfunction of the upper eyelid, extraocular muscles, and lacrimal system frequently occurs. Orbital hypotelorism is uncommon and is seldom present as an isolated anomaly. It is often seen in metopic craniosynostosis.

Facial clefts

Facial clefting occurs when the skeleton or soft tissues are interrupted. Clefts develop when the facial prominences fail to merge. Clefts that cannot be explained embryologically may be caused by disruptive factors [12]. The causes of most clefts are unknown, and the majority occur sporadically. Skeletal and soft tissue hypoplasia or aplasia are the anatomical defects of craniofacial clefts. Any part of the cranium or face may be involved. Various combinations of eye, ear, and central nervous system (CNS) deformities are associated with clefts.

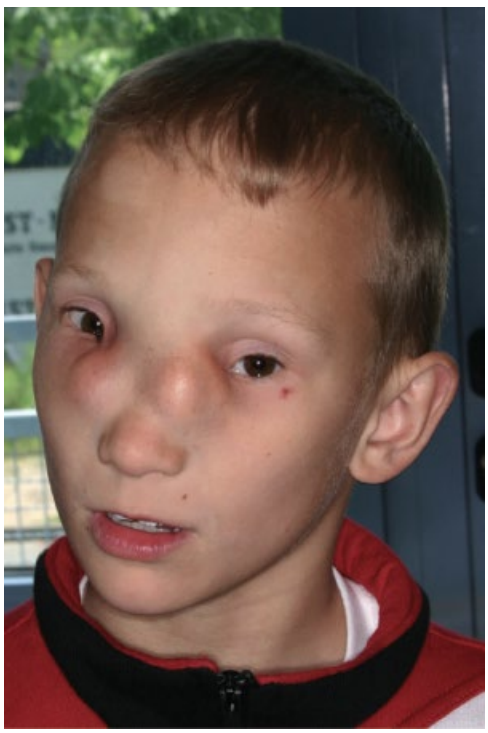


Figure 36.10 Twelve-year-old boy with frontoethmoidal encephalocele with maxillary involvement and hypertelorism.

Tessier devised an anatomical and descriptive classification that correlates clinical appearance with surgical anatomical findings [39]. This system designates l5 locations (numbered 0 through 14) for clefts and describes their respective courses through bone and soft tissue (Fig. 36.12). Many syndromes that include hypoplastic facial dysmorphology are categorized as clefts. Treacher Collins syndrome includes clefts 6, 7, and 8 in its complete form (see Fig. 36.9) and cleft 6 in its incomplete form. Cleft 6 accounts for the eyelid coloboma; cleft 7 for the absence of the zygomatic arch, anterior displacement of the scalp hair, and mandible deformities; and cleft 8 for the defects in the lateral orbital rim. The oculo-auriculovertebral spectrum (hemifacial macrosomia and Goldenhar) is cleft 7.

Cleft lip and palate

Cleft lip and/or palate are the most frequent congenital craniofacial malformations. They occur in one in 700 births in the United States, and there is a marked racial predilection. The highest incidence is found in parts of Latin America and Asia (China, Japan), the lowest in Israel, South Africa, and southern Europe. Rates of isolated cleft palate are high in Canada and parts of northern Europe and low in parts of Latin America and South Africa [9]. Clefts may be isolated, familial, or part of a syndrome. More than 400 syndromes are associated with facial clefts [12]. Cleft lip, cleft palate, or both can be part of a syndrome, but more syndromes are associated with cleft palate than with cleft lip. They constitute a heterogeneous group of malformations with great variability in the degree of cleft formation (Fig. 36.13). A cleft lip may be complete, incomplete, or only a microform with a small vermillion notch. Osseous defects in the alveolus and the palate of patients with complete labial clefts contribute to instability of the dental arch; sometimes there is collapse of the lateral segments of the arch. For cleft classification, Kriens proposed the LAHSHAL code to represent clefts of the left and right (L)ip and (A)lveolus, as well as the (H)ard and (S)oft palate based on the anatomical structures involved [40].

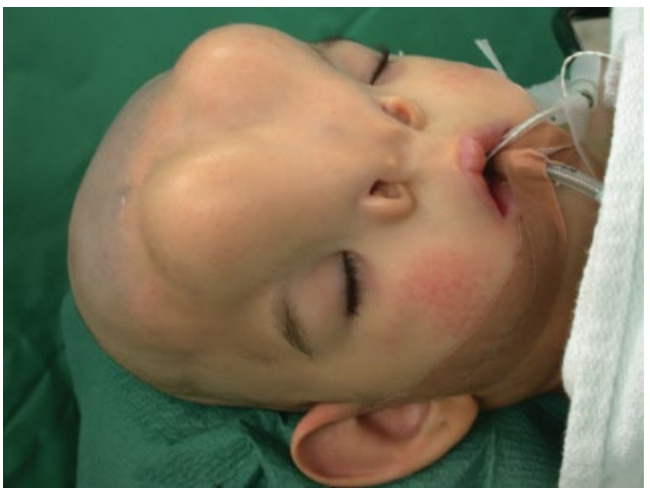


Figure 36.11 Infant with frontonasal cleft and related encephaloceles and hypertelorism.

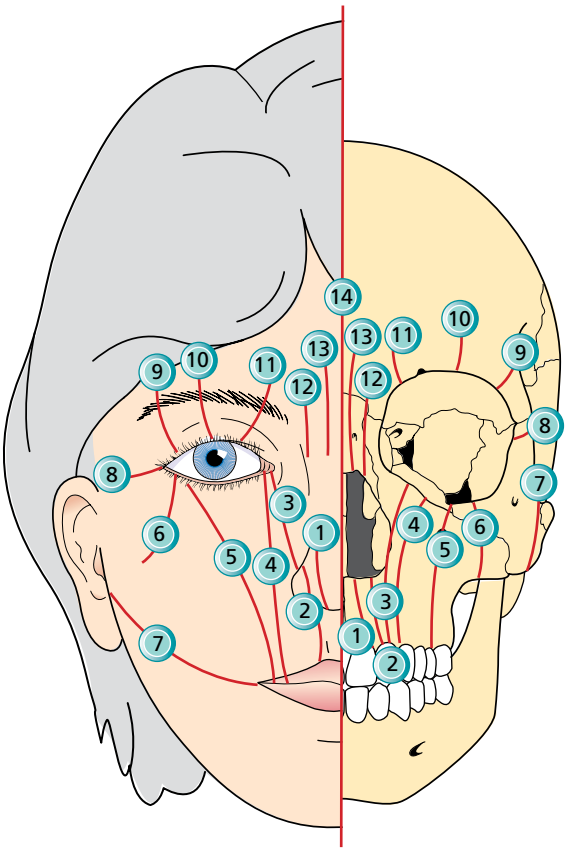


Figure 36.12 Tessier's classification of facial clefts. (Left) Locations of clefts on the face. (Right) Skeletal pathways.

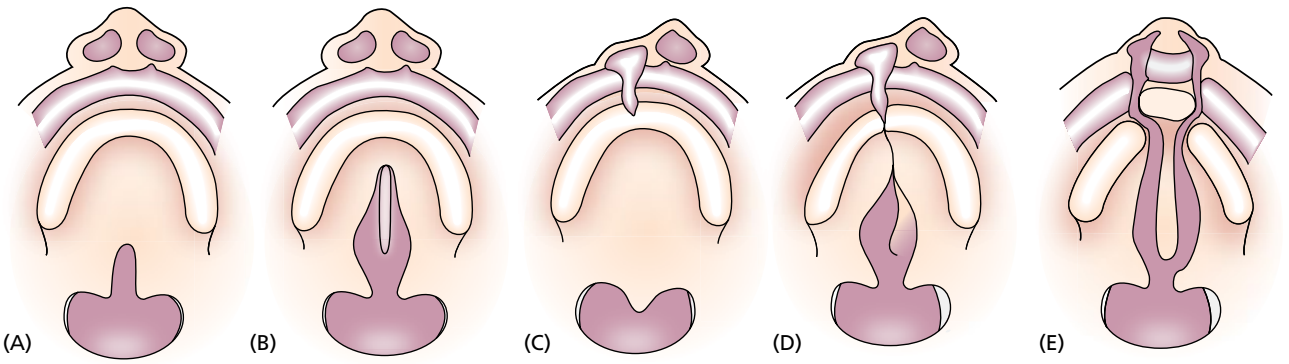


Figure 36.13 Various degrees of cleft palate and lip. (A) Cleft soft palate. (B) Cleft hard and soft palate. (C) Cleft lip and alveolus. (D) Complete unilateral. (E) Complete bilateral.

The etiology of clefting is multifactorial and has both genetic and environmental influences. The genes associated with orofacial clefting identified to date are those for non-syndromic cleft lip/palate *MSX1* (chromosome 4p16.1) and *TBX22* (chromosome Xq12-q21). Cleft palate genes are located on chromosome 14 and a locus for cleft lip (IRF6) on chromosome 1q [41,42]. Development of the upper lip and the palate is completed by postconceptional weeks 7 and 9. Maternal smoking during this time increases the risk of clefting by approximately 1.3 times.

The risk for oral clefting may be as high as 20% in some subgroups with maternal smoking (e.g. American Indians/Alaskan natives). Alcohol consumption, poor nutrition (folic acid and vitamin A deficiency), viral infection, medical drugs (e.g. anticonvulsant drugs; diazepam, phenytoin, phenobarbital, carbamazepine; retinoids; systemic corticosteroids), diabetes mellitus, and teratogenic agents (organic solvents, agricultural chemicals) also increase the risk of clefting [43].

Clefting of the upper lip and nostril is the result of failure of the nasomedial process to merge with the maxillary prominences (lateral cleft lip, either uni- or bilateral) or from failure of the two-nasomedial processes to merge (rare median cleft lip or bifid nose). Hypoplasia of the palatal shelves or mistiming of palatal shelf elevation results in cleft palate. Failure to remove the tongue from between the shelves and problems with shelf elevation and contact probably account for most human cleft palates [19]. There may be a critical time in gestation beyond which the palatal shelves cannot meet and fuse. If movement of the palatal shelves from vertical to horizontal is delayed and the head continues to grow, a widening gap is produced between the shelves, and they cannot meet. Clefting of the palate may or may not be associated with a cleft upper lip because the two conditions are separate developmental entities. However, failure of lip fusion may impair subsequent closure of the palatal shelves.

KEY POINTS: FACIAL CLEFTS

- Clefts that cannot be explained embryologically may be caused by disruptive factors. The causes of most clefts are unknown, and the majority occur sporadically
- Cleft lip and/or palate are the most frequent congenital craniofacial malformations. They occur in one in 700 births in the United States, and there is a marked racial predilection
- The risk for oral clefting may be as high as 20% in some subgroups with maternal smoking, alcohol consumption, poor nutrition (folic acid and vitamin A deficiency), viral infection, medical drugs, and many more

Physiological sequelae of craniofacial malformations

Hydrocephalus and intracranial pressure

In a retrospective review of 1727 patients treated over 20 years, hydrocephalus occurred in patients with non-syndromic craniosynostosis (1447 patients) with similar frequency to that observed in the normal population (0.3%) [44]. In patients with syndromic craniosynostosis, the frequency was 12%. Patients with Kleeblattschädel deformity and Crouzon syndrome were more likely to have hydrocephalus than those with other syndromes. Jugular foramen stenosis and crowding of the posterior fossa are two primary factors responsible for hydrocephalus in syndromic craniosynostosis [44]. Fusion of cranial base synchondroses produces alterations in the skull base and stenosis of the jugular foramen. The resulting venous hypertension increases the CSF hydrostatic pressure. If major calvarial sutures are open, the head will progressively enlarge and the ventricles and subarachnoid spaces will dilate. If the calvarial sutures are fused, intracranial pressure (ICP) will increase but ventriculomegaly may not occur until after the synostosis is surgically released. When the posterior fossa is small and crowded, especially if the lambdoidal suture is fused, cerebellar tonsillar herniation or compression of the basal cistern may produce obstructive hydrocephalus.

Intracranial pressure may be elevated without hydrocephalus in patients with craniosynostosis. Presumably, a restrictive cranium is a factor. Renier monitored ICP during sleep in 350 non-hydrocephalic patients with unoperated craniosynostosis (Table 36.3) [45]. The patients ranged in age from 6 weeks to 15 years, and 44% were less than 1 year old. The overall rate of intracranial hypertension was 23% but the proportion varied by type of craniosynostosis and age. For single sagittal synostoses (trigono- and scaphocephaly), the rates were 6% and 8%, respectively. The rate was 12% for single synostoses of a coronal suture (anterior plagiocephaly). Other authors have also reported elevated ICP with single-suture synostosis, which, in addition to cosmetics, provides a rationale for surgical correction [46,47].

In Renier's study, 26% of patients with synostoses of both coronal sutures (brachycephaly, excluding Apert and Crouzon syndromes) had intracranial hypertension. In extensive synostoses, usually involving both coronal and sagittal sutures (oxycephaly), intracranial hypertension occurred in 54% of patients. In this study, the incidence of intracranial hypertension also increased with age. After 1 year of age, the incidence was four times greater for scaphocephaly and double for plagiocephaly. With brachycephaly, intracranial hypertension was more precocious: 22% of children below 1 year of age had intracranial hypertension compared with 31% over 1 year of age. Oxycephaly is usually not seen before 3 years of age, but

Table 36.3 Intracranial pressure (ICP) before surgery

	Total no. of patients	Baseline ICP (mmHg)		
		≤10	11–15	>15
Trigonocephaly	31	21	8	2
Scaphocephaly	118	76	33	9
Plagiocephaly	65	40	17	8
Brachycephaly	34	17	8	9
Oxycephaly	66	23	7	36
Crouzon syndrome	9	3	0	6
Apert syndrome	16	3	6	7

Source: Reproduced from Renier [45] with permission of Wolters Kluwer.

can also be seen in very young infants, e.g. in syndromic forms. Eighty-five percent of children with oxycephaly had intracranial hypertension. However, clinical signs and symptoms of elevated ICP were uncommon. Intracranial volume measurements calculated from computed tomography (CT) scans were not a reliable indication of ICP, although markedly reduced intracranial volume did increase the likelihood of intracranial hypertension [46]. Raised ICP is also of concern after surgical correction and consecutive inappropriate skull growth and should be monitored in patients and followed up by regular ophthalmological examinations to rule out papilledema at least until 8–10 years of age. Papilledema may not be present despite significantly elevated ICP. In children without papilledema, ICP measurements may be indicated to rule out intracranial hypertension. These older children often complain of chronic headache.

In non-syndromic forms of craniosynostosis where the abnormality is confined to the calvarium, the effects of cranial vault expansion are predictable. In complex craniosynostosis, however, the effects are less certain. In Renier's series, 54 patients had postoperative ICP measurements. Before surgery the ICP was elevated in 74% and borderline in 11% of patients. After surgery 7% had elevated and 20% had borderline ICP. In another series, 22 patients had their ICP monitored postoperatively. The ICP was elevated in 45% and borderline in 32% [48]. In this series, 34 patients with complex craniosynostosis were evaluated with MRI up to 8 years after surgery. Cerebellar tonsillar herniation was found in 52% and hydrocephalus in 41% of patients, over half of whom developed the hydrocephalus after surgery. During follow-up, tonsillar herniation or Chiari malformation can develop as sequelae of insufficient intracranial space. Another report covering a 20-year period noted that the incidence of postoperative hydrocephalus was 45% for patients with syndromes and 4% for patients with isolated craniosynostosis. The incidence of shunt placement was 22% and 1%, respectively [49,50].

Upper airway obstruction

Severe malformations involving the face and cranial base are at high risk for upper airway obstruction and undetected obstructive sleep apnea (OSA). Almost 50% of patients with craniofacial dysostosis develop OSA and require airway intervention at some time [51–53]. OSA can be treated pharmacologically, non-surgically (continuous positive airway pressure (CPAP), nasopharyngeal tube) or surgically, depending on its severity and cause [17,54]. Fifty percent of patients with craniofacial dysostosis are treated with tracheostomy, but nearly 7% in the early and 5% in the late postoperative phase have complications [55–59]. Beside a high incidence of tracheal cartilaginous sleeve, laryngomalacia, tracheomalacia, and bronchomalacia, a reduced cranial base angle positions the pharyngeal wall forward and produces anteroposterior shortening of the nasal and oral airway [30]. In addition, the temporomandibular joint may be drawn posteriorly so that the mandible is positioned retrusively [31]. When the mandible is small and retrognathic (e.g. Pierre Robin sequence), the tongue is positioned posteriorly and impinges on the oro- and hypopharynx [28]. Midface hypoplasia and retroposition also diminish the dimensions of the nasal airway. Neurological dysfunction, such as pharyngeal hypotonia or incoordination, worsens airway obstruction in children with abnormal anatomy [60]. Other skeletal abnormalities, such as turbinate hypertrophy, septal deviation, and choanal narrowing or atresia (e.g. CHARGE syndrome), contribute to upper airway obstruction.

Obstructive sleep apnea is common in craniofacial syndromes [29,30,61–64]. Sher and colleagues [60] used flexible fiberoptic nasopharyngoscopy to identify the mechanisms of pharyngeal obstruction in patients with OSA. Four mechanisms were identified.

1. Posterior movement of the tongue against the posterior pharyngeal wall (Fig. 36.14).
2. Posterior movement of the tongue with compression of the soft palate or cleft palatal tags posteriorly against the

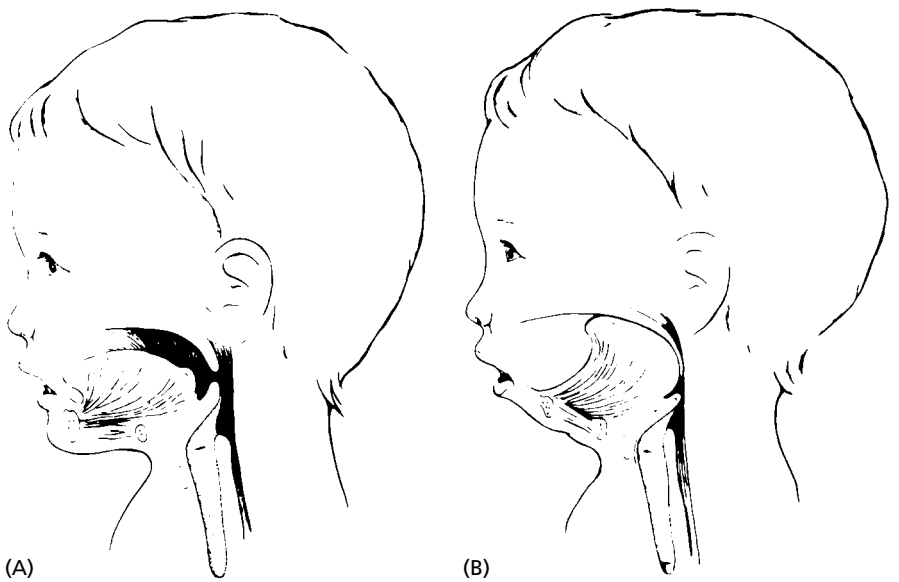


Figure 36.14 Anatomical features of the larynx. (A) Normal child. (B) Child with mandibular hypoplasia. Posterior placement of tongue makes the larynx appear to be more anteriorly situated than normal. Reproduced from Handler and Keon [183] with permission of SAGE.

posterior pharyngeal wall; the tongue, velum, and posterior pharyngeal wall meet in the upper oropharynx.
3. Movement of the lateral pharyngeal walls medially to appose each other.
4. Pharyngeal constriction in a circular or sphincteric manner.

Sleep apnea may occur from brainstem compression in children with Chiari malformation.

Some patients are successfully managed with nasal CPAP during sleep [63]. Others with severe airway obstruction may require tracheostomy. Of 251 patients with craniofacial anomalies who underwent surgery over a 5-year period, 20% required tracheostomy to relieve chronic airway obstruction or to manage the airway in the perioperative period [65]. Patients with craniofacial synostosis (Crouzon, Pfeiffer, or Apert syndromes) had the highest rate of tracheostomy (48%). Those with mandibular facial dysostosis (Treacher Collins or Nager syndromes) had the next highest rate (41%). Twenty-two percent of patients with OAVS (Goldenhar and hemifacial microsomia) required tracheostomy. The mean duration of cannulation in infancy or in early childhood was 4 years. Patients who had tracheostomy after 4 years of age required cannulation for less than 6 months, and 60% underwent decannulation 1 week after tracheostomy.

Ear, nose, and throat consultation is recommended to determine if an adenoidectomy or tonsillectomy is required prior to craniofacial surgery. Some cases of sleep apnea are effectively treated by adenotonsillectomy.

Patients with Robin sequence, especially non-syndromic patients, who have airway obstruction that is unresponsive to prone or lateral positioning alone respond to nasopharyngeal/nasotracheal intubation or glossopexy (tongue–lip adhesion). These procedures often relieve airway obstruction during the first months of life while the mandible grows and the airway expands [60,66,67]. In some syndromes (e.g. Treacher Collins and Apert), the anatomical inter-relationships become progressively distorted and the obstruction may worsen, not improve [28,61,68]. To minimize morbidity, the least invasive treatment should be used first. If conservative treatment, including wearing a soft palate plaque (e.g. Tübinger type) [69], does not resolve the problem, further management should be based on the oxygen saturation, feeding difficulties, and endoscopic findings. A lip–tongue plication is done in some patients for 6–9 months to move the tongue away from the pharynx and allows time for mandibular growth. A more aggressive approach is the tongue–lip adhesion or a perimandibular fixed extension device. Distraction osteogenesis can be used in older children [70]. Finally, if all else fails, a tracheostomy might be indicated.

Associated anomalies

With syndromic craniofacial anomalies, many systems may be malformed, particularly the CNS, the cardiac, and pulmonary systems. Cranial sensory and speech organs can also be malformed, and hearing, vision, and speech may be impaired. Cervical spine anomalies, including intervertebral fusion, occur commonly in the Goldenhar syndrome and with craniosynostosis syndromes such as the Crouzon, Apert, and Pfeiffer syndromes [71–73].

KEY POINTS: PHYSIOLOGICAL SEQUELAE OF CRANIOFACIAL MALFORMATIONS

- Hydrocephalus incidence with non-syndromic craniosynostosis is not increased; it increases to 12% with syndromic craniosynostosis
- Intracranial hypertension is present in 6–12% of patients with single-suture craniosynostosis, increasing to 26–74% of children with complex craniosynostosis
- Obstructive sleep apnea is present in a high proportion of patients with face and cranial base malformations. CPAP and tracheostomy are sometimes required in these patients

Craniofacial reconstruction: surgical procedures

Paul Tessier introduced major craniofacial surgery in Paris in 1967. He developed the first craniofacial dysjunction procedures that cleaved the face away from the base of the cranium by using both an intracranial and an extracranial approach [74,75]. Over the past 50 years, these techniques have been used to treat a variety of complex congenital and acquired deformities of the face and cranium, including traumatic and neoplastic entities [76]. A coordinated interdisciplinary approach is required for this surgery to succeed. There are many reasons for doing the surgery, including improving neurological, ocular, nasal, dental, and auditory functions as well as improving cosmetic appearance and psychological function [76]. The basic objective of craniofacial surgery is to correct skeletal deformity first and soft tissue afterwards. The basic treatment of the deformed skeleton comprises cutting, disjoining, mobilizing, repositioning, augmenting, and fixing the involved bony structures. Wide exposure of the skeleton is required. Therefore, the soft tissues, including the orbital contents, are extensively dissected and mobilized away from their bony attachments. Intracranial and extracranial approaches are utilized and scalp, preauricular, and intraoral incisions are made to avoid producing scars on the face. For intracranial and for upper and midface procedures, the surgical approach is through a bicoronal scalp incision that extends from ear to ear and from which the soft tissues of the scalp and face are reflected forward over the facial mass (Fig. 36.15). This provides wide exposure of the facial skeleton down to the maxillary alveolus. A craniotomy is done, the frontal lobes of the brain are retracted, and the anterior cranial base is exposed. To effectively provide anesthesia for major craniofacial surgery, the anesthesiologist must clearly understand both the lesion and the proposed surgical procedure.

Cranial and facial remodeling

Surgery for cranial and facial remodeling is performed with the goal of normalizing the child's appearance, ensuring sufficient head size and growth, and establishing normal function of the skull structures and related organs. In most cases, these aims cannot be fully met but significant improvement is possible. In the past, surgical techniques were employed that often did not take into account the substantial variations in

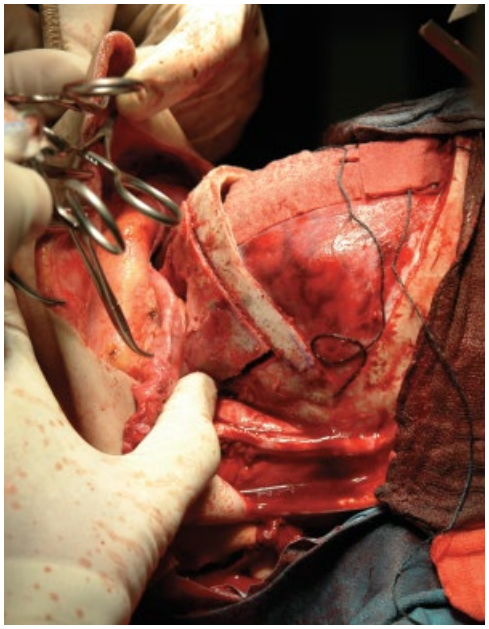


Figure 36.15 After bicoronal incision for intracranial upper and midface procedures, the face is peeled back for wide exposure of the facial skeleton bone.

the underlying pathology, the patient's age, and the skill of the surgical team. The first technique employed was to open the fused suture, with the hope that this would allow normal skull growth. In the past this method was not successful but recently Jimenez has had success with the procedure [77]. Since it became evident that cranial growth follows intrinsic pathways rather than mechanical rules, the entire cranial vault, including the skull base structures, have been addressed surgically. Whenever the fronto-orbital region is involved, additional maneuvers, such as fronto-orbital advancement, have been used to improve facial appearance and enlarge the intracranial and orbital cavity. In multisuture craniosynostosis, restricted skull growth and potential brain and orbital constriction are the major reasons for early surgery. In addition to fronto-orbital advancement and cranial vault remodeling, posterior distraction surgery can be an option.

In principle, the main surgical goals for these patients comprise three steps: opening of the cranial vault to allow the brain to expand, fronto-orbital advancement to ensure frontal brain expansion and eye protection, and midface advancement to improve nasopharyngeal pathways and dental alignment. Additional procedures may be necessary for orbital malposition and facial clefts.

The typical skin opening for cranial or craniofacial remodeling is a coronal incision. The incision can be straight, curved, or zigzag to prevent visible scarring. Attempts should be made to minimize unnecessary blood loss when dividing the galea [78].

Timing and general preparation for surgery

Timing of craniofacial repair is often controversial. As long as there is sufficient head growth, as occurs in most single-suture craniosynostoses and other craniofacial disorders that do not involve the cranial vault, surgery is scheduled in the second half of the first year, usually between 6 and 8 months of age. At that time, the hematological status is stabilized and the bony structures are firmer and easier to remodel than at younger ages. All systemic functions are checked to minimize the overall risk.

Multisuture craniosynostoses can lead to severe skull constriction and require early or even emergency procedures to relieve ICP; elevated ICP significantly increases the risks of surgery and anesthesia. These patients require early evaluation for cardiac, kidney, airway, and hematological disorders.

Parents must be informed about all aspects of craniofacial surgery, including early and late changes in the esthetic appearance of their child, potential surgical risks (mainly blood loss and the need for transfusion of blood and coagulation factors), and the possibility of infection. They should be prepared for significant facial swelling during the first postoperative days, but should also be assured that brain damage and severe complications are rare despite the extent of the surgical procedure. Long-term follow-up is important to detect late intracranial hypertension or recurrent deformity, both of which may require reoperation.

Craniectomy

The principle of craniectomy is to remove a piece of the cranial vault to permit directional skull expansion. Several forms of craniectomy have been used from simple suturectomy, to strip craniectomies, to wide vertex craniectomies in scaphocephalic patients. Barrel stave incisions and lateral strip craniectomies have been utilized to promote lateral skull expansion. Total removal of the cranial vault has been performed, with acceptable outcomes in some cases. Since craniectomies require spontaneous bone regeneration to reshape the skull and protect the brain, these techniques are not recommended in children older than 8–10 months of age.

Strip craniectomy improves craniofacial contour only for isolated sagittal synostosis. For other synostoses, removing, reshaping, and repositioning bone accomplish cranial remodeling. Cranial remodeling may involve any part of the cranium or the entire cranial vault. For complex craniosynostoses that involve the cranial base and face, the sutures involved are commonly those of the anterior cranial vault (coronal, sagittal, or metopic sutures) as well as the anterior cranial base (frontosphenoidal, frontoethmoidal, and sphenozygomatic sutures). The surgery releases the sutures and advances the upper part of the face forward (fronto-obital advancement) away from the cranial base (Fig. 36.16). The principal

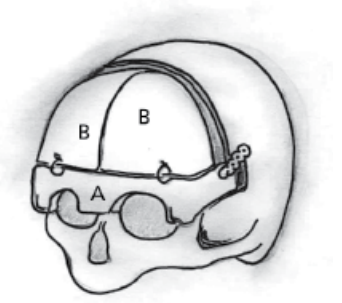


Figure 36.16 Fronto-orbital advancement. Both frontal bone flaps (B) or a coherent bifrontal flap are displaced forward together with the fronto-orbital bandeau (A). Rigid fixation with miniplates, wire loops, or tight suturing keeps the bone segments in place.

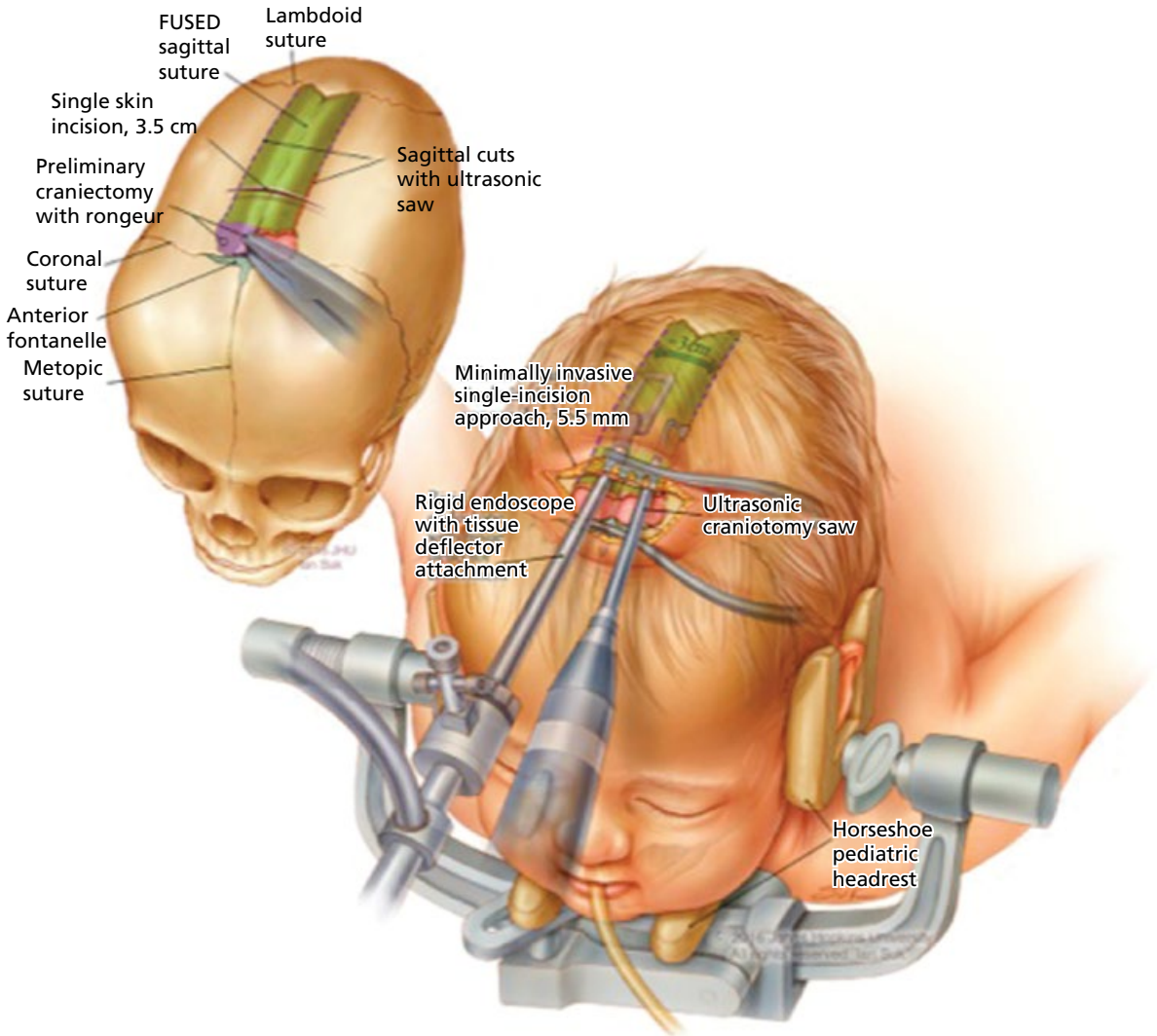


Figure 36.17 Surgical technique for single incision endoscope-assisted sagittal strip craniectomy. The upper panel depicts initial bony removal adjacent to the anterior fontanelle with a rongeur under direct visualization and the segment of intended bony removal (green) during the procedure. The lower panel depicts the intraoperative set-up and positioning with the rigid endoscope providing subgaleal visualization with lateral cuts made parallel to the sagittal suture using the piezoelectric instrument. Illustration by Ian Suk, Johns Hopkins University. *Source*: Reproduced from Iyer et al [79] with permission of Springer Nature.

functional objectives of the surgery are to open the cranium to allow normal brain expansion, to open the nasopharyngeal airway, to provide greater support and protection for the eyes, and to achieve proper alignment of the upper and lower dental arches. This surgery usually requires at least two steps: (1) frontocranial remodeling, with release of the synostosis and advancement of the frontal supraorbital area, and (2) midface advancement. The segments are fixed in place with wires or resorbable/non-resorbable miniplates, and bone grafts are used to fill gaps. In some cases the forehead is left "floating" with a wide osseous defect.

Minimally invasive strip craniectomy

Over the last two decades, techniques for minimally invasive strip craniectomy, initially for single-suture sagittal craniosynostosis, but more recently for multisuture and syndromic craniosysnostosis, have been reported. These techniques include endoscopically assisted strip craniectomy with one or two smaller incisions, and spring-assisted craniectomy (Figs 36.17 and 36.18) [79–81]. The major advantage of this approach is less bleeding and transfusion, shorter operative and anesthetic times, and shorter postoperative length of stay. Longer term outcome studies are being reported with equivalent results in terms of head shape, brain growth, ICP, and neurodevelopmental and social outcomes; but there still remains considerable debate about the best approach. One major difference in the minimally invasive approach is that it is best performed in younger patients aged 3–6 months, when the cranial bones are softer and more flexible, rendering them more amenable to this approach.

Cranial vault reconstruction

Total or partial reconstruction of the cranial vault is the method of choice when reshaping and stability of the skull are the aim of the operation. Vault craniotomies are performed and the bony plates are remodeled and transposed to reshape the skull. Stable fixation of bone with wire loops, stitches, or miniplates (either titanium or lactic acid polymer) is

necessary. Titanium miniplates tend to grow inwards and must be removed after 3 months. Cranial expansion is another surgical aim of total cranial vault reconstruction. Again, the cranial plates are excised, transposed, and refixed, leaving substantial gaps in between the bone edges, but the intracranial cavity is enlarged [82]. This technique is indicated for children with multisuture involvement or secondary intracranial hypertension, e.g. after scaphocephaly correction. Larger bone defects (>2 cm) will not close spontaneously after the second year of life, making it necessary to do this surgery before that time. Defects in the calvarium can be filled with autologous grafts, e.g. calvarian split grafts. Children with severe occipital deformity or flattening, e.g. in brachyturricephalic heads, undergo occipital advancement, including a suboccipital bone flap. For mechanical reasons a rigid fixation is necessary.

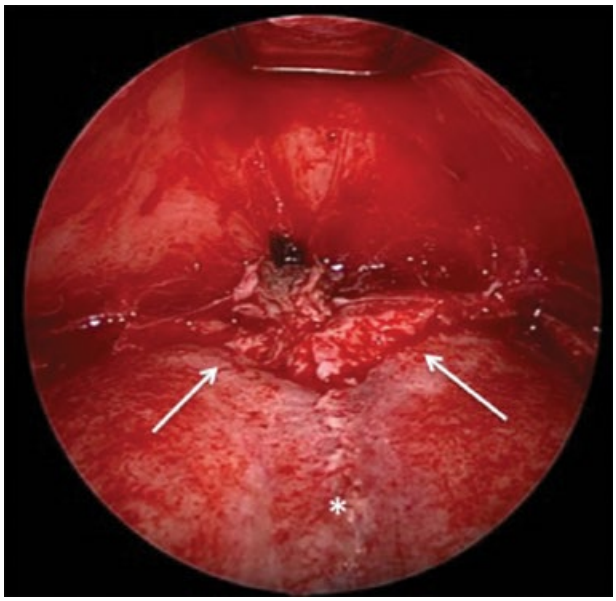
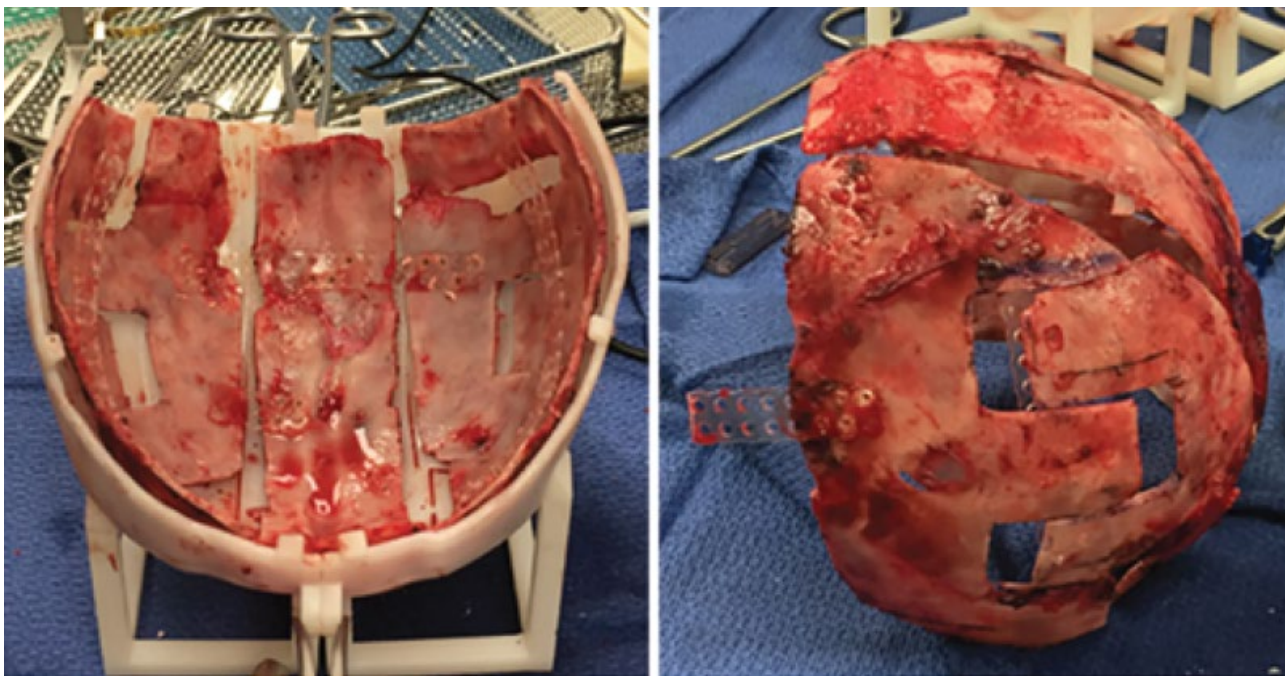


Figure 36.18 An intraoperative endoscopic view after craniectomy through a single incision demonstrating the exposed lambdoid suture on either side of the midline. White arrows represent the triangular shape of the lambda as it is approached and the sagittal sinus (asterisk) marks the midline. *Source*: Reproduced from Iyer et al [79] with permission of Springer Nature.

New surgical planning techniques including 3D reconstruction from CT scans, and 3D printing of the desired cranial vault shape, which can be used to produce sterile intraoperative acrylic models as a template for final osteotomies and reconstruction, are being reported (Fig. 36.19) [83]. These techniques, along with quantitative photographic techniques such as stereophotogrammetry are allowing more precise and objective surgery and follow-up of cranial vault reconstruction patients [84].

Fronto-orbital advancement

For anterior skull expansion and correction of the orbital portion, fronto-orbital advancement has been the standard technique since first described by Tessier and modified by Marchac [85,86]. First, a bifrontal flap is excised and removed, then the fronto-orbital bandeau, cutting the edges in a tongue and groove fashion. In trigonocephaly or anterior plagiocephaly, the bandeau and the frontal bones are reshaped and sometimes rotated to create the desired fronto-orbital shape. Refixation of bone may be with wire loops, miniplates, or tight stitches in older children. In multisuture synostoses, when the primary goal is to enlarge the cranial cavity,



(A) (B)

Figure 36.19 Three-dimensional printed intraoperative cranial mold. (A) Alignment of cut bone segments within the expansion guidelines of the normative cranial mold and fastening with absorbable plates and screws. (B) Final expanded calvarial construct (middle and posterior calvarial vault). *Source*: Reproduced from LoPresti et al [83] with permission of Journal of Neurosurgery.

fronto-orbital advancement is combined with total vault reconstruction. Shallow orbits are always enlarged to protect the eyes (Fig. 36.20).

Distraction osteosynthesis

Another method of enlarging the volume of the skull is based on the Ilizarov principle of bone distraction. For midface and mandibular correction, distraction osteosynthesis has become standard. The application of distracting devices to transected vault sutures or parts of bone flaps for dynamic skull expansion is less well established.

Additional neurosurgical procedures

Hydrocephalus is relatively common in multisuture or syndromic craniosynostosis and contributes to the elevated ICP. Ventriculoperitoneal shunting is the procedure of choice in these cases, but interferes with keeping cranial sutures or newly created gaps open as long as possible after cranioplasty procedures. Alternatively, an endoscopic third ventriculostomy can be done in selected cases.

As a consequence of insufficient skull growth, the expanding brain moves downward and causes a Chiari malformation with brainstem compression and secondary hydrocephalus. In some of the affected children, a craniocervical decompression (Gardner decompression) becomes necessary.

Midface advancement

Craniofacial dysjunction and midface advancement are delayed until the patient is at least 4 or 5 years of age. Certain indications or personal preferences lead surgeons to select a specific operative procedure, which usually includes a Le Fort osteotomy (Fig. 36.21). At the beginning of the 20th century, a French surgeon, René le Fort, found that the maxilla, naso-orbital complex, and zygoma fracture in predictable ways at weak points, i.e. the linea minoris resistentiae [87]. These fracture lines are used to produce controlled osteotomies for the correction of skeletal anomalies.

The Le Fort I osteotomy is the most common and most useful midface osteotomy (Fig. 36.22). Malocclusion of the teeth

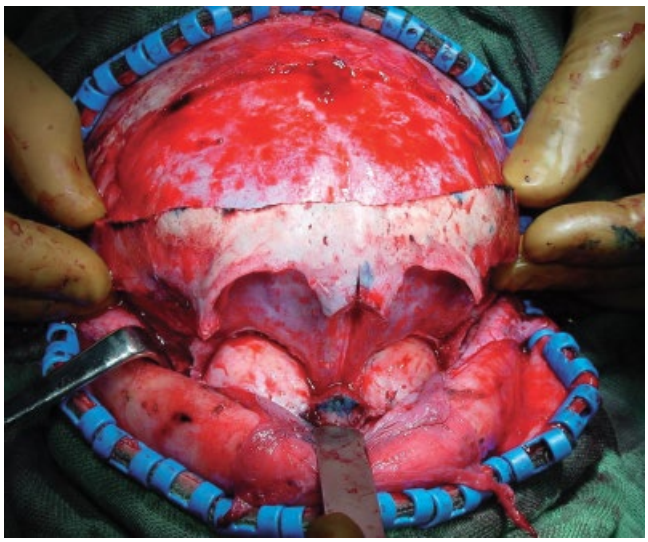


Figure 36.20 During fronto-orbital advancement, the primary goal is the enlargement of the cranial cavity which is combined with total vault reconstruction. After that both orbits are exposed.

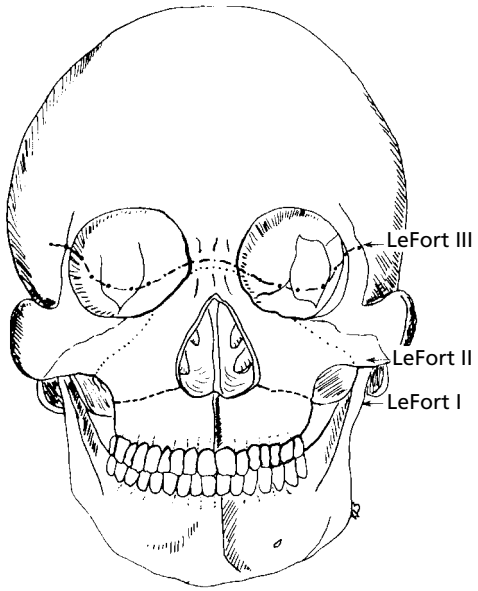


Figure 36.21 Le Fort I, II, and III osteotomies.

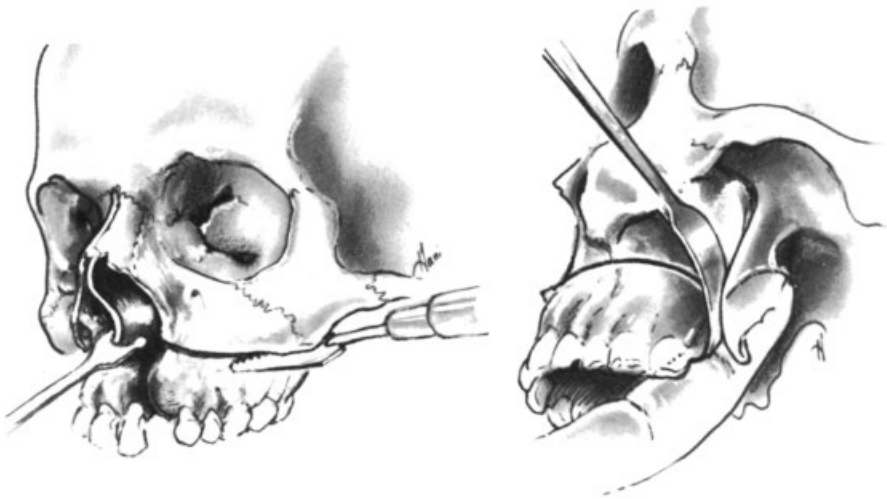


Figure 36.22 Le Fort I osteotomy. *Source*: Reproduced from Bardach and Salyer [184] with permission of Elsevier.

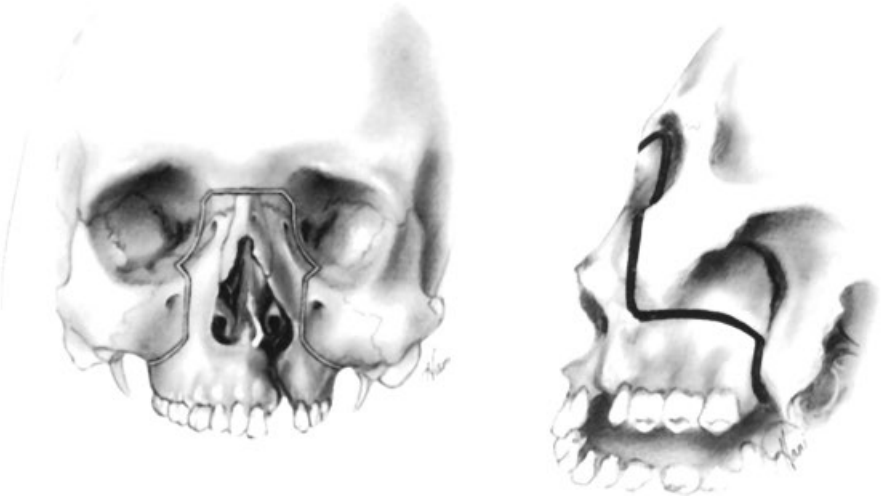


Figure 36.23 Le Fort II osteotomy. *Source*: Reproduced from Bardach and Salyer [184] with permission of Elsevier.

is always present and is treated by an interdisciplinary team of maxillofacial surgeons and orthodontists. Surgery is performed through an intraoral incision. Horizontal cuts are made across the nasal floor, the anterior maxilla, and through the pterygomaxillary junction. The maxilla is mobilized downward, advanced, and fixed. The occlusion is secured by arch bars and by a dental splint. Because of the intraoperative intermaxillary fixation, nasotracheal intubation is required. Bone grafts can be used to fill the spaces.

The Le Fort II osteotomy is done less often and is used to advance the lower maxilla and entire nose forward (Fig. 36.23). Normally, a bicoronal scalp incision and soft tissue reflection are combined with an intraoral incision to expose the midface. There are many variations of midface osteotomies. The osteotomy crosses the nasal bridge and then goes bilaterally down the lateral nasal bones through the inferior orbital rim and across the maxilla to the pterygomaxillary junction. The segment is mobilized and advanced. Bone defects are filled with bone grafts, and the entire segment is fixed with rigid miniplates or wires. Intermaxillary fixation is not really needed when rigid internal fixation plates are used.

Midface hypoplasia typically results in an Angle class III malocclusion (a relative mandibular prognathia) with an anterior overbite. A Le Fort III osteotomy is indicated, but an additional Le Fort I osteotomy is often necessary to achieve an intermaxillary relationship that enables stable occlusion. Le Fort III osteotomy (Fig. 36.24) is used for complete underdevelopment of the midface, typical of the Apert, Crouzon, Pfeiffer, and similar syndromes. It permits the nose, maxilla, and orbits to be advanced after dysjunction of the entire midface. A bicoronal scalp incision is made, the soft tissues are reflected forward over the midface, and the orbital contents are dissected free. The basic osteotomy starts at the frontozygomatic suture and then passes through the orbits below the supraorbital rim and across the nasal bridge. The pterygomaxillary junctions are separated, and the nasal septum is separated from the skull base. The facial block is advanced after down-fracture and side-to-side and rotary manipulations (Fig. 36.24). The spaces are filled with bone grafts and the bones are fixed in place. The use of rigid internal fixation plates precludes the need for intermaxillary fixation.

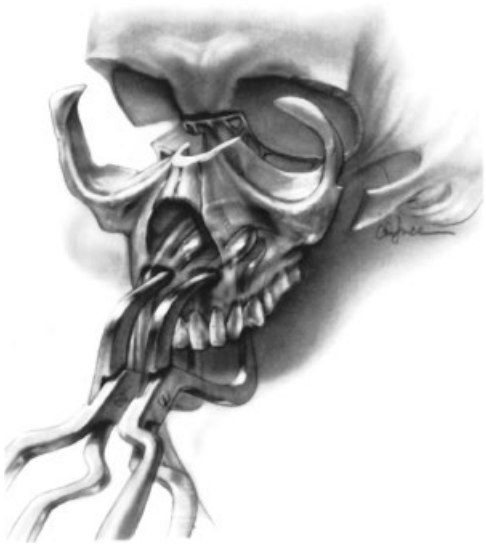


Figure 36.24 Le Fort III osteotomy. Rowe disimpaction forceps are used to "down fracture" the posterior maxillary wall and allow advancement of the midface. *Source*: Reproduced from Persing [185] with permission of Wolters Kluwer.

Monoblock frontofacial advancement moves the frontal and orbitofacial blocks forward simultaneously. While the early functional results are good, the complication rate is high and the poor postoperative midface growth makes a reoperation more difficult [88]. The supraorbital area and the facial mass are mobilized en bloc and advanced. The frontal bone flap is remodeled when necessary, e.g. exorbitism.

Various combinations and modifications of these osteotomies are performed either simultaneously or in stages. The transverse maxillary osteotomies (Le Fort I and II) are usually delayed until adolescence to avoid disruption of the permanent dentition.

Pediatric temporomandibular joint (TMJ) dysfunction from soft tissue or skeletal disorders may be congenital or acquired. The diagnosis and classification of TMJ disorders determine treatment options [89]. In cases of TMJ reconstruction or discontinuity defects of the mandible after trauma, hemimandibulectomy for tumor excision, condylar damage with juvenile

idiopathic arthritis, or congenital diseases (e.g. hemifacial dysplasia), the goal is to maximize function and cosmesis, preserve quality of life, and restore mastication, speech, and appearance [90]. Treatment includes autogenous bony, cartilage, and condylar grafts, free vascularized flaps, or an alloplastic TMJ prosthesis until the skeleton matures [91–94]. A variety of donor sites have been used for this purpose, including the iliac crest, radius, scapula, and fibula. TMJ diseases occurring during growth result in dentofacial deformity and require reconstruction of the occlusion plane. Surgical correction with total joint prostheses can be performed in a single-stage operation with a mono- or bimaxillary orthognathic osteotomy [95]. During surgery the occlusion has to be checked.

Surgical correction of hypertelorism and orbital malposition

Surgical correction of orbital malposition is performed to facilitate correction of strabismus, to normalize facial appearance, and to possibly achieve binocular vision. Surgery is usually performed at about 5 years of age unless there are mitigating circumstances. The orbit can be thought of as a box housing the eye. To correct hypertelorism or other orbital malposition, the box is freed from contiguous bone and repositioned (Fig. 36.25). In moderate and severe degrees of hypertelorism, an intracranial approach is employed: a bicoronal scalp incision is made; soft tissues, including orbital contents and nasal mucosa, are reflected down to the midface; a frontal craniotomy is performed; and the frontal lobes of the brain are retracted to expose the anterior cranial fossa. Intra- and extraorbital osteotomies convert the anterior orbit into a mobile box. A central block of bone (frontal, nasal, ethmoidal) is removed from between the orbits. The orbits, with the globe and other soft tissues, are then moved medially and fixed in place (Fig. 36.26). Bone grafts are inserted into the gaps created at the lateral orbital walls. The nose is rebuilt with bone grafts if necessary. For minor degrees of hypertelorism, an extracranial approach is possible; this eliminates the frontal craniotomy and brain retraction. Extensive soft tissue dissection is still required, but the osteotomies are less extensive. There is also danger of piercing the cribriform plate and causing CSF leakage.

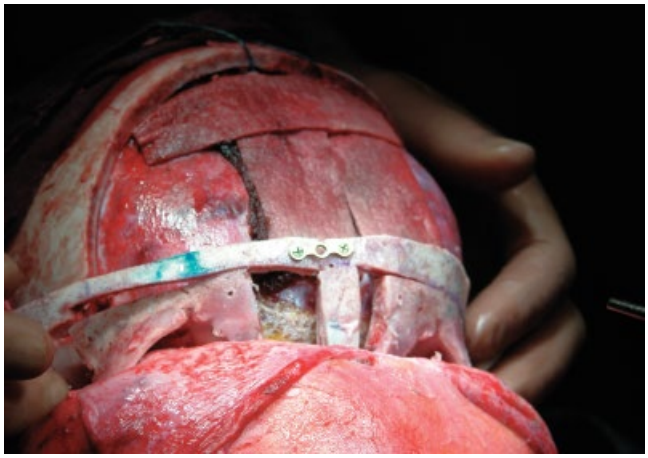


Figure 36.25 After osteotomies and removal of a central block of bone, the orbits are shifted medially. Orbits can be considered as boxes containing the eye. Each orbit can be moved in any plane.

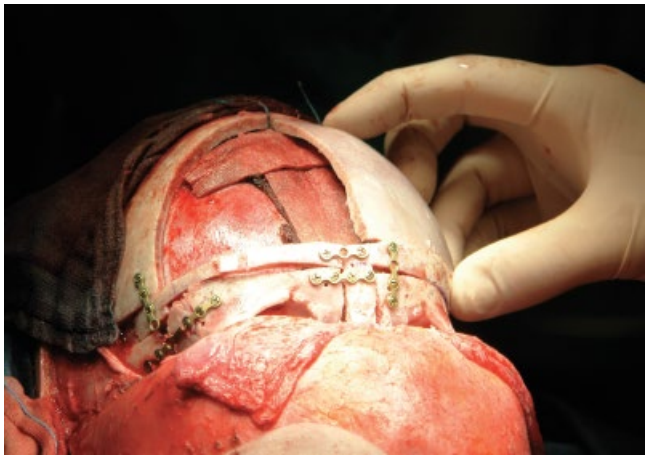


Figure 36.26 Orbits after medial shift and fixation with miniplates.

Reconstruction of facial clefts: major facial and mandibular malformations

The anatomical defects of the major facial and mandibular malformation syndromes are skeletal and soft tissue hypoplasias. Hypoplasia may involve any part of the face and cranium. Reconstruction of these lesions often requires multiple staged surgical procedures. The skeleton must be normalized, the soft tissues augmented, ears and nose reconstructed, and sometimes the face must be reanimated. For the hypoplastic skeleton, displacement osteotomies, repositioning of bones into more normal positions, and calvarial bone grafts are used to augment surfaces and fill spaces.

Soft tissue hypoplasia can involve skin, subcutaneous tissue, cartilage, and the muscles of mastication and facial expression. Various approaches can be taken to augment and restructure soft tissues. Skin and mucosal flaps from local or distant sites may be used. To add bulk and appropriate contours, dermis fat grafts from the groin can be placed subcutaneously. Contour can also be improved with inlay bone grafts. Temporal muscle transfers to the face also add bulk. These procedures may require extensive dissection of soft tissue. Facial nerve palsy can be compensated for with nerve transfer from the motor branch of cranial nerve V; if the malformation is unilateral, cross-face nerve grafts, facial–hypoglossal nerve anastomosis, and microneuromuscle transfers can be attempted.

Traditionally, mandibular reconstruction has followed the same principles as other craniofacial procedures: cut, mobilize, reposition, augment, and fix. In the past the mandible was mobilized through an intraoral incision with bilateral sagittal osteotomies and rotated and advanced into a normal position. Distraction osteogenesis is now replacing the traditional method in many cases. New mandibular parts are constructed from costochondral rib grafts or split cranial grafts. This surgery is usually done before eruption of the permanent teeth.

Distraction osteogenesis

Patients with severe craniofacial dysostosis who require early surgical correction of their deformity before skeletal maturity have clearly benefited from distraction osteogenesis compared with conventional osteotomy [96]. Distraction osteogenesis is

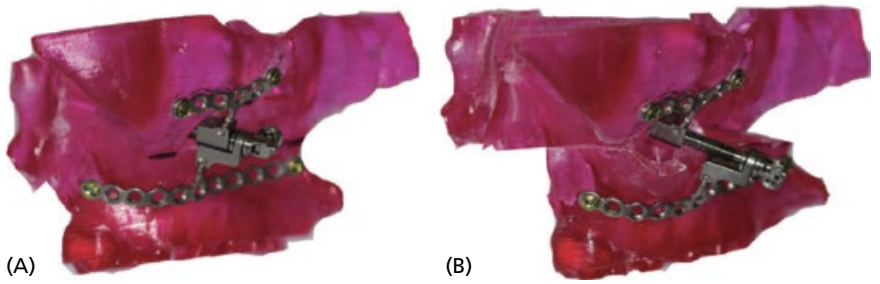


Figure 36.27 The trans-sinusoidal mandibular distractor on a stereolithographic model of the midface. Before (A) and (B) after distraction.

done by producing a bone callus (by osteotomy) and then distracting the proximal and distal ends of the callus. It has been used by some orthopedic surgeons for years to lengthen limbs but did not gain widespread acceptance because of the associated morbidity. In 1988, Ilizarov, a Russian orthopedic surgeon, described using distraction osteogenesis that required only corticotomy and minimal disruption of the periosteum and endosteum; this reduced the incidence of complications and allowed wider application of the technique [97].

Rosenthal first described distraction osteogenesis for widening the mandible in 1930 [98]. Its principal application in craniofacial surgery is for mandibular lengthening [99]. The technique consists of percutaneous insertion of pins into the mandible that are proximal and distal to a corticotomy. The pins are attached to an external fixator lengthening device, and the mandible is lengthened 1 mm/day by turning a bolt. The authors reported mandibular lengthening of 18–24 mm.

The procedure is considered minimally invasive and achieves an approximately 2–3-fold advancement compared with the conventional procedure. Using conventional osteotomy beyond the age of skeletal maturity has the advantage of a shorter treatment period and greater patient comfort. Distraction is often associated with less blood loss, less tissue exposure, and no need for bone grafting. With distraction osteogenesis the postoperative morbidity is decreased, the operation time is reduced, and the procedure can be performed on younger children. Several authors believe that mandibular distraction also induces facial soft tissue growth [100–102]. The disadvantage of this technique is the need for high patient compliance and the high psychological impact [103]. The major complication of extraoral devices is the development of hypertrophic scars when the pins migrate through the skin.

Since the original description, mandibular distraction has become increasingly popular for the treatment of mandibular hypoplasia and asymmetry [102–104]. Enoral (internal) distracters eliminate facial scars and are less likely to loosen or dislodge. Mandibular distraction has also been used to successfully alleviate the symptoms of respiratory distress and obstructive sleep apnea. A tracheostomy (if in place) can be removed. Mandibular distraction has been applied to infants as young as 14 weeks of age [105]. Both internal and external lengthening devices are being applied to distract the midface [103].

Patients with cleft lip and palate often have severe maxillary hypoplasia in the vertical, horizontal, and transverse dimensions. Traditional protocols rely on combined surgical–orthodontic treatment, including Le Fort I maxillary advancement, maxillary and alveolar bone grafting, and rigid internal fixation. Long-term results of this approach have been disappointing because relapse occurs in more than 20% of the cases. Trans-sinusoidal mandibular distractor (TS-MD) placement is a possible alternative for patients with cleft lip and palate. The major part of the TS-MD is done within the maxillary sinus and does not interfere with function during distraction and retention or with the patient's social life. Compared with headframe-based extraoral devices for midface distraction, TS-MD is easier for the patient and does not leave extraoral scars after removal of the device. Three-dimensional planning enables the surgeons to plan the distraction vector in three dimensions, but a correction of the vector by distraction is not possible, as it is with the headframe device (Fig. 36.27).

Cleft lip and cleft palate reconstruction

Surgical reconstruction of a cleft lip, palate, and/or nose is undertaken for cosmetic, psychological, and functional purposes. Functional goals are to separate the nasal and oral cavities, to improve speech and swallowing, to prevent middle ear disease, to improve hearing, and to provide normal dental occlusion (Fig. 36.28).

The treatment of children with cleft lip and palate starts during the first weeks after birth with preoperative orthopedics, such as presurgical nasal alveolar molding (PNAM) (Fig. 36.28) [106]. The PNAM appliance differs from traditional intraoral alveolar molding devices by having nasal prongs as part of the device [105]. An orthodontist adjusts the acrylic appliance by adding and removing material from the leading edge of the maxillary segments weekly. Despite the lack of long-term outcome studies, PNAM is used by many multidisciplinary cleft teams to reduce the width of the alveolar cleft and the corresponding soft tissues of the cleft lip [107].

Primary cleft lip repair is usually performed at 3–6 months of age and often includes a primary rhinoplasty (Fig. 36.29) [106]. Cleft palate reconstruction is done at 6–12 months of age before speech develops [108]. There are many ways to close the lip that have excellent results, each with its own advantages and disadvantages. The final result depends on the degree of primary dysmorphology, scarring (surgical technique), the experience of the surgeon, and the time schedule [109]. Tissue deficiency and displacement contribute to anatomical defects. Surgical reconstruction involves dissecting and freeing anatomical elements, undermining the tissue, repositioning the involved muscles in a correct anatomical position, and creating flaps for rotation and advancement of the lip. Reconstruction of the bony palate requires creating bone or mucoperiosteal flaps and also bone grafting. For example, mucoperiosteal

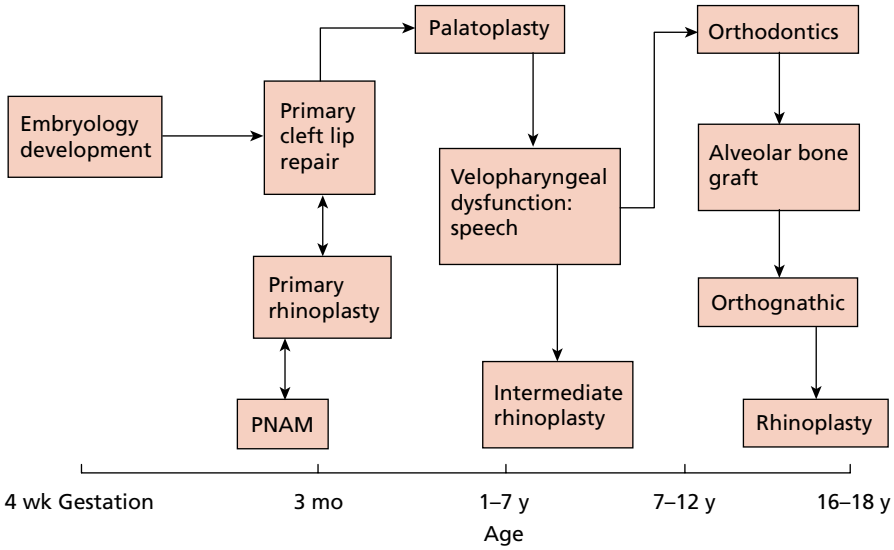


Figure 36.28 Timing and general procedures for cleft patients. PNAM, presurgical nasal alveolar molding. *Source*: Reproduced from Tollefson et al [105] with permission of JAMA Facial Plastic Surgery.

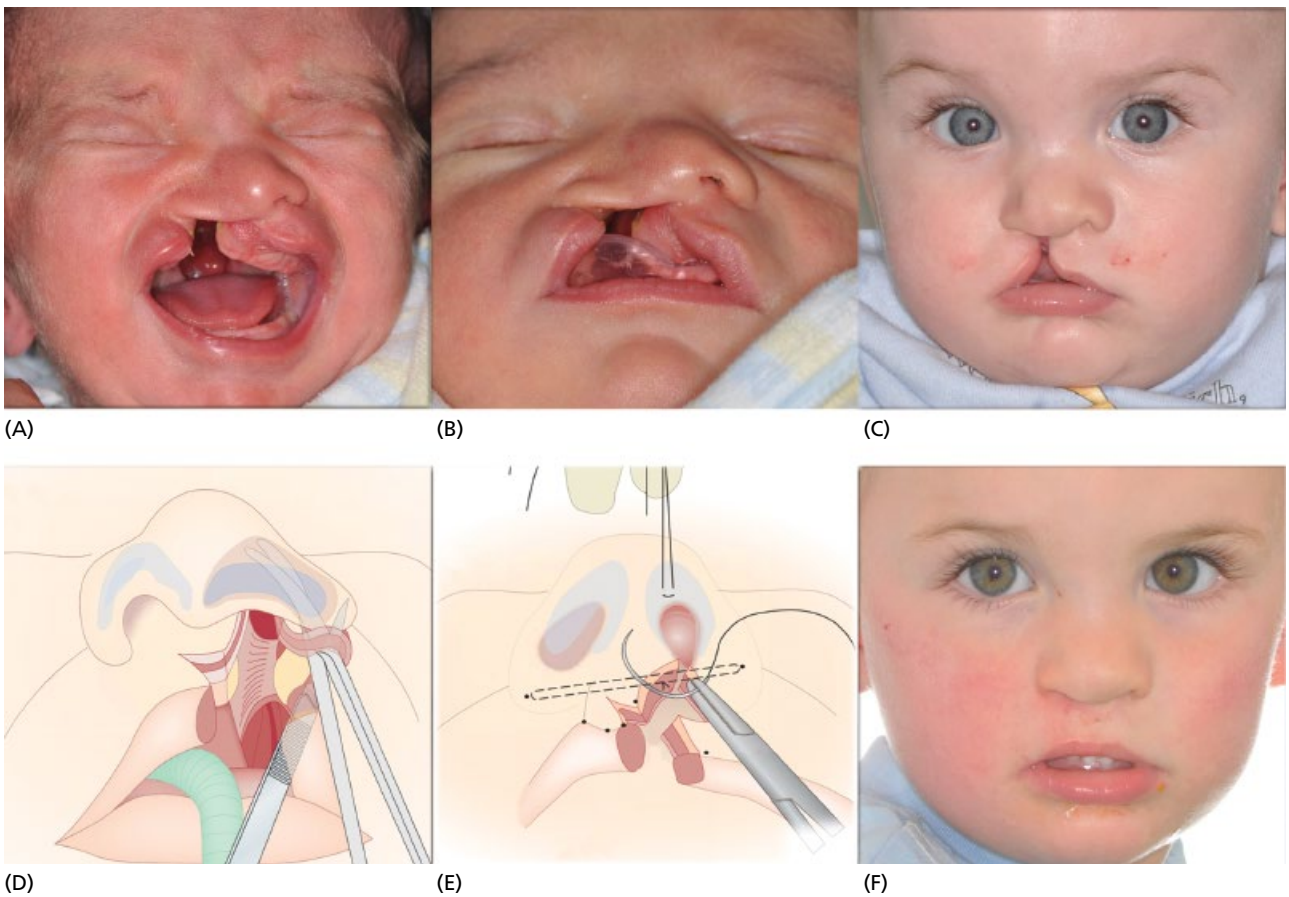


Figure 36.29 Patient with unilateral cleft (A), before and after nasoalveolar molding (B, C). (D, E) The lip closure technique (Tennison Randall) with primary rhinoplasty (Sayler). (F) One year after surgery. *Source*: Reproduced from Daratsianos et al [106] with permission of Georg Thieme Verlag KG.

flaps can be made from the palatal shelves and positioned medially to fill the cleft or they can be turned off the vomer and joined to the edge of the bony cleft to close it. If the cleft is sufficiently narrow, paring of the medial palatal edges and elevation of the nasal and palatal mucosa may allow closure.

Free bone grafting is required traditionally after orthodontic palatal expansion (8–11 years of age) of the alveolar ridge. This occurs when 30–60% of the canine tooth roots have developed but before eruption of the tooth into the cleft void. Bone is generally taken from the iliac crest.

Pharyngeal flap

Velopharyngeal incompetence is failure of the velum (soft palate) and posterior pharynx to close or contact appropriately during speech and swallowing. It occurs in 10–30% of patients after cleft palate repair. It can also occur if there is any anatomical or neuromuscular abnormality of the palate or pharynx [110]. Velopharyngeal incompetence causes hypernasal, misarticulated speech. Nasal regurgitation of food and liquid occurs with swallowing.

Diagnosis of velopharyngeal incompetence has greatly improved with videofluoroscopy and nasal endoscopy, which provide a dynamic view of the velopharynx. Direct visualization can identify the closure pattern and contributions of the velum, the lateral and posterior pharyngeal walls, and Passavant ridge to speech [111]. Surgical correction of this defect is commonly attempted by creating a pharyngeal flap in which flaps of mucosa and muscle are raised from the posterior pharynx and attached to the velum (Fig. 36.30). This results in a permanent midline connection between the palate and posterior pharynx. Alternatively, a sphincter pharyngoplasty is performed, in which small lateral pharyngeal flaps are tucked under a wide medial flap to create a bulky transverse roll in the posterior pharynx, which narrows the pharynx and allows contact with the velum.

The result of these procedures is a narrowed nasopharyngeal vault and the potential for obstructed nasal airflow. Obstructive sleep apnea is not uncommon after a pharyngeal flap is created, especially with the Robin sequence [112–114]. Velocardiofacial syndrome is the most common syndrome causing palatal clefting and velopharyngeal insufficiency. It is associated with medially displaced carotid arteries that increase the risk of pharyngoplasty [115]. Velopharyngeal insufficiency can be identified by nasoendoscopy but not with endoral examination. Blind nasal tracheal intubation or insertion of a nasogastric tube should *not* be attempted in patients who have a pharyngeal flap. However, Kopp reported performing nasotracheal intubation in patients with a pharyngeal flap by first passing a flexible suction catheter to determine the patency of each naris and to identify the pharyngeal flap passages [116]. When the catheter emerges through the ostium created by the flap, it is grasped with a clamp and the endotracheal tube gently passed over it. At times it has been necessary to take down the flap due to severe postoperative airway obstruction.

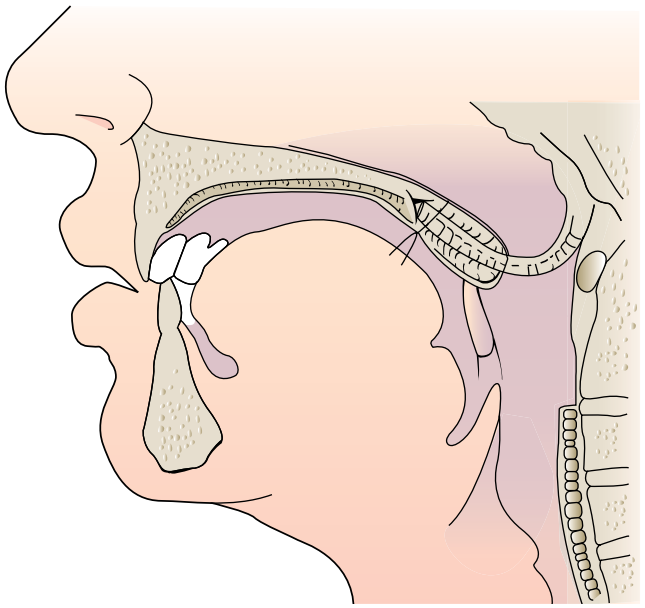


Figure 36.30 Pharyngeal flap. A flap of mucosa and muscle is raised from the posterior pharyngeal wall and attached to the soft palate. *Source*: Reproduced from Shprintzen et al. [186] with permission from the American Cleft-Craniofacial Association.

KEY POINTS: SURGICAL PROCEDURES FOR CRANIOFACIAL RECONSTRUCTION

- Timing of craniofacial surgery is often controversial. As long as there is sufficient head growth, as occurs in most single-suture craniosynostoses and other craniofacial disorders that do not involve the cranial vault, surgery is scheduled in the second half of the first year, usually between 6 and 8 months of age
- More extensive midface and orbital advancement procedures, and mandibular procedures, are normally performed at older ages, usually 4–5 years or later
- Primary cleft lip repair is normally performed at 3–6 months of age, and cleft palate repair at 6–12 months of age
- A pharyngeal flap may be needed at a later date to address velopharyngeal incompetence; the nasopharyngeal airway is usually obstructed after this procedure

Anesthesia for craniofacial reconstruction

Preoperative evaluation

Many factors influence the emotional state of patients and families who face major craniofacial surgery [117–120]. Pediatric patients with craniofacial anomalies often have behavioral problems, poor self-image, anxiety, introversion, and negative social experiences. These problems are rarely profound and represent limitations rather than severe psychopathology [120]. Most children with craniofacial anomalies make social and psychological adjustments to their appearance without functioning in a psychosocially deviant range. Surgery is stressful for the patient and parents [121]. They have fear of pain and of physical jeopardy because the surgery is extensive and potentially life threatening. Older children may also fear loss of identity because of the impending changes in their appearance. Parents may be very protective. Many patients undergo multiple surgical procedures over many years, and the child and family have invested great emotion in the process.

It is important to establish rapport and gain the confidence and acceptance of the patient and parents. One can be sensitive yet open and candid in discussing the anomalies. It helps to encourage the child and parents to express their concerns and expectations. The child may have problems with sight, hearing, or speech, and these must be accommodated during preoperative preparation. Various hospital activities such as

puppet plays, movies, storybooks, and other play therapy may help to prepare the child for the coming events.

It is appropriate to be reassuring to the patient and family, because the procedure offers hope and the surgical results are usually good. Eighty-seven percent of patients report subjective improvement in appearance after surgery [122]. In addition to increased satisfaction with body image and improvement in their emotional state, some patients also have improved behavior and school performance. Ninety-one percent of parents of small children and 77% of adolescents would undergo the surgery again [118,123].

A complete preoperative medical evaluation is required. There are potential differences between craniofacial and isolated orofacial procedures. Patients undergoing craniofacial surgery should have preoperative evaluation, including sleep studies. The possible need for ICP monitoring should be discussed with the parents preoperatively. Patients with craniofacial anomalies often have syndromes and have anomalies of other systems. Relevant and comprehensive information about rare diseases is available on the internet at sites such as Orphanet, the portal for rare diseases and orphan drugs. (www.orpha.net). Associated CNS pulmonary and cardiac anomalies are especially noteworthy. Because of the nature and extent of the surgery, a careful history of bleeding tendencies should be obtained. Twenty to 37% of patients undergoing major craniofacial surgery have airway problems [124,125]; 65% of patients with mandibular dysostosis (Treacher Collins, Goldenhar, or hemifacial microsomal syndromes) and 53% of patients with craniofacial synostosis have problems with their airways.

It is important to evaluate thoroughly and comprehensively the airway because not all airway abnormities are readily apparent. Patients often undergo multiple procedures, so a history of airway problems during previous procedures and how they were managed should be reviewed. If airway management is expected to be difficult and a tracheostomy may be required, this should be discussed with the patient and parents before surgery.

Certain facial, upper airway, and neck anomalies make airway management by mask and tracheal intubation difficult. It is difficult to get a good mask fit and seal when there is facial asymmetry, malar hypoplasia, or nasal deformities. Anatomical anomalies, such as choanal atresia or stenosis, macroglossia, micrognathia, and diminished nasopharyngeal space, may cause airway obstruction. Secretions or adenoidal hypertrophy may further obstruct small air passages. Awake patients may have signs of airway obstruction, e.g. mouth breathing. Other signs, such as snoring, noisy breathing, and apnea, may be present only during sleep. Snoring with frequent sleep arousals, abnormal movements during sleep, daytime somnolence, nocturnal enuresis, and morning headaches are signs of sleep apnea. A history of sleep apnea can be elicited by asking whether the child snores and holds his or her breath between snores. Poor attention spans and school performance and/or personality and behavioral changes are also symptoms of obstructive sleep apnea. In severe cases, the child may be underweight and have pulmonary artery hypertension or cor pulmonale. The child's heart should be auscultated for a loud second heart sound and the liver for enlargement, suggesting significant elevation of right heart pressures. Patients with upper airway obstruction during sleep may have airway obstruction during premedication-induced somnolence, during mask induction of anesthesia, and after extubation of the trachea.

Airway anomalies may render direct visualization of the larynx difficult or impossible. Mandibular hypoplasia or micrognathia, microstomia, macroglossia, trismus, and restriction of TMJ movement may make laryngoscopy difficult. Certain anatomical features should be carefully studied, including shape, size, and symmetry of the mandible, anteroposterior distance from the chin to the hyoid bone, tongue size, shape of the palate, movement of temporomandibular joints during mouth opening and during anterior displacement of the jaw, and mouth size when open (interincisor distance). Range of motion of the neck, especially extension, should be determined. Vertebral anomalies, such as cervical vertebral fusion in patients with Goldenhar, Apert, Crouzon, and other craniosynostosis syndromes, may limit neck motion [126]. During endotracheal intubation, retroflexion of the head may be necessary. Patients with Chiari malformation may have brainstem compression during flexion or severe extension of the head. Discussion should take place with the family and surgeon preoperatively about possible consequences of intubation maneuvers. It may be better to accomplish tracheal intubation with a fiberoptic bronchoscope without moving the head from a neutral position. It is recommended that every anesthesia department dealing with those patients have written standard operating procedures available for how to deal with expected and unexpected difficult airways. Moreover, regular simulation training in fiberoptic intubation techniques is necessary to ensure individual skills.

Laboratory evaluation

When large blood loss is expected, the minimal laboratory testing required in otherwise healthy children usually consists of hemoglobin or hematocrit determinations and type and cross-matching of blood. Tests of coagulation (e.g. prothrombin and partial thromboplastin times, platelet count, and bleeding time) should be considered, especially in young infants. Other laboratory evaluations, such as chest x-ray, electrocardiogram (ECG), pulmonary function tests, arterial blood gases, and serum electrolytes, may be required, depending on coexisting conditions. An echocardiogram is required if there is evidence of pulmonary hypertension.

Preoperative medication

Preoperative medication can be used to augment but not to substitute for psychological preparation. The use of preoperative medication must take into account the need for sedation and the presence of coexisting conditions and airway anomalies. For example, patients with increased ICP or potential airway obstruction may not safely tolerate respiratory depressants. Optimal sedation should smooth the induction process. Oral benzodiazepines are generally well tolerated for this purpose. Benzodiazepines, pentobarbital, and chloral hydrate can be administered orally or rectally. Fentanyl can be administered in a transmucosal form. Painful intramuscular injections should be avoided when possible. A local anesthetic cream patch (2.5% lidocaine and 2.5% prilocaine) placed

above a vein can minimize the pain of inserting a venous catheter. The patch is usually removed 1 h prior to puncture. High-resolution ultrasound may facilitate peripheral venous access for those patients in whom it is required. Antisialagogues can be included with oral premedication but should be used with care because they may cause a dry mouth and fever after the procedure.

Intraoperative anesthetic management

Successful anesthetic management requires close communication between the surgeon and anesthesiologist, especially when the surgeon is working near the airway or when rapid blood loss occurs. Anesthesia management is influenced by the patient's coexisting conditions, airway anomalies, and by particular features of the craniofacial procedure. In general, standard operating procedures written by anesthesiologists and surgeons help standardize the intraoperative management of the patient and assure optimal quality of care.

Associated conditions

Associated respiratory, cardiac, and neurological anomalies or disorders will influence anesthetic management. The presence of cervical vertebral anomalies can influence head positioning or the procedure being done. If the patient has complex craniosynostosis, consideration must be given to the possibility for raised ICP, as previously discussed. Signs and symptoms of elevated ICP are uncommon. Even when the ICP is normal, intracranial complications may occur in some areas if the cranial vault inadequately accommodates the brain in all dimensions. Anesthetic induction and maintenance techniques and agents should decrease not increase the ICP of these patients.

Airway anomalies

Unexpected airway obstruction may occur during the induction of anesthesia. Physical appearance is not always a reliable indication of potential airway obstruction, and a past uneventful anesthetic course does not preclude the occurrence of airway problems this time, especially when a cleft palate has been repaired or pharyngeal flap procedure has been done in the interim. When difficulty with the airway is anticipated, a general plan of how to deal with the problem should be formulated ahead of time – no single technique is foolproof. The plan should include provision for several alternative techniques, and the availability of a variety of equipment, especially laryngeal mask airways (LMAs) and small tracheal tubes. The presence of additional personnel with experience in securing a difficult airway is recommended. It is advisable to proceed cautiously with the anesthesia induction. Spontaneous ventilation offers a margin of safety. Airway catastrophes can be avoided by allowing the patient to breathe spontaneously until it is verified that controlled ventilation is possible and easy to establish.

Difficulty with the facemask fit can be overcome by building up the face with gauze, applying a large mask over the entire face, and by using high gas flows. Clear masks with moldable air cushions often fit best, but care should be taken to assure that the cushion does not impinge on the eyes or obstruct the nares. Some patients develop upper airway obstruction during light levels of anesthesia. This can be prevented or attenuated by clearing the nasal passages of secretions before the induction of anesthesia and by maintaining the "sniffing" position, opening the mouth, applying gentle positive airway pressure (5–10 cmH_2O), and employing a "jaw thrust" when the patient is sufficiently anesthetized to tolerate it. Nasopharyngeal and oral airways may also be useful.

With mandibular hypoplasia and other oral and cervical malformations, direct laryngoscopy may be impossible or possible only with unconventional maneuvers. The larynx of these patients is often described as being "anteriorly placed." The larynx is actually in a normal position with respect to the other cervical structures but the tongue, which is attached to the hypoplastic mandible, is more posterior than normal and overhangs the larynx, giving the impression that the larynx is anteriorly p1aced [127]. It is often impossible to open the mouth adequately and displace the tongue sufficiently to allow visualization of the larynx.

Laryngeal mask airway and fiberoptic bronchoscopy are important tools for airway management of patients with craniofacial malformations. The LMA can be inserted in awake infants (with topical anesthesia) or after induction of anesthesia in infants and children to aid blind or fiberoptic-guided tracheal intubation. A mobile "difficult airway" cart, including all devices for unexpected or expected airway difficulties, is recommended (see Chapter 16) [128–130].

Many reports describe difficulty with airway management in patients with craniofacial malformations. Before LMA and fiberoptic bronchoscopy were available, some unconventional maneuvers for obtaining an airway were described, such as forcefully pulling the tongue out with a suture, forceps, or custom-made retractors or using a Jackson anterior commissure laryngoscope with an "optical stylet." Blind or tactile tracheal intubation, with and without lighted guides, has also been described [131–134]. Video-assisted rigid endoscopes are now available to facilitate tracheal intubation of patients with a difficult airway. Oxygen is insufflated via the connector tube to prevent hypoxemia during video-assisted tracheal intubation. It is also helpful to use a laryngoscope to open the airway before inserting the rigid scope (Fig. 36.31).

Some patients require a tracheostomy for airway management. In some centers elective tracheostomy is performed

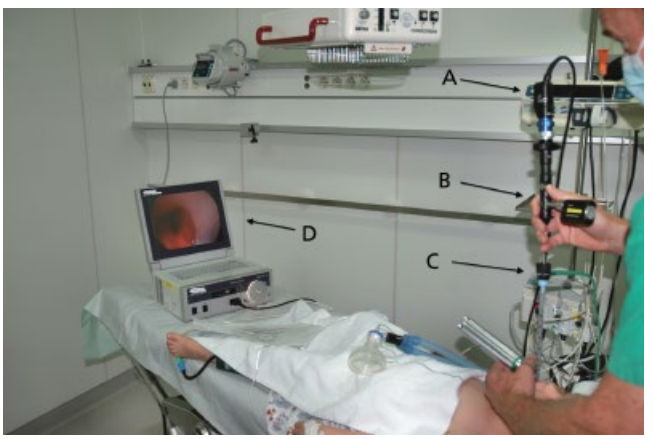


Figure 36.31 Single-handed usage of a Bonfils rigid optical scope for tracheal intubation in a difficult airway situation. (A) Optical unit. (B) LED light source. (C) Tube connector with oxygen insufflation. (D) Monitor.

when extensive facial osteotomies are planned in small children or when the airway would be difficult to manage if intraoperative reintubation were necessary [135]. When rigid internal fixation with plates is used rather than using intermaxillary ligation, tracheostomy can sometimes be avoided. Some patients already have a tracheostomy in place to treat severe respiratory obstruction. The complications and hazards of tracheostomy in pediatric patients include accidental decannulation of the trachea, tube obstruction, hemorrhage, and air leaks (pneumothorax, pneumomediastinum, subcutaneous emphysema). Chapter 16 presents an extensive discussion of management of the difficult airway.

KEY POINTS: PREOPERATIVE EVALUATION FOR CRANIOFACIAL RECONSTRUCTION

- Children with craniofacial anomalies often have problems with sight, hearing, or speech, and these must be accommodated during the preoperative preparation
- There are potential differences between craniofacial and isolated orofacial procedures. Patients with craniofacial anomalies often have syndromes and/or anomalies of other systems
- Airway anomalies may render direct visualization of the larynx difficult or impossible. Mandibular hypoplasia or micrognathia, microstomia, macroglossia, and trismus, may make laryngoscopy very difficult
- Range of motion of the neck, especially extension, should be determined and needs to be discussed with the surgeon. During endotracheal intubation patients with Chiari malformation may have brainstem compression during flexion or severe extension of the head
- Patients with increased intracranial pressure or potential airway obstruction may not safely tolerate respiratory depressants for anxiolytic premedication

Features of the craniofacial procedure

Several features of craniofacial surgical procedures will influence anesthetic management: the procedure may be long with extensive tissue exposure; massive blood loss may occur; the procedure may be intracranial; and the airway may be in the surgical field.

Long procedure with wide tissue exposure

Major craniofacial procedures average 4–5 h but can last for more than 12 h; operating time is reduced with an experienced surgical team [136,137]. Meticulous attention must be paid to protecting the anesthetized patient during prolonged surgeries. This includes proper positioning with the joints comfortably flexed, peripheral nerves protected, and pressure points, including the head, adequately padded. The patient may be in a supine, prone, or modified prone position for the surgery (Fig. 36.32).

During a long period of wide tissue exposure, large amounts of body heat are lost. Temperature homeostasis is maintained by employing measures to conserve and provide heat, including minimizing the amount of time the patient is exposed to cold air before draping, warming the room to 23–24°C, and using a heat lamp before draping. A warming blanket or forced-air warming device should be used, along with passive insulation (plastic or cloth covers) around the body. Irrigation and intravenous fluids and blood should be warmed, and airway gases should be heated and humidified. When large portions of the cranium are exposed, the skull should be repeatedly bathed in warm irrigation fluid. Corticosteroids are often administered before craniofacial surgery to reduce postoperative facial swelling, but there is little evidence to support doing so.

Excessive blood loss

The magnitude of blood loss is related to the extent and duration of the surgical procedure and may equal multiples of the patient's blood volume for major craniofacial surgery. Blood loss reportedly decreases with greater experience of the team [136,137]. In one study, patients undergoing craniosynostosis repair had a mean estimated red cell volume loss of 91% of total estimated volume (range, 5–400%) [138]. The amount of red cell volume loss was greater for infants less than 6 months of age, for complex versus simple synostosis, and for complex vault remodeling compared with forehead reconstruction and strip craniectomy. Infants who underwent strip craniectomy lost about 60% of their blood volume [139].

Bleeding from the osseous venous plexus is generally continuous and may be quite brisk during osteotomy and bone mobilization. Rapid loss of large volumes of blood can occur with uncontrolled arterial bleeding or inadvertent opening of a dural sinus. For example, the internal maxillary artery may be divided during mandibular osteotomy, and the palatine artery may be cut during a Le Fort I procedure. The severed artery may be difficult to identify and clamp if it retracts into an inaccessible location. Irregularities on the internal surface of the cranium (e.g. bone spurs invaginating the dural sinuses) can cause dural sinus tears and hemorrhage that often cannot be controlled rapidly. Other sources of major bleeding are the major extradural and pharyngeal veins. Scarring and adhesions increase persistent bleeding and make major arterial, sinus, and venous bleeding more likely during repeat operations [140–143].

Blood loss should be aggressively replaced milliliter for milliliter in infants. It is unwise to fall behind in blood replacement as sudden, rapid blood loss may occur. For larger children and adolescents, initial blood loss replacement can be with appropriate volumes of crystalloid or colloid solutions until a reasonable level of hemodilution is achieved. Much of the blood loss is unmeasurable because it is hidden in the surgical field and drapes. Close communication with the surgeon about the pace of bleeding and close monitoring of the patient's intravascular volume are necessary. Normovolemia should be maintained with a combination of packed red blood cells and fresh frozen plasma (FFP). Because the child's blood volume is small, serial blood gas analyses should be made and include hematocrit and the level of lactic acidosis to detect decreased tissue perfusion.

Blood and blood components should be available close to the operating room. At least two relatively large-bore intravenous catheters should be in place to permit swift infusion of blood. Blood transfusion may be rapid and massive and have

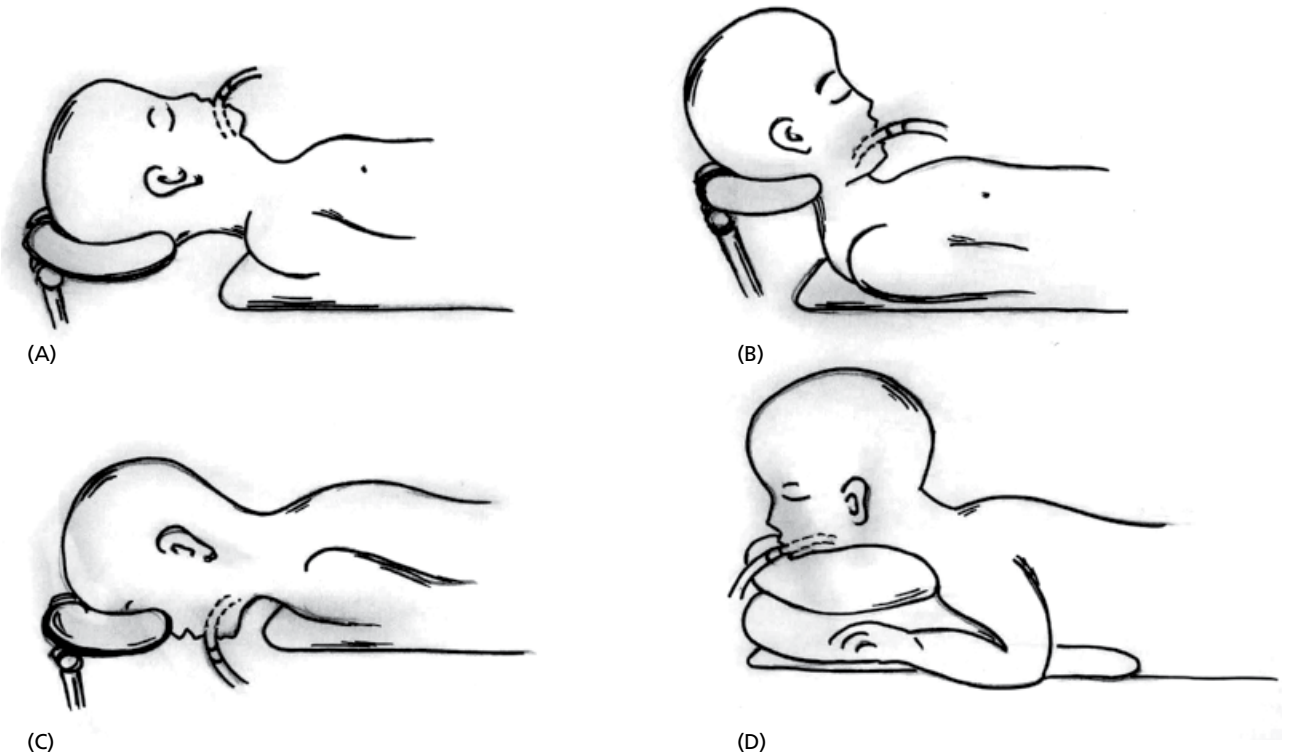


Figure 36.32 Positions in craniosynostosis surgery. (A) Supine position for frontal, frontoparietal, and orbitofacial lesions. (B) Supine with head inclination for frontal, parietal, and frontobasal lesions. (C) Prone position for parieto-occipital and suboccipital lesions. (D) Prone position with head reclination for total cranial vault exposure.

all the attendant problems (e.g. hypocalcemia, hyperkalemia, coagulopathy). When blood replacement exceeds one blood volume, coagulation factors, especially platelets, may need replenishment. Osteotomies, especially of the maxilla, may continue to ooze after surgery, so the child's hematocrit should be adequate when they leave the operating room. Induced hypotension is used to limit blood loss and create a drier surgical field, but there is no consensus on its utility and no objective data to support its use in cranial surgery.

Both induced hypotension and hyperventilation can cause cerebral hypoxia [144,145]. Therefore, it is probably unwise to combine the two. Regional brain ischemia may occur even when global perfusion is normal (e.g. when the frontal lobes are retracted). For these reasons, deliberate hypotension may be better suited to extracranial rather than intracranial procedures, although it has been used for both. Nowadays these techniques are seldom used. Other techniques that have been used to reduce or eliminate homologous blood transfusion during craniofacial surgery include preoperative administration of erythropoietin and intraoperative autologous blood salvage [146]. The cost of erythropoietin treatment makes its routine use prohibitive. The usefulness of intraoperative autologous blood salvage in small children is limited because transfusion is usually required before sufficient autologous blood can be collected. Further miniaturization of the available devices may make this technique more attractive.

For many years, antifibrinolytic agents such as aprotinin and tranexamic acid (TXA) were used to decrease intraoperative blood loss [147]. Since the withdrawal of aprotinin from the market, only TXA and ε-aminocaproic acid (EACA) are available for this purpose. A randomized, double-blind, placebo-controlled study of TXA in 46 children aged 2 months to 6 years undergoing craniosynostosis surgery revealed a dramatic decrease in blood loss (65 versus 119 mL/kg, $p < 0.001$) and blood transfusion (33 versus 56 mL/kg, $p = 0.006$) with TXA [148]. New pharmacokinetic data about TXA use in craniofacial surgery has recently been published [149]. Using data from 23 patients who received TXA in the randomized controlled trial described, a two-compartment pharmacokinetic model was devised, with co-variates of bodyweight and age in the final model. A loading dose of 10 mg/kg TXA, followed by 5 mg/kg/h infusion, was predicted to achieve and maintain plasma concentrations above the 16 μg/mL threshold for adequate inhibition of fibrinolysis and plasminogen activity. This regimen avoids the high plasma levels seen with higher loading doses, and presumably reduces risk for seizures. A recent report of 1638 patients undergoing cranial vault reconstruction from the multicenter Pediatric Craniofacial Surgery Perioperative database, in which 36% received TXA, 23% EACA, and 40% no antifibrinolytic, found a seizure incidence of 0.6%, with no difference between those receiving TXA and the remainder of patients in the database [150].

There are recent reports of the use of point of care thromboelastography (TEG®, Haemonetics Corp., Braintree, MA, USA) and thromboelastometry (ROTEM®, Instrumentation Laboratory, Bedford, MA, USA) to both predict the risk of a significant blood loss of >60 mL/kg, and to direct coagulation factor replacement [151,152]. Specifically, the TEG maximum amplitude <55 mm was the best predictor of massive blood loss, and the ROTEM measure of fibrinogen concentration, FibTEM, maximum clot firmness with a value of <8 mm, as a trigger to transfuse fibrinogen concentrate reduced the transfusion of FFP and costs of transfusion significantly.

If there is excessive bleeding, recombinant factor VIIa can be administered. This factor is not approved for

intraoperative use in coagulation disorders but is frequently used off label. It is an interesting substance that has promising effects on refractory non-surgical bleeding [153]. Chapter 12 presents an extensive discussion of intraoperative bleeding, blood transfusion, and coagulation factor therapy.

Intracranial procedures

Anesthetic techniques that decrease intracranial volume should be employed for intracranial procedures. Fronto-orbital procedures require brain manipulation and retraction to allow adequate exposure of the anterior cranial fossa and facial bones. Reducing the brain bulk decreases the amount of brain retraction necessary. Therefore, anesthetic agents such as ketamine, which increase intracranial volume, should be avoided. Opioids, benzodiazepines, thiopental, propofol, isoflurane, sevoflurane, and desflurane, in combination with mild hyperventilation (end-expiratory measured CO_2 between 30 and 35 mmHg) are preferred. Other measures used to decrease intracranial volume include 20–30° head-up positioning and the use of diuretics (mannitol and furosemide) [154,155]. The respiratory pattern during mechanical ventilation should not inhibit intracranial CSF and venous drainage. Therefore, positive end-expiratory pressure should be avoided, and mean airway pressure should be maintained as low as is consistent with adequate oxygenation by using a long expiratory time, if possible.

Potential hazards during intracranial procedures include dural sinus tears, cerebral edema, and venous air embolism. Dural sinus tears may produce rapid, massive blood loss. Manipulation and retraction of the brain may cause cerebral injury and edema. Air embolism occurs through open venous channels because the open cranium is usually positioned above the central circulation [155–157]. Meticulous surgical technique may prevent this complication.

Intraoperative airway management

During a Le Fort midface advancement, the surgeon must work around the airway. With maxillary osteotomy and down-fracturing maneuvers, the nasotracheal tube may be lacerated, transected, or dislodged from the trachea. Pilot tubes for endotracheal tube cuffs are easily cut. A plan should be formulated ahead of time between the surgeon and anesthesiologist for how an endotracheal tube will be replaced should this become necessary. Usually, the surgical field is quickly covered with sterile drapes, and the anesthesiologist is allowed access to the airway. Replacement tubes, catheter guides, and other appropriate equipment for reintubation must be readily available.

When the tracheal tube is in the surgical field, care must be taken to ensure an adequate airway despite lack of access to the face. The anesthesia circuit should be lightweight and all connectors should be well secured. The head of the operating table may be turned 180° from the anesthesia machine. Consequently the airway circuit must have adequate length to allow this. If the surgeon will move the head during the procedure, it must be ensured that the endotracheal tube and circuit are unencumbered. Care must be taken when initially positioning the endotracheal tube to avoid either tracheal extubation when the neck is extended or when the maxilla is advanced or endobronchial intubation when the neck is flexed. The maxilla or mandible can be advanced by as much as 3 cm with neck flexion. The tracheal tube should be secured with wires or sutures tied around teeth, nasal septum, mandible, or alveolar ridge. Nasotracheal intubation is required when the procedure is intraoral or when intermaxillary fixation is required. Armored tubes prevent compression of the airway by surgical manipulation. Close communication between the surgeon and anesthesiologist is required prior to tracheal intubation to determine the best position for the tracheal tube. Care must be taken to prevent nasal necrosis when a nasotracheal tube will be in place for hours. The hypopharynx should be packed to prevent intraoperative aspiration of blood, bone chips, and tissue. At the end of the procedure, the nose, mouth, and pharynx should be cleared and the stomach aspirated of gas, blood, and other material.

Postoperative swelling of the face and scalp may be severe. The swelling after bilateral midface and mandibular osteotomies may dictate that the tracheal tube remains in place for 12–48 h. This is especially true when intermaxillary fixation and occlusive intraoral prostheses limit access to the airway. Persistent oropharyngeal bleeding, cerebral edema, or pulmonary disease may also delay tracheal extubation. Tracheal extubation should occur when the patient is fully awake, has intact airway reflexes and an empty stomach, and is able to follow commands. Ensuring that an air leak is present around the endotracheal tube with the cuff deflated is a method often used to predict an unobstructed airway after extubation. Provisions should be made for immediately re-establishing an artificial airway (including wire cutters to release intermaxillary fixation wires) should this become necessary.

Other anesthetic considerations

Anesthetic drugs should be chosen on the basis of the preceding considerations. Depth of anesthesia can be balanced with muscle relaxation to prevent coughing, bucking, or patient movement with erratic surgical stimuli. Preferably, the patient should be awake and comfortable at the end of the procedure so that neurological assessment can be made. This can be accomplished by using a potent narcotic or "balanced" technique or by titrating narcotics when the patient is emerging from anesthesia. Extracranial bone graft sites (rib or iliac crest) may cause more postoperative pain than the cranial sites.

Fluids should provide maintenance requirements, replace interstitial and evaporative losses, and maintain urine output above 0.5 mL/kg/h. The exact amount of fluid required to accomplish these goals will depend on the extent of tissue dissection and exposure. For small infants, electrolyte solutions, like Ringer acetate with 1% of glucose, provides optimal maintenance of fluids and blood glucose concentrations. A urinary bladder catheter should be placed to prevent bladder distension and for intravascular volume monitoring. Serial blood analyses of arterial pH and blood gases, hemoglobin, electrolytes, ionized calcium, glucose, and coagulation parameters are made.

A high level of physiological monitoring is required. Routine anesthesia monitors, such as ECG, pulse oximeter, temperature, and airway gas and pressure monitors, are used. In addition, an intra-arterial catheter is placed to allow direct blood pressure monitoring and blood sampling. A central venous catheter is useful for monitoring intravascular volume and for

rapidly infusing drugs and fluids. Central venous oxygen saturation can be used to estimate cardiac output in children. A central venous oxygen saturation of <50–60% should prompt detailed evaluation of the patient's circulatory condition. Arterial blood pressure and waveform are good indicators of intravascular volume. A broad-based pressure wave, with the dichrotic notch in the upper half of the downslope of the curve and little or no variation with respiration, is a good indicator of normovolemia. During intracranial procedures, evidence of venous air embolism should be sought with capnography (see Chapter 19) and a precordial Doppler because the open cranium is generally above the central circulation. A central venous catheter may occasionally allow aspiration of entrained air, although early detection and prevention of further entrainment are more important than trying to aspirate the gas.

Perioperative hazards, complications, and outcomes

Although large series of major craniofacial surgery attest to its relative safety, significant morbidity and mortality can occur [158]. Intraoperative death has occurred with massive blood loss and air embolism. Postoperative death has resulted from cerebral, respiratory, and circulatory causes (e.g. cerebral edema, massive extradural hemorrhage, respiratory arrest, respiratory obstruction or tracheal extubation, tracheostomy blockage, and hemorrhage) [159–161]. A recent study analyzed 8101 major craniofacial procedures and determined the mortality rates and major morbidity. The authors found that serious complications have significantly decreased and suggested that protocols for airway management, blood salvage and replacement, age-appropriate deep venous prophylaxis, and timing of subcranial midfacial advancements might further reduce the mortality rate [162].

Other reported intraoperative complications include cardiac arrest from severe blood loss, air embolism, and pneumomediastinum (a complication of tracheostomy), pneumothorax during rib graft procurement, subdural hematoma, and bradycardia from the oculocardiac reflex [163–165]. Stimulation of any sensory branch of the 5th cranial nerve (maxillary, mandibular, ophthalmic) can cause reflex bradycardia and asystole. Reflex bradycardia and asystole have also been noted during maxillofacial and temporomandibular surgery [165]. Ocular pressure should be avoided because it too can cause severe bradycardia.

Several complications related to the endotracheal tube have been reported, including intraoperative tracheal extubation (usually during midface advancement), endotracheal tube blockage by kinking (also during midface advancement), and endotracheal tube laceration [127]. Pilot tubes for cuffed endotracheal tubes have also been lacerated. There are several reports of emergency endotracheal tube replacement intraoperatively. Complications of tracheostomy have included tube kinking, laceration of the posterior tracheal wall, esophageal perforation, and cardiac arrest from pneumoperitoneum [127,166,167]. Subgaleal or epidural drains require special care, especially when placed next to venous sinuses. The vacuum used for drains is related to the size of the used subgaleal or epidural drains. Rapid opening of the suction can cause significant blood loss. Non-fatal postoperative complications have included respiratory obstruction after tracheal extubation, pulmonary edema, cerebral edema, extradural hematoma, subgaleal hemorrhage, seizures, infection, blindness, CSF leaks, facial nerve damage, bone resorption, and hydrocephalus [168].

A recent report of the Pediatric Craniofacial Surgery Perioperative Registry of 1223 cases of complex cranial vault reconstruction gives a comprehensive picture of the challenges that the anesthesiologist faces in caring for these patients (Table 36.4) [169]. This same group also reported a case–control study of endoscopic versus open craniosynostosis repair [170]. Using a 2:1 matching by propensity scoring of control open surgeries versus endoscopic surgeries in a total of 933 patients, major intraoperative parameters (such as transfusion volume and anesthesia and surgery time) and postoperative events (including postoperative intubation and length of stay in the intensive care unit (ICU) and in hospital) were significantly improved in the endoscopic group. Incidence of critical intraoperative events such as hypothermia, hypotension requiring pressors, venous air embolism, and cardiac arrest, was not different between groups.

Postoperative care and outcomes of major craniofacial surgery

Many patients undergoing major craniofacial surgery will require postoperative ICU care for one to several days. Criteria for ICU admission vary by institution, but a recent study by Goobie and colleagues of 225 patients undergoing open craniosynostosis repair in a single center developed a risk prediction model for clinically significant cardiorespiratory or hematological postoperative events, such as reintubation, or significant postoperative blood transfusion [171]. Fifteen percent of this cohort had cardiorespiratory events, and 30% had hematological events. Major risk factors were weight <10 kg, American Society of Anethesiologists (ASA) physical score (PS) 3 or 4, intraoperative transfusion of >60 mL/kg blood products, or TXA not administered (Fig. 36.33) [171].

KEY POINTS: FEATURES OF THE CRANIOFACIAL PROCEDURE

- Major craniofacial procedures average 4–5 h but can last for more than 12 h. Meticulous attention must be paid to proper positioning with the joints comfortably flexed, peripheral nerves protected, and pressure points, including the head, adequately padded
- Blood loss is greater for infants <6 months of age, for complex versus simple surgery, and for complex vault remodeling compared with forehead reconstruction and strip craniectomy. However, even infants who undergo strip craniectomy may lose up to 60% of their blood volume
- Although large series of major craniofacial surgery attest to its relative safety, significant morbidity and mortality can occur. Intraoperative death has occurred with massive blood loss and air embolism
- Recent registry and large single-center studies have demonstrated risk categories for adverse intraoperative events, excessive bleeding, and need for ICU care. These include weight <10 kg, ASA PS3 or 4, intraoperative transfusion of >60 mL/kg, and not using intraoperative TXA.

Table 36.4 Reported adverse events, complications, and outlier outcomes (all ages)

	n	%
Cardiovascular		
Intraoperative vasopressor infusion	89	7.3
Intraoperative hypotension	65	5.3
Intravenous epinephrine bolus	39	3.2
Bradycardia requiring treatment	19	1.6
Postoperative vasopressor infusion	7	0.6
Suspected venous air embolism (VAE)	7	0.6
Suspected VAE with end-tidal CO_2 plus blood pressure changes	6	0.5
Suspected VAE with cardiovascular collapse	1	0.1
Postoperative hypovolemic shock or hypotension	6	0.5
Intraoperative cardiac arrest	3	0.2
Postoperative cardiac arrest, code, or rapid response call	2	0.2
Respiratory		
Unplanned postoperative intubation/mechanical ventilation	29	2.4
Difficult airway	27	2.2
Postoperative respiratory failure	16	1.3
Unintentional intraoperative extubation	13	1.1
Intraoperative bronchospasm	11	0.9
Reintubation (failed extubation in operating room)	10	0.8
Postoperative reintubation	4	0.3
Postoperative pneumonia	3	0.2
Postoperative pulmonary edema	2	0.2
Neurological		
Postoperative seizures	9	0.7
Seizures attributed to hyponatremia	2	0.2
Transfusion		
Intraoperative erythrocyte-containing blood product transfusion		
>40 mL/kg	328	26.8
>60 mL/kg	115	9.4
>80 mL/kg	50	4.1
Total blood perioperative blood donor exposures, ≥6	46	3.8
Suspected transfusion reaction	2	0.2
Hematological		
Initial postoperative INR >1.5, PTT >45 s, or fibrinogen <100 mg/dL	59	4.8
Initial postoperative platelet count, <100,000/μl	41	3.4
Initial postoperative hemoglobin, <6.5 mg/dL	7	0.6
Electrolytes		
Hyponatremia: [Na^+] <135 mEq/l	251	20.5
Hyperkalemia: [K^+] >5.5 mEq/l	3	0.2
Other		
Intraoperative hypothermia (temperature, <35°C)	35	2.9
Unplanned second surgical procedure	8	0.7
Cerebrospinal fluid leak	7	0.6
Surgical site infection	5	0.4
Diabetes insipidus	1	0.1
Central catheter-associated bloodstream infection	1	0.1
Deep venous thrombosis	1	0.1
Sepsis	1	0.1
Length of stay		
ICU length of stay ≥6 days	39	3.2
Hospital length of stay ≥9 days	46	3.8

ICU, intensive care unit; INR, international normalized ratio; PTT, partial thromboplastin time.

Anesthesia for cleft lip and cleft palate reconstruction

Preoperative evaluation

The anesthesiologist's approach to patients with a cleft lip and palate is similar to that described in the preceding section for patients with other craniofacial deformities. In this case, however, the surgical procedure is less extensive. By the time the infant with a cleft lip comes for surgery at 3 months of age, the parents have usually overcome their initial reactions to their infant with a craniofacial anomaly and are hopeful that surgery will restore normal appearance and function. Preoperative preparation must accommodate the older child with a cleft palate who may have communication problems due to poor speech and hearing. Many children require multiple procedures. Every effort should be expended to ensure that the anesthetic experience is not unpleasant for either the parent or child.

A complete medical evaluation should be made, with special attention to the presence of other anomalies and syndromes. All patients with a cleft palate have Eustachian tube dysfunction and usually have chronic serous otitis with clear rhinorrhea. Acute otic infections should be resolved before surgery. Preoperative sedation is appropriate for children who have no airway compromise.

Intraoperative management of anesthesia

Induction

Most patients with an isolated cleft lip or palate present no difficulty with airway management. Only 3% of 800 patients undergoing repair of cleft lip and palate had difficult laryngoscopy [172]. Those with a difficult airway had retrognathia and/or were less than 6 months of age [173]. The protruding premaxilla associated with extensive bilateral clefts of the lip and alveolus sometimes prevents visualization of the larynx. While the incidence of failed intubation is low [167], it does occur. Therefore, it may be wise to induce anesthesia while the patient is spontaneously breathing. It is useful to have a second anesthesiologist to help with the airway management. The ability to manage the airway should be assessed before the patient is rendered apneic. Airway obstruction may occur if the tongue is impacted in a palatal cleft. This is easily remedied when recognized. Care must be taken to avoid injuring a protruding premaxilla during laryngoscopy. Antisialagog drugs are useful for oral procedures. Inserting a preformed, curved tracheal tube (Ring–Adair–Elwyn tube) that lies flat against the face minimizes the potential for tube kinking and dislodgment. A stylet can be used to facilitate tracheal tube insertion when necessary. The tube should be fixed in the midline, with the lip immobile and not distorted (Fig. 36.34).

Maintenance

There are several intraoperative special anesthetic considerations for cleft lip and palate reconstruction procedures. The first is that the airway is shared with the surgeon. Thus, the tracheal tube must be well secured to prevent inadvertent

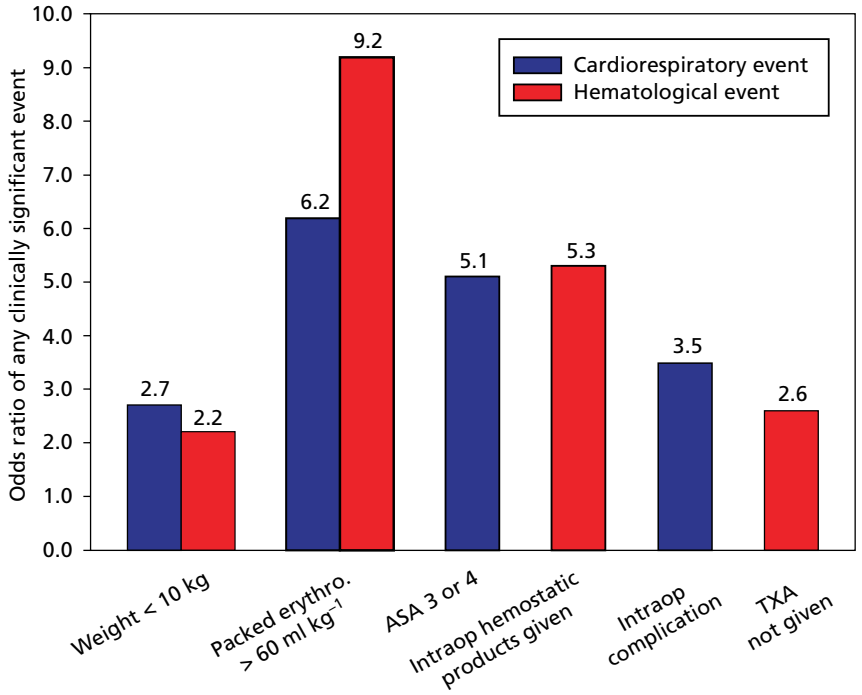


Figure 36.33 Odds ratios for the six multivariate predictors of any clinically significant postoperative event requiring ICU admission. The multivariate risk factors include bodyweight <10 kg, packed erythrocyte transfusion >60 mL/kg, ASA class 3 or 4, hemostatic blood product transfusion (platelets, fresh frozen plasma, and/or cryoprecipitate), intraoperative complication, and tranexamic acid (TXA) not given. *Source*: Reproduced from Goobie et al [171] with permission of Wolters Kluwer.

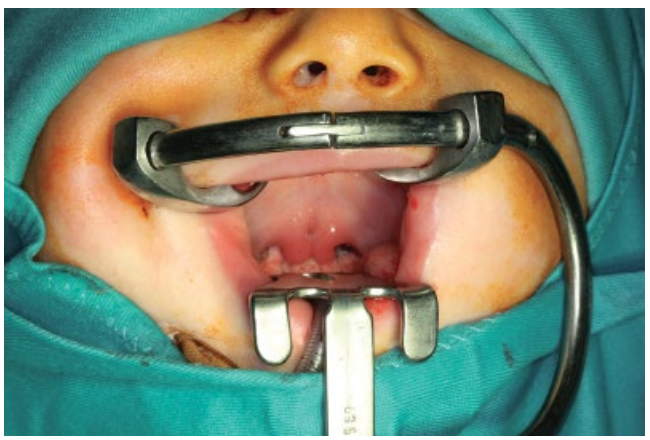


Figure 36.34 "Kilner Dott" mouth gag in place for cleft palate repair in a patient with Pierre Robin sequence (bifid uvula). The metal armored tube is safely secured under the lower part of the mouth gag.

dislodgment. Adequacy of the airway should be continuously assessed, especially after patient positioning and placement of a mouth gag or pharyngeal packs. For palate and pharyngeal procedures, correct positioning may require exaggerated neck extension, which may bring the endotracheal tube up and out of the trachea. A mouth gag provides surgical exposure and stabilizes the endotracheal tube, but it may also occlude the tracheal tube (Fig. 36.34). Pharyngeal packs are placed to prevent aspiration of blood. Compression or kinking of the tube may occur with these maneuvers. Care should be taken by the surgeon to avoid contacting the tracheal tube with a cautery, as this may cause an airway fire. The FiO_2 should be <0.3 when possible.

Other anesthesia considerations are routine. Fluid and temperature homeostasis must be maintained. Blood loss is rarely sufficient to require transfusion, although it is occasionally necessary in palate and pharyngeal procedures, especially when the hemoglobin concentration is at least 10 g preoperatively. Inhalation anesthesia is commonly used, but the choice of anesthetic agent is not crucial as long as the considerations outlined here are accommodated.

KEY POINTS: ANESTHESIA FOR CLEFT LIP AND CLEFT PALATE RECONSTRUCTION

- Patients with a cleft palate have Eustachian tube dysfunction and usually have chronic serous otitis with clear rhinorrhea
- Most patients with an isolated cleft lip or palate present no difficulty with airway management
- For palate and pharyngeal procedures, surgical positioning may require exaggerated neck extension, which may displace the endotracheal tube out of the trachea
- The most common acute postoperative problems are bleeding and airway obstruction

Postoperative management

The most common acute postoperative problems are bleeding and airway obstruction. At the conclusion of palate and pharyngeal surgery, the pharynx must be inspected for bleeding and the presence of pharyngeal packs. Leaving a pharyngeal

pack in place can be lethal when the endotracheal tube is removed. Some surgeons place a heavy silk tongue suture which is secured to the face, to allow for rapid opening of the airway with traction on the suture for anterior displacement of the base of the tongue. Placing the infant or child in the lateral position permits drainage of blood and secretions from the pharynx. Extubation of the trachea should be delayed until the patient is fully awake and has regained normal neuromuscular function to minimize potential airway obstruction from either anatomical causes or from bleeding. Applying a mask or artificial airway may damage a lip or nose repair, so it is advisable to delay extubation until the patient can maintain a patent airway without assistance. After lip procedures, infants are restrained with arm boards to prevent them from disrupting the repair.

After a palatoplasty or pharyngoplasty, the infant or child awakens from anesthesia with an altered upper airway. The presence of constricting flaps and nasopharyngeal edema compromises the nasal airway and may abruptly convert the child to a mouth breather. This problem is magnified in patients who have Pierre Robin complex. After pharyngoplasty, 10% or more of patients experience temporary obstructive sleep apnea [173]. Sleep apnea is completely eliminated when the surgical technique is modified and a nasopharyngeal airway is kept in place for the first 48 h after surgery. Fifty-seven percent of patients are predominantly or exclusively mouth breathers after palatoplasty or pharyngoplasty [174]. Up to 72% of patients develop sleep apnea after pharyngoplasty.

Pharyngeal anomalies are common with craniofacial syndromes and place the patients at high risk for airway obstruction, especially after pharyngoplasty [174]. The anomalies may be structural (pharyngeal narrowing related to malformation of the basicranium (Treacher Collins syndrome) or mandibular (Robin sequence). They may also be functional, e.g. the pharyngeal hypotonia of the velocardiofacial syndrome. One patient died 4 weeks after surgery [175].

Acute postoperative airway obstruction caused by massive lingual swelling has also been reported after palatoplasty. The mouth and tongue should be carefully inspected before tracheal extubation, particularly if the mouth gag has been in place for more than 2 h. If the mouth gag must be in place for 2 h, it should be let down for a few minutes to allow the tongue to be perfused. The lingual swelling is often the result of a reperfusion injury.

Infiltration of local anesthetic will decrease the need for postoperative analgesia. Non-narcotic analgesics are preferred, but when narcotics are required they should be titrated to effect. Infraorbital nerve blocks can be performed while the patient is asleep to prevent pain after cleft lip surgery [176,177]. Postoperative pain therapy can be guided by using pain scales [178–180].

CASE STUDY

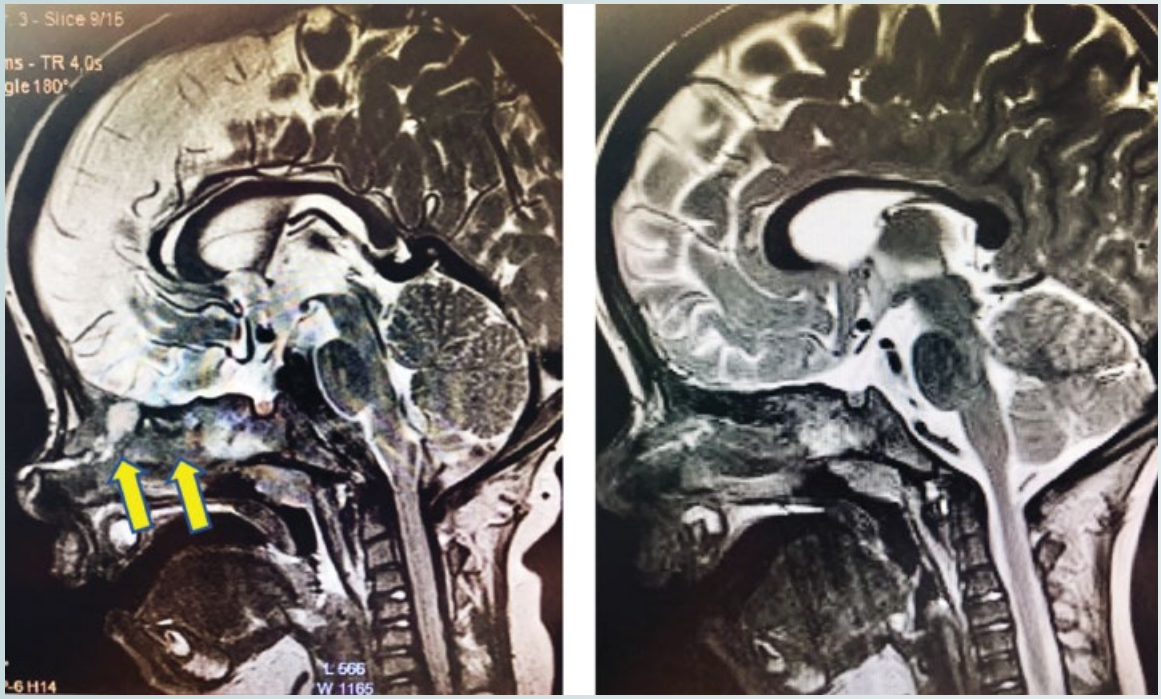
A 2-year-old, 10.8 kg, 84 cm tall, male patient was scheduled for resection of a congenital dermal sinus of the nose together with a resection of an epidermoid tumor located subcranially at the base of the scull (Fig. 36.35A). The planned procedure was a cranioplastic surgery with a fronto-orbital advancement. There were no congenital genetic disorders, but the patient had undergone multiple surgeries due to a congenital heart defect. The boy was a preterm infant (34 weeks of gestation, birthweight 2200 g). The primary diagnosis at that time was a tricuspid atresia type Ib. The patient underwent a cavopulmonary anastomosis ("Glenn" operation) at the age of 5 months. Since then he was doing well hemodynamically with routine cardiology follow-up. Another problem was that the child had chronic, multiple episodes of aspiration and pneumonias of unclear etiology. Bodyweight gain and overall development were normal. Baseline pulse oximeter saturation of the child was between 79% and 85%. He was receiving anticongestive medication together with a low dose of aspirin. The preoperative echocardiography revealed normal myocardial function, no mitral regurgitation, and a patent cavopulmonary anastomosis.

Considerations for anesthesia

Because it was suspected that a large amount of blood might be lost during surgery, 4 units of packed red blood cells (PRBC) and 2 units of FFP were available for the patient preoperatively. Additionally, the patient was on anticoagulants and therefore platelets were ordered too. The use of an antifibrinolytic agent, e.g. TXA (initial dose 10 mg/kg bodyweight by bolus followed by 5 mg/kg/h), was planned. Because of the cyanotic congenital cardiac disease the goal was to maintain a high hemoglobin (14–15 g/dL) throughout the procedure. The anesthesiologist decided to administer blood and blood components (FFP) early in the case to prevent low hemoglobin in order to maintain patient-adjusted "normal" oxygen carrying capacity. Because patients with cavopulmonary anastomosis benefit from spontaneous breathing rather than mechanical ventilation, early extubation was the primary goal. Normally it is preferred to perform nasal intubation in small children because of improved tube fixation and ease of weaning ventilation in the emerging patient. In this case, the nose had to be free so oral intubation was preferred. Meticulous attention to prevention and detection of venous air embolism is important for all craniofacial surgery, and even more so in cyanotic congenital heart disease. In this patient, venous air from the surgical site would travel down the superior vena cava and enter the pulmonary arteries, potentially causing obstruction. Systemic air in the arterial circulation would not be expected.

Induction of anesthesia

Anesthesia was induced with propofol (2.5 mg/kg) and remifentanil (1 μg/kg) with oxygen. Special care was taken to keep the intrathoracic pressure as low as possible to ensure unobstructed venous backflow to the heart. Tracheal intubation with direct laryngoscopy was facilitated by



(A) (B)

Figure 36.35 Preoperative (A) and postoperative (B) MRI scans of a dermal sinusoid together with a skull based epidermoid tumor. The arrows in (A) point to the tumor.

administering rocuronium (1 mg/kg). No further muscle relaxation was needed during the case. An orogastric tube and a urinary catheter and temperature probe were placed into the urinary bladder after induction of anesthesia. Sevoflurane and remifentanil (0.3–0.5 μg/kg/min) were used to maintain anesthesia. The inspired oxygen fraction was 0.3 to maintain a SaO_2 between 75% and 85%. Thirty minutes before the end of anesthesia, a longer acting opioid, together with a NSAID, was administered.

Cardiovascular monitoring

A double-lumen 4 Fr central venous catheter was inserted in to the right femoral vein to measure cardiovascular pressure continuously. The internal jugular vein was avoided because of the cavopulmonary connection with its high venous pressure equal to pulmonary artery pressure, to not take any chance of obstructing cerebral venous drainage. Another large-bore peripheral IV was added after induction. The right radial artery was cannulated with a 22-gauge catheter for on-line arterial blood pressure monitoring and blood sampling. Monitoring in the perioperative period consisted of continuous measurement of arterial and venous pressures, temperature (via the urinary catheter), oxygen saturation by pulse oximetry, end-expired CO_2, and urine output. Blood gases, pH, electrolytes, and glucose and lactate concentrations were measured every 1 h or more frequently, as required. Venous oxygen saturation was determined from central venous blood samples and used to estimate cardiac output and blood volume status, although it must be remembered that in patients with a femoral venous catheter with its tip in the inferior vena cava, the measured venous saturation is not equal to the central venous saturation in the superior vena cava – it is normally higher. For this case the trend over time was most important, not the absolute values.

Airway management

Preoperatively there was no concern that oral tracheal intubation might be difficult. The patient's mouth opening was not limited and he had been intubated easily for previous surgery. Therefore, equipment for fiberoptic tracheal intubation was not necessary for this patient. It was known from his previous surgeries that facemask ventilation was without problems. Because the patient would be in the prone position, free access to the nose and airway was not possible due to fronto-orbital advancement (see Fig. 36.20), so an armored oral tracheal tube was inserted. Care was taken to fix the tracheal tube securely to the face with liquid adhesive and tape to avoid accidental tracheal extubation during surgery. Because surgery would last several hours, great care was taken to prevent the compression of soft facial tissues (eyes, nose) when the patient was placed in the prone position (see Fig. 36.32).

Body temperature

Care was taken to prevent intraoperative hypothermia for several reasons. First, to prevent inhibition of the coagulation system; second, to prevent hypoperfusion and local ischemia (e.g. metabolic acidosis and lactate production); and third, to prevent hypoventilation and respiratory acidosis once spontaneous ventilation returned and the trachea was extubated. Prevention of hypothermia would also avoid the negative effects of shivering and cardiovascular depression after surgery.

Intraoperative management

After induction of anesthesia and insertion of the tracheal tube, the surgeons and anesthesiologists together positioned the patient for surgery. Maintenance fluid consisted of acetate buffered Ringer solution with 1% dextrose added (4 mL/kg/h) to maintain a normal glucose concentration. Volume losses were initially replaced with 4 mL/kg/h of Ringer solution without dextrose as needed. During reflection of the scalp, packed red blood cells and FFP (5 mL/kg each) were administered. The primary goal was to maintain a supranormal hemoglobin concentration of >14 g/dL due to the palliated congenital heart defect. Once the scalp and bone were reflected and surgical coagulation was accomplished, PRCBs and FFP were given as needed to maintain the hemoglobin concentration and to prevent bleeding. Despite prophylactic administration of PRBCs, the hemoglobin concentration decreased below initial values (Table 36.5). The estimated blood loss during surgery was 340 mL, about 40% of the patient's blood volume. These losses were initially replaced with Ringer solution and then with PRBCs and platelets (15 mL/kg) at the end of the procedure. Heat loss was prevented by wrapping the patient's extremities with sheet wadding and by actively warming him with a thermal blanket and warmed-humidified inspired gases. Despite this he initially lost about 1°C in body temperature. Anesthesia was maintained with a combination of sevoflurane and remifentanil, as described earlier.

Because the intraoperative period was uneventful and because spontaneous ventilation returned and was adequate, the trachea was extubated in the operating room once the child was awake as planned before the operation. The oxygen saturation measured with pulse oximeter was 90% 15 min after extubation. He was transferred to the PICU to monitor for bleeding and for signs of elevated intracranial pressure. Postoperative blood loss was 75 mL, which was replaced with PRBCs. Tracheal extubation occurred at the end of surgery because (1) it was superior to positive pressure ventilation to ensure unobstructed venous backflow through the cavopulmonary anastomosis, and (2) it was felt that it would be easier to monitor for signs of increased intracranial pressure if the patient was awake and spontaneously breathing, remembering that because of the cavopulmonary connection with its elevated pressure, the margin of safety for elevated ICP is smaller. The patient was positioned with head elevated 30°, both to minimize edema and bleeding, and to facilitate venous drainage through the cavopulmonary connection. Postoperative fluid administration was restricted to that which maintained urine output at about 1 mL/kg/h. This fluid restriction was done to reduce the likelihood of increasing ICP and of causing pulmonary edema. The day after surgery all monitoring lines were removed, and the patient was transferred to the ward in good condition. He was discharged home several days later and has done well. The postoperative MRI several months later revealed a good surgical result (Fig. 36.35B).

Conclusions

This case demonstrates several important points.

- Because of the underlying additional congenital heart defect the oxygen content of the blood needed to be maintained throughout surgery. Patient-adjusted "normal" hemoglobin values (>14 g/dL) were required. Blood loss is common in these cases, especially when there has been previous surgery. This child lost 340 mL of blood during the case despite an infusion of PRBCs and plasma at the beginning of the case and attempts to maintain normal coagulation. Adequate fluid and blood products were administered to maintain normal arterial and central blood pressures and to prevent metabolic acidosis.
- Patients with cyanotic heart defects may have coagulation disorders due to platelet dysfunction (see Chapter 27). In those cases the use of an antifibrinolytic agent,

Table 36.5 Laboratory values determined before and at each hour during craniofacial surgery in a patient with extensive craniofacial surgery complicated because of operated congenital heart defect

	Preop	1 h	2 h	3 h	End of operation	PICU
Hemoglobin (mg/dL)	15.2	14.4	12.4	13.7	15.3	14.2
PaO_2 (mmHg)	68.3	79.3	87.1	79.5	80.3	87.8
$PaCO_2$ (mmHg)	44.1	43.2	39.8	42.1	49.3	41.5
SaO_2 (%)	77	70	75	75	90	82
pH	7.39	7.41	7.40	7.39	7.29	7.35
BE (mEq/L)	0.9	1.0	0	0	–3.6	–2.0
International normalized ratio (INR)	1.0	1.2	1.5	1.2	1.2	1.0
Prothrombin time (PT) (sec)	12.0	13.3	16.5	13.4	13.2	13.1
Activated partial prothromplastin time (PTT) (s)	36.2	40.1	43.2	41.0	40.9	37.2
Platelets (× 10^9/L)	352	205	168	210	289	301
Lactate (mmol/L)	0.9	0.9	1.0	1.2	0.9	0.9
Body core temperature (°C)	36.5	35.5	35.9	36.1	36.4	36.3
PRBC transfused (mL)	–	50	60	50	20	40
FFP (mL)	–	25	25	25	20	20
Platelets (mL)				70	50	20

BE, base excess; PRBC, packed red cells; FFP, fresh frozen plasma; PICU, pediatric intensive care unit.

e.g. tranexamic acid (initial dose 10 mg/kg bodyweight by bolus followed by 5 mg/kg/h), is recommended. Additionally, platelets must be available because the patient was on anticoagulants preoperatively. There is a fine balance required. One does not want to have excessive bleeding, and at the same time one does not want to cause excessive clotting that may obstruct the child's cavopulmonary shunt.

- It is important to take measures to maintain a normal body temperature during surgery, especially when it is desirable to extubate the trachea at the end of the surgery. Hypothermia may cause hypoventilation, increased $PaCO_2$, and increased intracranial pressure. If the case lasts long enough, hypothermia may cause clotting abnormalities and increase intraoperative bleeding. Maintaining a normal body temperature must be balanced against the fact that a 1–2°C reduction in brain temperature is neuroprotective (see Chapter 8).
- Measuring intravascular pressures and urine output during surgery helped determine the adequacy of fluid and blood products replacement. Urine glucose concentrations were measured several times during the case because high concentrations of glucose in the blood may cause an osmotic diuresis that gives the false impression of normal urine flow, even in hypovolemic patients.

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A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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Further reading

Rath GP, Bithal P, Chaturvedi A, Dash H. Complications related to positioning in posterior fossa craniectomy. J Clin Neurosci 2007; 14: 520–5. This retrospective study is an example of how positioning is influencing neurosurgical operations.

CHAPTER 37
Pain Management in Children

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Introduction

The management of pain and related symptoms is part of the daily practice of pediatrics, pediatric anesthesiology, and pediatric intensive care. In this chapter, we will outline aspects of how the experience of pain changes with age, how analgesics act at different ages, and how to treat some common acute and chronic pain conditions in pediatrics.

Developmental neurophysiology of pain

Studies by Fitzgerald and others have shown that there is considerable maturation of peripheral, spinal, and supraspinal neurological pathways necessary for nociception by late in the second trimester of human gestation [1]. Although the general architecture of the sensory nervous system is established by midgestation, there are some differences in preterm and term neonates compared with older infants as patterns of connections and functions mature over the first months of life. Peripheral sensory fibers involved in nociception have larger, more overlapping, receptive fields and lower thresholds for impulse activation in infant animals, compared with mature animals [2]. Descending pain inhibitory pathways, such as the dorsolateral funiculus [3], tend to develop postnatally. This has been interpreted to suggest that neonates and young infants may perceive pain more intensely or have hyperresponsiveness to pain compared with older infants and children with a more mature nervous system.

Many of these initial studies emphasized maturation of peripheral and spinal mechanisms and simple withdrawal reflexes. More recently, attention has focused on cortical representation of responses to injury in neonates and young infants [4]. Studies of brain activation using near-infrared spectroscopy have shown that a noxious stimulus to the heel of a neonate evokes increased signals overlying the contralateral cerebral cortex [4]. This implies that a specific pattern of activation occurs in response to a noxious stimulus as opposed to the global, non-specific pattern of activation seen with autonomic arousal. This and other evidence suggests that painful stimuli reach the cerebral cortex in infants although this evidence does not establish that pain is perceived as a conscious experience or as suffering in neonates. Despite the delay in the development of spinal descending pathways and neurotransmitters, α-adrenergic agonists and opioids administered via epidural or spinal routes exert analgesic effects in newborn animals [5,6] and humans [7,8]. Adult functional magnetic resonance imaging (fMRI) studies of cortical networks involved in pain have emphasized activation of both somatosensory pathways as well as pathways involved in salience, emotion, learning, and fear. Recent fMRI studies of brain activation from noxious events have found extensive overlap of regional brain activation, but with some differences [9–11].

Several studies have been interpreted as providing evidence that infants are able to form implicit memory of pain and that there are potentially negative behavioral consequences of untreated pain in infants. Taddio showed that infants who were circumcised with little or no analgesia had significantly increased pain behaviors at their 2-, 4-, and 6-month immunizations when compared with infants who were uncircumcised or who had received adequate analgesia [12]. Studies of adult rats who had received persistent inflammatory stimuli as neonates showed long-term changes in the dorsal horn synaptic organization and nociceptive functioning [13]. Newborns undergoing major surgeries when

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

randomized to relatively light versus relatively deeper anesthetic techniques showed better suppression of stress responses with deeper anesthetic techniques, as well as some reductions in postoperative morbidities [14–17]. Conversely, studies of critically ill newborns undergoing mechanical ventilation have not shown a clear benefit from routine administration of morphine infusions compared with controls who just received intermittent morphine prior to suctioning or other painful procedures [18].

Pain assessment in infants and children

Assessing pain in infants and children is a fundamental aspect of pediatric care and serves as the foundation for treating pain. Most pain assessment tools for infants, toddlers, and preschool children are based on the developmental age of the child and often combine behavioral and physiological parameters, since self-report measures may not be possible in preverbal children or accurate in hospitalized young children. Readers interested in this topic are referred to a consensus statement on pediatric pain measurement [19]. Studies indicate that healthcare providers tend to underestimate pain using observational measures compared with parents' or children's own ratings. Children who are ill, hospitalized, and confronted with strangers may not participate with self-report measures; pain assessment tools designed for younger children may be more useful in these cases.

Pain assessment in infants and preterm babies is particularly challenging. Infants rely on caregivers to interpret their behavior and other signs in determining whether they have pain. Numerous studies have examined pain responses in infants and have shown that infants exhibit predictable response patterns with respect to stress hormone levels, behavior patterns, and changes in heart rate, oxygen saturation, blood pressure, and other physiological patterns. Neonates who are subjected to repeated heel lancing for blood analyses consistently swipe at the affected foot, indicating their ability to localize to the site of pain. Infants display gradations in heart rate, blood pressure, and oxygen saturation in response to varying intensities of pain, indicating their ability to discriminate severity of pain. Nevertheless, physiological parameters are non-specific indicators of pain and can reflect fear, hunger, anxiety, and emotional distress as well as pain [20]. As a result of these studies and others, pain assessment tools in infants are typically composite pain scores that combine observed distress behaviors such as facial grimacing, sleep–wake cycles, and body posture with physiological parameters, including heart rate, oxygenation, and blood pressure measurements. Behavioral responses to pain in premature infants may be much more subtle than those observed in full-term infants. In addition, behavioral and physiological pain scales are not applicable to critically ill infants who may be septic, hemodynamically unstable, or mechanically ventilated. The premature infant pain profile (PIPP) is a pain assessment tool for procedural pain that has been validated in premature and full-term infants (Table 37.1) [21]. The PIPP is unique in that gestational age is included in the scoring system in addition to distress behaviors, heart rate, and oxygen saturation. The FLACC scale combines five types of pain behaviors, including facial expression, leg movement, activity, cry, and consolability, and has been shown to have good inter-rater reliability and validity in children (Table 37.2) [22]. It is widely used because it is quick, versatile, and can be applied to infants and older children, including those with developmental disabilities [23].

Concrete thinking and variations in cognitive and language development in toddlers and preschool-age children can make pain assessment challenging in this age group. Preschool age children are often able to give simple measures of self-report such as location of pain but cannot provide more abstract details such as quality of pain. It is generally useful to involve parents or other familiar caregivers when questioning young children about their pain. A variety of pain assessment tools have been developed for young children. Studies indicate that many children tend to prefer faces scales where pictorial representations of faces are used to denote varying degrees of pain. Young children are able to differentiate pain intensity when presented with facial expressions, although more than five choices seems to interfere with the child's ability to reliably indicate pain. The Oucher scale (Fig. 37.1),

Table 37.1 Premature infant pain profile (PIPP)*

Indicators	0	1	2	3
Gestational age in weeks	≥36 weeks	32–35 weeks and 6 days	28–31 weeks and 6 days	<28 weeks
Observe the NB for 15 s alertness	Active	Quiet	Active	Quiet
	Awake	Awake	Sleep	Sleeping
	Opened eyes	Opened eyes	Closed eyes	Closed eyes
	Facial movements present	No facial movements	Facial movements present	No facial movements
Record HR and SpO_2				
Maximal HR	↑ 0–4 bpm	↑ 5–14 bpm	↑ 15–24 bpm	↑ ≥25 bpm
Minimal saturation	↓ 0–2.4%	↓ 2.5–4.9%	↓ 5–7.4%	↓ ≥7.5%
Observe NB for 30 s†				
Frowned forehead	Absent	Minimal	Moderate	Maximal
Eyes squeezed	Absent	Minimal	Moderate	Maximal
Nasolabial furrow	Absent	Minimal	Moderate	Maximal

* In this scale, scores vary from 0 to 21 points. Scores equal to or lower than 6 indicate an absence of pain or minimal pain; scores above 12 indicate the presence of moderate to severe pain.

† Absent is defined as 0–9% of the observation time; minimal, 10–39% of the time; moderate, 40–69% of the time; and maximal as 70% or more of the observation time.

bpm, beats per minute; HR, heart rate; NB, newborn.

Table 37.2 The faces, legs, activity, cry, and consolability (FLACC) scale

Category	Scoring		
	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to, distractable	Difficult to console or comfort

Each of the five categories face (F), legs (L), activity (A), cry (C), and consolability (C) is scored from 0 to 2, which results in a total score of between 0 and 10.

Figure 37.1 Oucher pain scale.

the Wong–Baker scale (Fig. 37.2) and the Bieri faces scale (Fig. 37.3) are examples of face scales that have been validated for use in children as young as 4 years of age. The Oucher scale, developed for use with children of all ethnicities, uses actual photographs of children and is available in several versions, each tailored to child ethnicity. Among the different face scales, in our view there are some psychometric advantages to the revised faces pain scale by Hicks et al [24]. Parental responses can affect a child's levels of observed behavioral distress and increased parental anxiety tends to correlate with increased levels of self-report pain scores in children undergoing painful procedures. Older school-age children and adolescents usually have the emotional and cognitive maturity as well as the language development to use self-report scales, although self-report is sometimes not accurate in this age range due to issues regarding behavioral control and self-esteem. Illness, hospitalization, and separation from parents may cause some older children and adolescents to regress emotionally, making pain scales designed for younger children more applicable. The meaning that pain has for a child also can influence their self-report. The color analog scale (Fig. 37.4) is a slide-rule device where gradations of color are used to denote degree of pain which has been validated for use in children as young as 5 years [25].

Pain assessment should be part of everyday practice in caring for hospitalized children. A successful, hospital-wide pain assessment program requires a committed, multidisciplinary team of healthcare providers, standard protocols of assessment methods and documentation, staff and parental education programs, and protocols for reassessment after pain treatment interventions. Essential to pain assessment is the use of validated, age-appropriate pain assessment tools as well as consideration of the child's developmental level, presence of fear and anxiety, parental factors, and the context of the child's pain.

KEY POINTS: PAIN ASSESSMENT IN CHILDREN

- Pain assessment for preverbal children is based on developmental age and combines behavioral and physiological parameters
- The FLACC scale and PIPP system are validated for young infants
- Faces scales, including Oucher, Wong–Baker, and Bieri, are validated for children as young as 4 years
- Visual or color analog scales can be used for older children

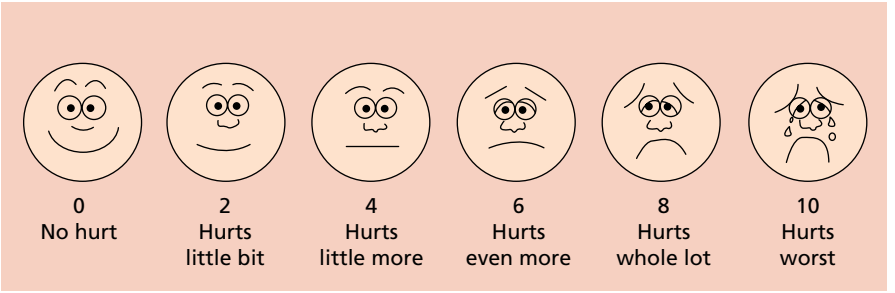

Figure 37.2 Faces (Wong–Baker) pain scale.

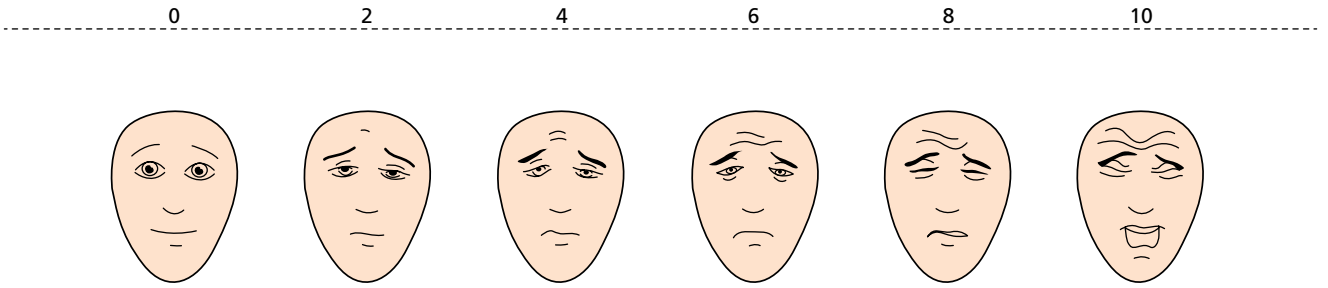

Figure 37.3 Faces pain scale revised (FPS–R) version.

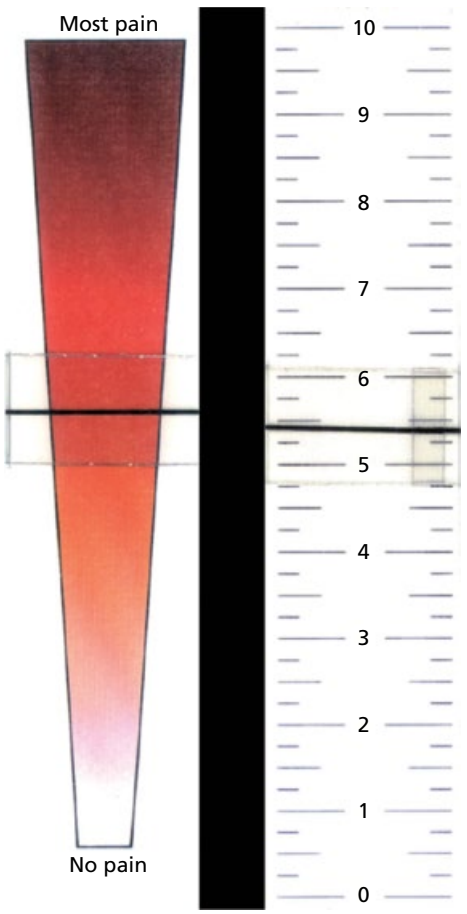

Figure 37.4 Color analog pain scale.

Developmental analgesic pharmacology in infants and children

A number of pharmacokinetic and pharmacodynamic factors produce age-related differences in responses to analgesics [26]. Neonates and young infants have immature hepatic enzyme systems involved in conjugation, glucuronidation, and sulfation of analgesics such as opioids and amide local anesthetics, causing prolongation of the elimination half-life and increasing the risk of drug accumulation. Rates of maturation of individual enzyme functions vary, but for most analgesics, metabolism has matured by around age 6 months. Glomerular filtration and renal tubular secretion are reduced in the first several weeks of life. Along with slower elimination of some native drugs that depend primarily on renal clearance, renal immaturity also results in a slower elimination of glucuronides of morphine and hydromorphone (which produce analgesia, sedation, respiratory depression, and excitatory reactions) and slow elimination of MEGX, a principle metabolite of lidocaine, which can cause seizures. Neonates and young infants have reduced levels of α1-acid glycoprotein and albumin, leading to decreased plasma protein binding for many drugs and increased concentrations of free, pharmacologically active, unbound drug. Infants have immature ventilatory reflexes in response to hypoxia [27,28] and hypercarbia [29]. The increased risk of hypoventilation in response to opioids in infants observed in clinical case series [30] probably reflects a combined effect of pharmacokinetic and pharmacodynamic immaturity, as well as the impact of disease states that are over-represented in hospitalized infants.

Non-opioid analgesics

Non-opioid analgesics refer to acetaminophen, aspirin, the non-steroidal anti-inflammatory drugs (NSAIDs), and the selective cyclo-oxygenase 2 (COX-2) inhibitors. COX enzymes convert arachidonic acid to various prostaglandins that have diverse physiological roles, contributing to pain, hypersensitivity, inflammation, thermoregulation, vasodilation, and protection of gastric mucosal integrity. The COX isoenzymes differ in their distribution and function in a variety of peripheral tissues and in the central nervous system. Aspirin and NSAIDs act on a broad spectrum of COX enzymes. Aspirin's irreversible inhibition of COX-1 in platelets contrasts with the reversible action of NSAIDs; this accounts for the much longer duration of aspirin's antihemostatic actions. The COX-2 inhibitors were

developed to specifically inhibit the COX isoenzyme subtype 2, which is expressed preferentially in leukocytes and other cell types involved in inflammation, as well as in neurons and glial cells in the peripheral and central nervous systems. While these drugs are commonly regarded as "peripheral" analgesics, analgesia from all of these drugs involves a combination of peripheral and central actions [31].

Ontogeny of prostanoid biosynthesis and cyclo-oxygenases

Studies by Ririe and co-workers have shown that administration of a COX-1 inhibitor does not reduce hypersensitivity to mechanical stimuli in infant rats. This lack of efficacy of COX-1 inhibitors in infant rats appears to be a result of developmental differences in the COX-1 expression in the spinal cord [32]. The data raise the question of whether commonly used analgesics acting on COX isoforms might be ineffective in infants due to delayed maturation of COX-mediated processes in spinal microglia.

Acetaminophen

Acetaminophen is one of the most widely used analgesics and has a good safety record for use in pediatric patients. It is often combined with opioids for additional analgesic effect. Acetaminophen is also sometimes dosed alternating with ibuprofen, although there are no clinical trials examining the effectiveness of this approach. Although the actual mechanism of analgesic and antipyretic action is somewhat controversial, acetaminophen seems to have an effect on the COX-3 isoenzyme, on endogenous cannabinoid receptors, and on TRPV1(transient receptor potential cation channel subfamily V member 1) receptors [33]. Cannabinoid receptor type 1 (CB1) and TRPV1 receptors are involved in pain and thermoregulatory pathways. Acetaminophen's analgesic actions appear to occur largely via sites within the central nervous system, though there is controversy regarding the importance of central COX-3 inhibition in acetaminophen's analgesic effects [34]. When compared with NSAIDs, acetaminophen exerts minimal peripheral anti-inflammatory effects and is associated with significantly less gastropathy, platelet dysfunction, and anti-inflammatory effect. Approximately 90% of acetaminophen undergoes sulfation and glucuronidation to water-soluble products, which are then eliminated by the kidneys. A small percentage of acetaminophen is metabolized by the CYP450 system to a toxic metabolite that binds to glutathione to form a non-toxic conjugate. Inadvertent dosing errors have led to fulminant hepatic necrosis and failure in infants and children when large doses overwhelm the binding capacity of existing hepatic glutathione stores. Therapeutic oral doses of 10–15 mg/kg result in peak plasma concentrations after 2–3 h. Pharmacokinetic studies show that peak plasma concentrations of IV acetaminophen are greater and are achieved more rapidly compared to oral dosing with evidence of good cerebrospinal fluid penetration [35,36]. The use of IV acetaminophen has been shown to be cost effective for pediatric tonsillectomy and idiopathic scoliosis surgery due to reduced adverse events and reduced postanesthesia care unit or hospital length of stay [37,38].

Because rectal absorption is inefficient and variable, peak drug levels with rectal dosing generally peak at 70 min but can vary considerably. Some studies have recommended much higher dosing than traditionally prescribed: rectal dosing with a first dose of 30–45 mg/kg followed by 20 mg/kg every 6–8 h produced generally therapeutic blood concentrations in several studies [39]. Even though the overall bioavailability of rectal acetaminophen is roughly half that of oral formulations, previous recommendations by the American Academy of Pediatrics have listed the same daily maximum doses for oral and rectal acetaminophen.

The analgesic efficacy of acetaminophen in newborns has not been established in controlled clinical trials. One study of rectal dosing of acetaminophen in infants following major surgery was negative [40,41], while a subsequent study by the same group of investigators found evidence for an analgesic/opioid-sparing effect of intravenous acetaminophen in a similar population [42].

It remains unclear whether some of these negative results reflect a true lack of efficacy due to any of the following: delayed maturation of the analgesic targets of acetaminophen, variable absorption, inadequate sensitivity of the pain models used, insensitivity of the pain measures used, or wash-out of treatment effects by the choice of an overly generous rescue analgesic regimen [43].

Non-steroidal anti-inflammatory drugs

The NSAIDs are widely prescribed as antipyretics, analgesics, and anti-inflammatory agents in children and, considering their widespread use, have a very good safety margin. They are often combined with opioids for improved analgesic effect and to reduce opioid use and side-effects. They are often first-line therapy for inflammatory pain. They produce their anti-inflammatory effect by reversibly inhibiting COX-1 and COX-2 isoenzymes and inhibiting the conversion of arachidonic acid to prostanoids. The clearances of several NSAIDs are slower in neonates and infants but more rapid in young children aged 3–10 years when compared with adults [44]. In postsurgical patients randomly assigned to receive an NSAID or placebo, with parenteral opioids as rescue analgesics, the NSAID groups typically show both lower pain scores and a 30–40% reduction in opioid use. Other studies have shown that standard doses of NSAIDs produce more effective analgesia than 30–60 mg of codeine in adults following surgery [45].

The incidence of serious side-effects from NSAIDs is very low in children 6 months and older, particularly with short-term use. A large-scale study in young children less than the age of 2 years of age receiving ibuprofen showed a very low incidence of serious side-effects [46]. There are few efficacy data on the use of NSAIDs in neonates. Many of the pharmacokinetic and safety data for use in neonates come from the use of ibuprofen and indomethacin in treating patent ductus arteriosus; ibuprofen appears to have less renal toxicity and less risk of hyponatremia than indomethacin in this age group. Many of the safety data for long-term use of NSAIDS are based on experience in treating juvenile rheumatoid arthritis [47]. Although children frequently complain of mild gastrointestinal upset with long-term NSAID use, serious gastropathy, gastrointestinal bleeding, and renal toxicity appear to be less common in children than adults. The risk of NSAID-induced renal toxicity can be increased in states of dehydration, concomitant use of other nephrotoxic drugs, use in pre-existing renal disease, and hypotension.

The use of NSAIDs in children undergoing tonsillectomy has become increasingly common over the past 10 years. NSAIDs are an attractive choice in patients with obstructive sleep apnea who are at risk for airway obstruction and hypoventilation with opioids after a tonsillectomy. Moreover, in a large number of analgesic trials and meta-analyses for tonsillectomy, NSAIDs provide good analgesia. Previously, there had been concern

regarding the impact of NSAIDs on immediate and delayed postsurgical bleeding that can occur after a tonsillectomy. While results of initial meta-analyses gave conflicting results, subsequent meta-analyses have largely found no significant impact of NSAIDs on clinically important bleeding events [48–50]. At Boston Children's Hospital, as with many pediatric centers around the USA, practice has changed towards the use of NSAID–acetaminophen combinations as a routine analgesic regimen for pain after tonsillectomy. COX-2 inhibitors for tonsillectomy are reviewed in a subsequent section.

Another controversy surrounding the use of NSAIDs is the concern of bone healing in postsurgical patients who require active bone formation, such as children with scoliosis who have undergone posterior spinal fusion and instrumentation. NSAIDs and COX-2 inhibitors clearly provide good analgesia and reduced opioid requirements for several types of orthopedic surgery [51]. NSAIDs are thought to interfere with bone healing since prostanoids produced by osteoblasts are associated with new bone formation and are involved with the balance between bone formation and bone resorption. Meta-analyses of case–control and cohort studies have suggested that the effects of short-term use of NSAIDs in most patient groups are clinically minor [52]. Reviews of heterotopic bone formation in adult patients after hip replacement have suggested a higher frequency of non-union; however, the number of patients studied was small and other risks for non-union may have been present. A meta-analysis of the effects of NSAIDs in adult patients with spinal fusions showed that short-term use of normal-dose NSAIDs appear to be safe after spine fusion but high-dose ketorolac increased the risk of non-union, implying that the risk may be in part dose dependent [53,54]. In general, children seem much less likely than adults to have impaired bone healing after surgery. In many pediatric centers, there is a growing trend towards use of NSAIDs following most types of orthopedic surgery, including scoliosis surgery, based on their opioid-sparing effects and major role in enhanced recovery after surgery (ERAS) protocols [55,56], as discussed further later in this chapter.

These authors' recommendation is to adopt a middle course pending more specific data on clinical outcomes and risks. For children at high risk for non-union or impaired bony fusion, NSAIDs probably should be avoided. Conversely, for children who are at comparatively low risk of non-union, who have had severe and difficult to control side-effects from opioids, or who have significantly increased risks from opioids, an NSAID or COX-2 inhibitor can be administered for 1–2 days postoperatively. Some studies suggest that selective COX-2 inhibitors are less likely to inhibit bone formation than traditional NSAIDs.

Ketorolac is a commonly prescribed parenteral NSAID often used as an adjuvant to opioids in the postoperative period. Despite the common belief regarding the "magic" of a parental route, ketorolac provides no stronger analgesia than other NSAIDs when given in recommended or equitoxic doses. Typical doses are 0.25 mg/kg every 6 h for a maximum of approximately 5 days. The recommendation duration of 5 days is based on the pivotal adult studies used to obtain US Food and Drug Administration (FDA) approval for postoperative use and because of an impression that more prolonged use further increases the risks of adverse events, especially gastropathy. In a randomized controlled trial of infants and children undergoing cardiac surgery, ketorolac did not increase the risk of surgical bleeding or gastrointestinal bleeding [57]. Small case series have not reported harm with use after surgeries in neonates and young infants [50,51], though larger prospective studies are needed to better define the risks of NSAIDs in those age groups.

Prostanoids produced by COX-1 isoenzymes are associated with the protection of the gastric mucosa and platelet aggregation. Randomized controlled trials in adult patients show that COX-2 inhibitors provide the anti-inflammatory effects of traditional NSAIDs but with a lower incidence of gastrointestinal symptoms and bleeding. Anti-inflammatory effects, analgesic efficacy, and incidence of renal toxicity with COX-2 inhibitors are comparable to other NSAIDs. NSAIDs and COX-2 inhibitors both alter the balance of pro- and antithrombotic products of arachidonic acid. For adults with risk factors for coronary artery disease, peripheral vascular disease, and carotid artery disease, COX-2 inhibitors appear to increase risks of cardiovascular events. Rofecoxib and valdecoxib were withdrawn from the US market due to reports of cardiovascular complications in adult patients; celecoxib and meloxicam remain available in the USA, but with warnings regarding these potential risks. With a few exceptions (e.g. children with genetically based hypercoagulability, children with Moya Moya disease), there is little basis to anticipate significant cardiovascular risks from COX-2 inhibitors in children [44]. We consider them to have a potentially favorable risk–benefit ratio for selected children with inflammatory pain who have severe gastrointestinal side-effects with traditional NSAIDs or those with underlying bleeding disorders, such as children with hemophilia. Certain modified non-acetylating salicylates with relatively mild gastric effects, including salsalate, diflunisal, or choline-magnesium salicylate, may also be considered in children who have gastrointestinal side-effects with NSAIDs. Since COX-2 inhibitors have minimal antiplatelet/antihemostatic effects, they should in principle be ideal analgesics for children undergoing tonsillectomy. Available data on COX-2 inhibitors regarding efficacy are mixed; some trials found COX-2 inhibitors equal to NSAID comparators and better than placebo [52], while other trials found COX-2 inhibitors either inferior to an NSAID or not distinguishable from placebo [53,57]. Overall numbers of subjects in these trials were small, and there is the potential for failing to identify analgesic effects due to type II error, or for study designs washing-out treatment effects by scheduled use of other analgesics. We could not identify a meta-analysis to assign a confidence interval for their odds ratio for post-tonsillectomy bleeding.

See Table 37.3 for dosing guidelines of commonly used non-opioid analgesics.

Table 37.3 Dosing guidelines for non-opioid analgesics

Analgesic	Dose <60 kg	Dose >60 kg
Acetaminophen	10–15 mg/kg q 4 h PO/IV	650–1000 mg q 4 h PO/IV
Naproxen	5 mg/kg q 12 h PO	250–500 mg q 12 h PO
Ibuprofen	6–10 mg/kg q 6–8 h PO	400–600 q 6 h PO
Celecoxib	2–4 mg/kg q 12 h PO	100–200 mg q 12 h PO
Ketorolac	0.5 mg/kg q 6–8 h IV, not for >5 days	30 mg q 6–8 h IV, not for >5 days

Dosing guidelines listed refer to children >1 year of age. Further modifications in dosing are required for use of these agents in term and preterm neonates and in infants. Modifications are detailed in the text.
IV, intravenous; PO, orally; q; every.

KEY POINTS: NON-OPIOID ANALGESICS

- Non-opioid analgesics refer to acetaminophen, aspirin, NSAIDs, and the selective COX-2 inhibitors
- Acetaminophen affects the COX-3 isoenzyme, cannabinoid, and TRPV1 receptors; has minimal anti-inflammatory effects; and IV doses are effective for mild pain or adjuncts to moderate–severe pain
- NSAIDs ketorolac and ibuprofen reversibly inhibit COX-1 and -2 isoenzymes and are effective in moderate pain; side-effect risk is low but includes renal dysfunction, gastropathy, bleeding, and bone non-union
- Celecoxib and meloxicam are COX-2 inhibitors with a low risk of side-effects, and are effective for inflammatory pain in children who have gastrointestinal and bleeding side-effects

Opioids

Opioids are widely used for the treatment of moderate to severe pain in infants and children, particularly in the immediate postoperative period. Safe and effective administration of opioids requires careful patient selection, knowledge of age-related differences in metabolism, dose titration, and aggressive treatment of opioid side-effects. Opioid prescribing for children over the past 30 years has undergone "pendulum swings." Case series from the 1960s and 1970s indicated that pediatric patients, particularly infants and young children, received inadequate doses of opioids for pain after surgery or advanced cancer, partly because of a lack of understanding of how opioids are metabolized and limitations in ability to assess pain in children. A greater understanding of the pharmacokinetics of opioids, developmental neuroanatomy, and validated pain scores have led to more appropriate dosing and the widespread use of opioids for pain management in infants and children. Over the 1980s and 1990s, opioids were prescribed more liberally for postoperative pain and cancer pain in many developed countries. In the past 15 years, opioid misuse has emerged as a major public health concern, especially in the USA. Aside from issues around misuse, opioid sparing has emerged as a major theme in postoperative analgesic management, because of the adverse effects of opioids on aspects of postoperative recovery [58,59].

There has been growing interest in multimodal approaches to pain management and ERAS programs for children. There is good evidence to support opioid-sparing effects and postoperative analgesic efficacy for acetaminophen–NSAID combinations combined with regional anesthesia [60,61]. Studies of gabapentin and low-dose ketamine as part of a multimodal regimen has shown mixed results [56,62–65]. Although there are limited multicomponent ERAS studies in children, outcomes among adolescents with idiopathic scoliosis having posterior spine fusions show early postoperative mobilization and reduced length of hospital stay using different care bundles [55,66].

Ontogeny of opioid actions

Opioid receptors are present by midgestation in a widespread distribution in the forebrain, brainstem, and spinal cord. Functional maturation occurs gradually in prenatal and postnatal life. For example, while the infant rat (postnatal day 5) has an extensive complement of opioid receptors in brainstem and forebrain distributions, coupling to Gi/o proteins, as assayed by the ratio of guanosine triphosphate binding to DAMGO binding in brain striosomal preparations, is less than 5% of that seen in adult rat brain preparations [67].

There is an extensive series of animal studies of the effects of acute or chronic opioid administration on subsequent development. For example, chronic opioid exposure in the prenatal and early postnatal life in the rat can lead to reductions in brain size, neuronal packing density, and dendritic development, with corresponding functional impairments in learning and locomotion [68]. Chronic opioid exposure in infant rats produces tolerance, withdrawal syndromes, and opioid-induced hyperalgesia [69]. The effects of opioids, ketamine, and other drugs on the developing animal are also modified by the presence of pain, injury, and/or inflammation [70]. In some models, there are apparent long-term benefits of administering opioids prior to injury or inflammation. Thus, extrapolations from animal studies regarding either benefit or harm of analgesics for newborns undergoing intensive care should be very cautious, in part because most animal models do not fully simulate all the types of perturbations seen with prolonged intensive care in humans.

Newborns undergoing intensive care are subjected to a large number of noxious procedures and mechanical ventilation, which per se produces stress and distress. Several studies have examined analgesia, side-effects, and potential long-term consequences of opioids for ventilated newborns, given either on schedule or around specific noxious procedures. In the NEOPAIN trial, infants receiving chronic morphine infusions did not show more long-term neurological impairments compared with controls, but there was essentially no evidence of benefit on distress measures, and increased open-label episodic morphine administration for distress was associated with worse outcomes [71]. Moreover, morphine has only mild effect on behavioral indices of distress during painful procedures in preterm neonates [72]. At present, there is very little consensus regarding either benefit or harm from opioids or sedatives in critically ill neonates [73]. Prolonged opioid therapy in critically ill neonates and children often leads to opioid tolerance; withdrawal can occur as opioids are weaned or discontinued [74].

The specific choice of opioid depends on numerous factors including the ability to tolerate oral intake and gut absorption, side-effects, severity of pain, and whether pain is escalating. Oral routes are preferred for mild to moderate pain in children who are able to tolerate oral intake and who have adequate gastrointestinal absorption. Intravenous routes should be used for children who have severe pain that needs to be rapidly controlled, for rapidly escalating pain, and for those who cannot tolerate oral opioids.

Codeine is considered a weak opioid and is often combined with acetaminophen to improve analgesia. It is also used as an antitussive agent; the FDA recently restricted the use of any opioid-containing antitussive to adults. Compared with other opioids, codeine seems to be associated with higher risk of nausea. Analgesic effect is through the hepatic metabolism of codeine to morphine by CYP2D6 although there is significant variability in both the pharmacokinetics and pharmacodynamics of codeine. Studying a British cohort of children coming for surgery, 47% of children studied had reduced CYP2D6

enzyme concentrations and 36% had no detectable levels of morphine or metabolites after a parenteral dose of 1.5 mg/kg of codeine [75]. In children who lack or have significantly reduced enzyme levels, codeine is essentially inactive and provides no analgesia. Conversely, for patients with CYP2D6 gene duplication or with an ultrarapid metabolizing allele, codeine may cause respiratory depression or death [76]. In the USA in 2012, the FDA began a series of positions and then black box warnings against the use of codeine as an analgesic for children. At Boston Children's Hospital and many other pediatric hospitals, codeine is no longer prescribed. In 2015 and again in 2017, the FDA issued a warning regarding pediatric use of tramadol, based on a somewhat smaller number of pediatric adverse events. Tramadol is a complex drug with multiple actions. It acts in part via monoamine pathways and in part as a prodrug by conversion to an opioid agonist. Metabolism involves both CYP3A4 and CYP2D6, so even though genetic variants can alter production of active products, it is overall probably less susceptible to extreme pharmacogenomic effects compared with codeine.

Oxycodone is a frequently used oral opioid for children with mild to moderate pain and is often used in the postoperative setting of converting from parenteral to enteral opioids. While historically oxycodone was used for moderate pain in relatively fixed doses, studies in adults showed that the dose of oxycodone, like morphine, can be escalated for moderate to severe pain. Oxycodone undergoes hepatic metabolism by CYP3A enzymes to normoxycodone and to a lesser extent to oxymorphone by CYP2D6 enzymes. Genetic variability of CYP2D6 enzymes results in a less profound effect on analgesia and adverse effects for oxycodone compared with codeine since CYP3A pathways to normoxycodone are predominant [77]. A pharmacokinetic study of oxycodone in infants showed great variability in both clearance and in the elimination half-life, especially in neonates [78]. Oxycodone is available as an elixir for children unable to swallow pills and as a controlled-release preparation for a small subset of older children with severe or prolonged postoperative pain, e.g. for pain due to cancer or other serious illnesses. Dosing for immediate release is 0.1–0.2 mg/kg/dose every 4 h as needed.

Hydrocodone is an oral opioid used for mild to moderate pain and is often formulated with acetaminophen. Metabolism is primarily through CYP2D6 and CYP3A4 pathways to hydromorphone and norhydrocodone, respectively, and to a lesser extent by non-CYP pathways. Although patients with genetic polymorphism of CYP2D6 enzymes resulting in "slow metabolizers" have lower peak concentrations of hydromorphone compared with "rapid metabolizers", there are insufficient data to conclude whether analgesic response and potential for toxicity can be predicted based on the CYP2D6 phenotype [79–81].

Morphine is generally considered a first-line opioid for parenteral use. Metabolism occurs in the liver, primarily through glucuronidation to morphine-3-glucuronide, which has neuroexcitatory actions, and morphine-6-glucuronide, which has analgesic, sedative, and respiratory depressant actions. Both glucuronides are renally eliminated and can accumulate in patients with renal failure, which accounts for the prolonged response and increased side-effects seen in patients with renal failure. Accumulation of morphine-3-glucuronide can contribute to delirium, myoclonus, agitation, and seizures. There is some evidence that morphine is preferentially metabolized in neonates to morphine-3-glucuronide and has an increased risk of seizures in this age group [82]. The elimination half-life of morphine in neonates and young infants is more than twice that of older children and is even more prolonged in premature infants [82]. Clearance of morphine in premature infants is less than half that measured in adults. Studies of morphine efficacy in neonates have yielded mixed results with some studies showing no apparent analgesic effect of morphine infusion in ventilated neonates in response to endotracheal suctioning. Because of the significant variation in pharmacokinetics of morphine among patients, dosing should be based on age, weight, side-effects, and careful dose titration [82]. Erythema and local urticaria at the site of intravenous administration is sometimes seen and does not imply an allergy to morphine. Morphine is generally well tolerated with minimal hemodynamic changes during infusions in blinded studies [83], but rapid bolus dosing can be associated with hypotension. Morphine and other opioids produce dose-dependent depression of ventilation by decreasing the brainstem response to hypoxia and hypercarbia and by interfering with central ventilatory centers. Morphine reduces the sense of air hunger in children with cancer and end-stage lung disease and can be given sublingually in this setting for ease of administration and for more rapid onset than enteral dosing. Dosing guidelines for morphine can be found in Table 37.4.

Hydromorphone has similar duration of action to morphine and is frequently used in patient-controlled analgesia (PCA) and epidural analgesia. Like morphine, it is commonly given orally and intravenously, although there is no long-acting preparation available. It differs from morphine in that it is slightly more lipid soluble and approximately five times more potent in steady state when given intravenously [84]. Like morphine, it is metabolized principally by glucuronidation. Hydromorphone is often prescribed for patients with renal insufficiency but this practice is not evidence based. Excitatory effects of either morphine or hydromorphone in patients with renal insufficiency correlate poorly with plasma concentrations of glucuronides [85]. While individual patients may report differences in analgesia or side-effects between morphine and hydromorphone, randomized blinded comparisons have found few clinically meaningful differences in the frequency of side-effects [86].

Methadone is a long-acting opioid that is supplied as a racemic mixture of d- and l-isomers. It has a prolonged elimination half-life, resulting in a long duration of analgesia. There is, however, wide variation in elimination half-life, ranging from 6 to 30 h. The bioavailability is quite high, approximately 70–90%. Because of these unique properties, methadone can be dosed intermittently, either orally or intravenously, and can provide prolonged, steady-state analgesia similar to a continuous infusion or controlled-release preparations of other opioids.

The l-isomer of methadone acts as a mu opioid; the d-isomer acts as a non-competitive antagonist at the N-methyl-D-aspartate (NMDA) subgroup of excitatory amino acid receptors in the brain, spinal cord, and peripheral nerves. NMDA receptor antagonism results in analgesia, reduction in hyperalgesia, and partial reversing of tolerance to mu opioids [87]. Methadone's

Table 37.4 Initial dosing guidelines for opioids for patients over 1 year of age*

Drug	Equianalgesic doses and intervals		Usual starting intravenous or subcutaneous doses		Parenteral: oral dose	Usual starting oral doses and intervals	
	Parenteral	Oral	Child <50 kg	Child >50 kg	Ratio	Child <50 kg	Child >50 kg
Morphine	10 mg	30 mg (long term) 60 mg (single dose)	Bolus: 0.1 mg/kg every 2–4 h Infusion: 0.03 mg/kg/h	Bolus: 5–8 mg every 2–4 h Infusion: 1.5 mg/h	1:3 (long term) 1:6 (single dose)	Immediate release: 0.3 mg/kg every 3–4 h Sustained release: 20–35 kg: 10–15 mg every 8–12 h; 35–50 kg: 15–30 mg every 8–12 h	Immediate release: 15–20 mg every 3–4 h Sustained release: 30–45 mg every 8–12 h
Oxycodone	NA	15–20 mg	NA	NA	NA	0.1–0.2 mg/kg every 3–4 h	5–10 mg every 3–4 h
Methadone†	10 mg	10–20 mg	0.1 mg/kg every 6–12 h	5–8 mg every 6–12 h	1:2	0.1–0.2 mg/kg every 6–12 h	5–10 mg every 6–12 h
Fentanyl	100 mg (0.1 mg)	NA	Bolus: 0.5–1.0 µg/kg every 1–2 h Infusion: 0.5–2.0 µg/kg/h	Bolus: 25–50 µg every 1–2 h Infusion: 25–100 µg/h	NA	NA	NA
Hydromorphone	1.5–2 mg	6–8 mg	Bolus: 0.02 mg every 2–4 h Infusion: 0.006 mg/kg/h	Bolus: 1 mg every 2–4 h Infusion: 0.3 mg/h	1:4	0.04–0.08 mg/kg every 3–4 h	2–4 mg every 3–4 h

* Doses are for patients over 6 months of age. In infants under 6 months, initial per kilogram doses should begin at roughly 50% of the per kilogram doses recommended here. Higher doses are often required for patients receiving mechanical ventilation. All doses are approximate and should be adjusted according to clinical circumstances. Recommendations are adapted from previous summary tables, including those of a consensus statement from the World Health Organization and the International Association for the Study of Pain.

† Methadone requires additional vigilance because it can accumulate and produce delayed sedation. If sedation occurs, doses should be withheld until sedation resolves. Thereafter, doses should be substantially reduced, the interval between doses should be extended to 8–12 h, or both.

NA, not applicable; NR, not recommended.

combined effect of mu receptor agonist and NMDA antagonism results in incomplete cross-tolerance so that dose conversion between methadone and other opioids depends, in part, on the patient's degree of opioid tolerance [88]. In opioid-naïve patients, the average daily requirement of intravenous methadone is approximately 30% of the corresponding intravenous morphine requirement. However, in opioid-tolerant patients, the average daily methadone requirement may be as little as 10% of the total daily morphine dose. This is especially relevant when converting from morphine to methadone in children who are opioid tolerant and when weaning non-ventilated infants and children from prolonged opioid therapy [89]. Because of incomplete cross-tolerance, slow and unpredictable elimination half-life, and variability in plasma concentrations, methadone dosing requires careful titration and frequent assessment for respiratory depression. Methadone has been associated with prolongation of the QT interval, especially when combined with other drugs known to cause prolonged QT. For patients showing oversedation or mild hypoventilation, it may be necessary to hold multiple doses rather than make small incremental changes due to the prolonged duration of action.

For opioid-naïve patients in the postoperative period, one approach is to dose methadone on a "sliding scale" every 4 h where patients receive 0.075 mg/kg for severe pain, 0.05 mg/kg for moderate pain, and 0.025 mg/kg for mild pain. After 24 h of this dosing regimen, patients are then placed on a more regular dosing schedule with shorter acting opioids such as morphine or hydormorphone, offered for rescue therapy. Methadone is particularly useful in children with cancer who have nociceptive as well as neuropathic pain. It can be dosed in small children with chronic pain who are unable to swallow sustained-release pills.

Fentanyl is highly lipophilic and is 70–100 times more potent than morphine in single-dose administration and 30–50 times more potent when given as a continuous intravenous infusion. Because fentanyl has a rapid onset and brief duration, it is often used for brief painful procedures, such as lumbar punctures, bone marrow biopsies, and dressing changes either by itself or in combination with benzodiazepines or general anesthesia. Doses of 0.5-1 µg/kg, titrated every 1–3 min generally provide good analgesia for brief painful procedures in non-ventilated patients. Fentanyl primarily undergoes conversion in the liver to inactive metabolites, making it useful in patients with renal failure. The effect of a single dose of fentanyl is terminated in large measure by rapid redistribution [90,91]. However with repeated doses or continuous infusion, the termination of fentanyl effect is more determined by elimination rather than redistribution, resulting in prolonged duration of action. The context-sensitive half-life of fentanyl is particularly prolonged in neonates receiving continuous infusions [92]. Rapid administration may cause glottic and chest wall rigidity; treatment can consist of neuromuscular blockade, assisted ventilation, and in some cases administration of naloxone.

Oral transmucosal fentanyl is also used for brief painful procedures [93] and for children with cancer breakthrough pain.

The oral transmucosal dose is partially absorbed through the buccal mucosa and partially swallowed so that the overall bioavailability is approximately 50%. The peak analgesic effect occurs at 30–45 min. Most children tolerate oral transmucosal fentanyl well, although almost 90% experience facial pruritus.

Transdermal fentanyl is used in selected children with cancer pain [94]. It is also used for a very small number of children with chronic pain who require regular dosing of opioids and have a better side-effects profile with fentanyl than other opioids. Transdermal fentanyl is also used for patients who have difficulty with oral opioids or who have limited intravenous access. Following initial application or with dose escalation, approximately 12–24 h are required to reach steady-state plasma levels because of depot accumulation of fentanyl in the skin; this also accounts for continued absorption of the drug at a declining rate after the transdermal fentanyl is removed. Because of these properties, transdermal fentanyl is not useful in patients with acutely fluctuating pain. Additional short-acting opioids are required with initial application and dose escalation. Drug uptake can be influenced by a number of patient factors, including temperature, thickness, adiposity, and inflammation. Transdermal fentanyl should be used only in patients who are opioid tolerant and who have fairly constant pain. Adverse events, including deaths, have been reported among opioid-naïve adult and pediatric patients who were treated with transdermal fentanyl for acute postsurgical pain.

Meperidine is approximately 10 times less potent than morphine. It is metabolized in the liver through hydrolysis and N-demethylation to normeperidine, a metabolite that is renally eliminated. The elimination half-life is 3–4 h. Accumulation of normeperidine can cause hyper-reflexia, agitation, delirium, and seizures. Life-threatening events have occurred with the use of meperidine in patients taking monoamine oxidase inhibitors and in patients with untreated hypothyroidism. Doing so has resulted in metabolic and hemodynamic changes, excitability, seizures, and death. Meperidine is unique among opioids in that it reduces rigors associated with general anesthesia and the administration of blood products. Beyond its use in low doses for rigors or shivering, we recommend against the use of meperidine for analgesia in children.

Table 37.4 gives the initial dosing guidelines for opioid analgesics.

KEY POINTS: OPIOIDS

- Codeine and tramadol have been restricted by the US FDA because of variations in metabolism due to CYP2D6 genetic polymorphisms
- Oxycodone and hydrocodone are appropriate for oral opioid analgesia and have less variation in metabolism since they depend more on CYP3A pathways for metabolism
- Morphine is first line for parenteral opioid analgesia; young infants have both reduced metabolism and increased brain levels of morphine and dosing must be reduced
- Hydromorphone, methadone, and fentanyl are also standard drugs for parenteral opioid analgesia; methadone may prolong the QT interval

Methods of opioid administration

Intermittent opioid bolus dosing

Intermittent parenteral dosing of opioids can be useful for episodic pain or for initial loading doses in the treatment of acute pain. Particularly with longer dosing intervals, this approach results in wide fluctuations in plasma opioid concentrations and fluctuations in side-effects and pain intensity. Continuous infusions and patient (or nurse) controlled analgesia are often used instead of intermittent parenteral bolus dosing to avoid fluctuations in plasma opioid concentration, analgesia, and opioid side-effects.

Continuous opioid infusions

Continuous opioid infusions are useful for maintaining steady-state plasma opioid concentrations [82,95,96]. This approach is often used in intensive care units for ventilated patients who have relatively constant levels of pain; intermittent boluses of opioids are administered for any increases in pain, such as endotracheal tube suctioning. Although continuous infusions achieve steady-state plasma opioid levels and near-constant levels of analgesia, patients who have fluctuations in pain, such as with coughing, chest physiotherapy, or getting out of bed may have increased levels of pain which are not readily relieved by a continuous infusion of drug. In this setting, additional opioid boluses are required. Typical starting dose for continuous infusions of morphine is 0.025 mg/kg/h. Because of patient variations in opioid metabolism and pain intensity, effective starting doses vary considerably. Neonates and young infants require lower starting doses, ranging from 0.005 mg/kg/h in preterm neonates to 0.015 mg/kg/h in young infants aged 2–6 months.

Patient- and nurse-controlled analgesia

Patient-controlled analgesia takes into account individual variations in opioid pharmacokinetics and individual fluctuations in pain intensity that cannot be achieved by intermittent opioid bolus dosing or continuous infusions [97–100]. PCA involves a delivery system that administers a small preset dose of opioid, usually intravenously, when the patient depresses a button. There is a preset lock-out time during which no additional boluses can be administered, even if the button is depressed. PCA can also administer a continuous opioid infusion in addition to the intermittent boluses.

PCA has been shown to be safe and effective in children aged 7 years and older. Some children as young as 4 or 5 years are able to effectively use PCA. However, there is a higher incidence of failure in younger children because of their inability to understand the causal relationship between depressing the button and obtaining medication for pain relief. PCA is widely used for a variety of painful conditions such as postoperative pain, painful vaso-occlusive crises, and cancer pain. There are conflicting data comparing PCA with continuous opioid infusions. Some studies indicate that PCA use tends to reduce patients' overall opioid use with fewer opioid side-effects and similar or lower pain scores. Other studies did not find lower total opioid use with PCA compared with continuous opioid infusions. Many of these comparative studies were conducted in an era before a very widespread use of multimodal opioid-sparing analgesia (acetaminophen, NSAIDs, regional anesthesia, gabapentinoids, etc.). In the authors' current practice, continuous infusions have become infrequent

for postsurgical pain except for patients receiving prolonged mechanical ventilation.

Nurse-controlled analgesia (NCA) is commonly used for infants and children who are unable to push the PCA button, either due to lack of cognitive abilities or due to physical limitations. Outcome studies indicate that NCA is generally safe and effective in children with good patient, nurse, and parent satisfaction [99,100]. NCA is commonly used in pediatric hospitals for opioid administration to young children following surgery.

Parent-controlled analgesia is widely accepted for use in children with advanced cancer pain and in palliative care, both in home and hospital settings. There is, however, controversy surrounding parent-controlled analgesia for opioid-naïve children or in the setting of acute postoperative pain. Advocates of parent-controlled analgesia point out that parents know their children best, especially children with developmental or physical disabilities. The counterargument is that parents, unlike nurses, do not have the training or expertise to effectively assess risks of opioid dosing or impending respiratory depression. There have been several serious adverse events, including deaths, with the use of parent-controlled analgesia by well-meaning parents. Our view is that parent-controlled analgesia for opioid-naïve patients should be restricted to hospitals that have formal education parent programs, protocols for close nurse observation and assessment, and electronic cardiorespiratory monitoring [100].

Commonly used opioids for PCA include morphine, hydromorphone, and fentanyl. Some studies have shown that adding a basal infusion at night for postsurgical patients improves sleep and pain scores. Other studies have shown that basal infusions with PCA increase risk of desaturation episodes, especially at night. Whether to add a basal infusion depends on a number of factors, including severity of pain, tolerance to opioids, and an underlying patient condition that may increase the risk of hypoventilation or airway obstruction. In general, patients with mild to moderate pain experience good analgesia with demand-only PCA. Our practice is to use PCA bolus dosing without a background basal infusion for children who have received a peripheral nerve block intraoperatively, who have increased risks of respiratory compromise, and for those who are expected to have mild–moderate but not severe surgical pain. We do tend to include a basal infusion for children who have cancer pain or pain from vaso-occlusive crises. For these patients, we often provide approximately 40–50% of their daily opioid dosing through basal infusions to provide effective analgesia without the need for frequent demand boluses. We often add a basal infusion for 1–2 days postoperatively for patients who have had surgeries expected to result in severe postoperative pain, such as scoliosis surgery or major hip surgery. When fentanyl is chosen for PCA, such as for patients who have had side-effects to other opioids, a basal rate is often used because fentanyl is shorter acting than morphine or hydromorphone. Typical starting doses for PCA (and NCA) are listed in Table 37.5.

Table 37.5 Typical starting doses for patient-controlled and nurse-controlled analgesia

Drug	Bolus dose (μg/kg)	Continuous rate (μg/kg)	4-hour limit (μg/kg)
Morphine	20	4–15	300
Hydromorphone	5	1–3	60
Fentanyl	0.25	0.15	4

Opioid side-effects and treatment

Opioids are associated with a range of side-effects, including nausea, vomiting, constipation, urinary retention, pruritus, sedation, and respiratory depression. Although some children may experience different side-effect profiles with different opioids, there are few data to suggest that side-effects differ greatly among commonly used opioids. To many children, severe opioid side-effects, such as relentless nausea or pruritus, may be as distressing as pain. Opioid-sparing approaches to postoperative analgesia, including the use of NSAIDs, should be considered to avoid the complications of opioids on postoperative recovery [101].

Opioid side-effects occur by actions at both peripheral and central sites [102]. For example, opioid-induced nausea and vomiting involve agonist activity at receptors in the chemoreceptor trigger zone as well as in the gastrointestinal tract. Some opioids produce pruritus by peripheral release of histamine; however small doses of intrathecal morphine are associated with profound pruritus, implying a more central cause of signaling and neurotransmission in the spinal dorsal horn and nucleus caudalis.

Opioid side-effects should be anticipated and treated aggressively. A proactive program with protocols for side-effect management allows for rapid implementation of treatment. The evaluation of the patient with opioid side-effects should include assessment of the severity of side-effects, the degree of patient distress, the expected duration of opioid therapy, and careful consideration of other factors that may masquerade as opioid side-effects. For example, severe itching may be a result of opioids but may also be due to an allergic reaction to other medications.

Constipation is nearly universal among patients receiving opioids, even with short-term use. Stimulant laxatives should be routinely used for all patients anticipated to require more than one or two doses of opioids. Methylnaltrexone has a decreased ability to cross the blood–brain barrier and acts as a peripheral opioid antagonist [102]. It has been used for opioid-induced constipation that is refractory to laxatives. Doses of methylnaltrexone for children are extrapolated from adult studies.

Opioid-induced pruritus can be relentless and as distressing as pain to some patients. Pruritus occurs in approximately 13% of patients receiving parenteral opioids and 20–80% of patients receiving intrathecal or epidural opioids. Opioid-induced pruritus is thought to occur through activation of opioid receptors in the brain and substantia gelatinosa. Although antihistamines have traditionally been used to treat pruritus, there is good evidence for use of mu receptor antagonists such as naloxone infusions for both opioid-induced pruritus and opioid-induced nausea. In addition, antihistamines can exacerbate sedation, constipation, and urinary retention caused by opioids. In a prospective, randomized trial of 46 children receiving low-dose naloxone infusion (0.25 μg/kg/h) and morphine PCA postoperatively, the incidence and severity of opioid-induced pruritus and nausea were significantly reduced [103]. There was no

Table 37.6 Management of common opioid side-effects

Side-effect	Comments	Drug dosage*
Nausea	Consider switching to different opioid Use antiemetics Exclude other processes (e.g. bowel obstruction)	Ondansetron 10–30 kg: 1–2 mg IV q 8 h >30 kg: 2–4 mg IV q 8 h Naloxone infusion 0.25 μg/kg/h Metoclopramide 0.1–0.2 mg/kg PO/IV q 6 h
Pruritus	Exclude other causes (e.g. drug allergy) Consider switching to different opioid Use antipruritics	Nalbuphine 0.01–0.02 mg/kg/dose IV q 6 h Naloxone infusion 0.25 μg/kg/h Diphenhydramine 0.25-0.5 mg/kg PO/IV q 6 h
Sedation	Add non-sedating analgesic (e.g. ketorolac) and reduce opioid dose Consider switching to different opioid	Methylphenidate 0.05–0.2 mg/kg PO bid (morning and midday dosing) Dextroamphetamine 5–10 mg every day for children >6 years of age
Constipation	Regular use of stimulant and stool softener laxatives	Naloxone infusion 0.25-1 μg/kg/h Docusate: Child: 10–40 mg PO daily Adult: 50–200 mg PO daily Dulcolax: Child: 5 mg PO/PR daily Adult: 10 mg PO/PR daily Methylnaltrexone (adult) 0.15 mg/kg

* In the absence of more specific data, patients weighing >60 kg should be dosed based on a 60 kg weight-scaled dose.
bid, twice a day; PO, orally; PR, rectally; q, every.

increase in pain scores or increase in morphine use with the administration of low-dose naloxone. Ultralow-dose naloxone infusions show differential binding to opioid receptors coupled to G-stimulatory versus G-inhibitory proteins so that analgesia is not reversed. Nalbuphine is a widely used mu receptor antagonist used for opioid-induced nausea and vomiting although there are conflicting efficacy data among pediatric patients [104].

Nausea and vomiting are a major source of distress for patients, especially in the postoperative period. There is a strong relationship between postoperative nausea and vomiting and the amount of opioids used postoperatively [105], however other causes should also be considered such as electrolyte abnormalities or impaired kidney function. Ondansetron is a selective 5-hydroxytryptamine-3 (5-HT3) receptor antagonist often used in the treatment of nausea and vomiting. Phenothiazines, butyrophenones, and metoclopramide have traditionally been used but have the associated risk of extrapyramidal reactions. There is good evidence to support the use of low-dose naloxone infusions in the treatment of nausea and vomiting associated with opioids. The typical dose of low-dose naloxone used in the treatment of opioid-induced pruritus and nausea is 0.25 μg/kg/h.

Children with advanced cancer often experience fatigue and somnolence, and opioid use often exacerbates these symptoms. Other treatable causes of fatigue should be considered, such as anemia, sleep disturbances, and depression. A cross-sectional study of the parents of 141 children who died of cancer reported that 96% of children had fatigue and nearly 50% experienced significant suffering from fatigue [106]. Only 13% of children with fatigue received directed treatment. More aggressive treatment of pain with opioids may further exacerbate fatigue and somnolence [107]. Methylphenidate is a stimulant that acts as an adrenergic receptor agonist to indirectly increase the release of dopamine and norepinephrine. Studies in adults support the use of methyphenidate to antagonize opioid-associated sedation and fatigue. Methylphenidate can also provide additional analgesic and antidepressant effects, which can be particularly beneficial for children with advanced cancer.

See Table 37.6 for the management of common opioid-induced side-effects.

KEY POINTS: OPIOID DOSING AND SIDE-EFFECTS

- Intermittent IV opioid dosing is used for acute pain, but continuous opioid infusions are more effective to maintain steady-state plasma concentrations
- Both patient- and nurse-controlled opioid analgesia for children are safe and effective; parent-controlled analgesia should be reserved for advanced cancer pain and palliative care
- Opioid side-effects include nausea, vomiting, constipation, urinary retention, pruritus, sedation, and respiratory depression and should be anticipated and treated aggressively

Local anesthetics and regional anesthesia

Developmental pharmacology of local anesthetics

The amino amide local anesthetics, including lidocaine, bupivacaine, levobupivacaine, and ropivacaine, undergo hepatic metabolism more slowly in neonates and young infants, and weight-scaled clearances reach mature values generally around 6 months of age [108]. In addition, reduced renal clearance of metabolites (e.g. MEGX, the primary metabolite of lidocaine) can contribute to the risk for seizures in neonates. Although

plasma esterases involved in the metabolism of amino ester local anesthetics are present in reduced amounts in neonates, chloroprocaine clearance occurs quite rapidly in neonates [109]. Local anesthetics have somewhat larger volumes of distribution and reduced protein binding in neonates [108]. The plasma concentrations that produce cardiotoxicity or risk of seizures in human neonates, infants, and children are extrapolated from case reports, adult case series, and adult preclinical toxicological studies [110]. Infant rats tolerate a higher weight-scaled dose of either bupivacaine or ropivacaine (higher median lethal dose (LD50)) than adult rats [111]. In our view, it seems prudent to conclude that the maximum systemically safe single dose of bupivacaine, levobupivacaine, ropivacaine, or lidocaine scales directly with bodyweight, and that the hourly maximum infusion rates in neonates and infants less than 3–5 months of age should be reduced by about 50% relative to the recommended rates for older infants and children.

Topical anesthetics

Topical anesthetics are widely used in children for pain associated with immunizations, venipuncture, accessing indwelling central venous ports, and other types of needle pain [112,113]. The stratum corneum of the epidermis is a relatively impermeable barrier to local anesthetics and a variety of strategies have been developed to permit uptake of local anesthetics across this barrier.

EMLA

The eutectic mixture of local anesthetics (EMLA; lidocaine and prilocaine) was one of the first topical anesthetics commercially available for use on intact skin and has been extensively used and studied [114,115]. The physicochemical feature of this type of mixture is that it permits a higher aqueous solubility of the uncharged forms. This physical feature permits a higher effective concentration at the stratum corneum and increases the rate of uptake. A meta-analysis of controlled trials in children and adults showed that EMLA reduced pain associated with venipunctures in 85% of patients [114].

Applying a thicker layer and increasing the duration of application to 90–120 min can increase its effectiveness. Applying a thin layer (0.5 mm) compared to a thick layer (2 mm) resulted in significantly less pain relief with venipunctures. Even with longer duration of application, absorption into the epidermis was limited to no more than 6 mm. Application times of less than 45 min resulted in high failure rate, and with short application times, tetracaine gel appeared more effective than EMLA [115]. Blanching is commonly seen with EMLA and is due to vasoconstriction of superficial capillaries.

Clinical trials have shown the effectiveness of EMLA in reducing pain or distress of a number of common pediatric procedures, including venous cannulation, venipuncture, circumcision, urethral meatotomy, immunizations, allergy testing, accessing implanted central venous access ports, and laceration repair.

LMX cream

Lidocaine 4% (LMX) is a topical preparation. A randomized cross-over trial showed that LMX was as safe and effective as EMLA for reducing pain associated with venepuncture [116]. Advantages over EMLA include minimal vasoactive properties and shorter onset of action without the need for an occlusive dressing [117]. Additionally, LMX is not associated with methemoglobinemia.

S-Caine patch

The S-Caine patch™ (Synera®) is a drug delivery device consisting of a eutectic mixture of lidocaine (70 mg) and tetracaine (70 mg) integrated with an oxygen-activated heating element. The heating element enhances the delivery of the local anesthetics across the epidermis. When removed from its storage pouch, the heating element becomes activated and the patch begins to heat, warming the skin after application. Controlled trials in children and adults showed that application of the patch for 20 min produced good skin analgesia for venous cannulation [118]. A randomized, placebo-controlled trial of S-Caine Patch use showed that the majority of patients had good pain relief with vascular access procedures. The most common side-effects were local transient skin reactions, such as localized pruritus and erythema. Unlike EMLA, the S-Caine Patch is associated with mild vasodilation due to the vasodilating properties of lidocaine and mild heating of the skin.

Jet propulsion injectors

Jet propulsion injectors (J-tip system® and Powerject) are needless syringe devices that utilize compressed gas, typically carbon dioxide, to rapidly propel a predetermined amount of local anesthetic through the stratum corneum. These types of devices are attractive in that the local anesthetic effect occurs within several minutes and it is a needleless system. However, efficacy data are somewhat mixed. A randomized trial in adult patients showed that subcutaneous lidocaine infiltration was significantly more effective at reducing pain from venous cannulation. Other randomized studies in adults have found a failure rate of approximately 10%, and 17% of patients had mild bleeding at the site. A study comparing the J-tip system to EMLA in children found that the former provided better analgesia than EMLA for IV cannulation [119].

Iontophoresis

Iontophoresis employs an electrical field to drive local anesthetics in their charged ionic form across the stratum corneum. Iontophoresis produces cutaneous anesthesia in a much shorter time. The most common anesthetic used by this route is 2% lidocaine with 1:100,000 epinephrine. Skin analgesia occurs within 10–15 min and typically lasts for 15 min. Iontophoresis appears to result in deeper levels of dermal anesthesia and may penetrate deeply enough to numb both skin and veins, allowing for less painful venous cannulation. Randomized prospective studies in children comparing EMLA with iontophoresis of 2% lidocaine and 1:100,000 epinephrine found no significant differences in pain relief with venous cannulation. Superficial and partial thickness burns have been reported with lidocaine iontophoresis when placed over areas with skin defects or when high currents have been used. A mild tingling sensation often occurs during drug delivery. It is recommended that the system be removed if pain rather than tingling is experienced. Longer application

times are needed when lower currents are used, but the tingling sensation can be made almost undetectable.

Epidural analgesia

Epidural analgesia can provide excellent postoperative analgesia for infants and children undergoing a variety of surgical procedures including thoracic, perineal, lower extremity, and abdominal procedures. (Detailed discussion of peripheral nerve blocks can be found in Chapter 20.) Epidural analgesia is also used for certain chronic pain conditions such as complex regional pain syndrome, especially when used as part a rehabilitation program that emphasizes active mobilization (Figure 37.5).

An inherent difference between epidural catheter placement in adults and children is that, unlike for adults [120], most epidural catheters in children are placed while anesthetized. Most pediatric anesthesia providers agree on the safety of placing a lumbar epidural catheter in an anesthetized rather than an awake, moving child. However, there is somewhat more controversy surrounding the safety of direct needle placement in the thoracic region, particularly in infants due to concerns of neurological complications. Published case series and prospective clinical outcome studies showed generally good safety, though from available data it is difficult to ascribe confidence intervals on the risk specifically for anesthetized thoracic needle puncture in different age groups [121,122]. To avoid the potentially increased risk, an alternative method is to advance catheters from the caudal region cephalad to thoracic dermatomes. This may be performed blindly, or with additional guidance by fluoroscopy, ultrasound [123], nerve stimulation guidance [124], or electrocardiography [125]. Several reports in infants show that these techniques can be safe alternatives to direct needle placement, with success rates ranging from roughly 80% to 98%. Failure rates with blind placement are greater for infants greater than 5 kg. Infants clear amide local anesthetics more slowly than older children so that lower infusion rates are necessary and repeated local anesthetic dosing is more likely to produce systemic accumulation of drug and toxicity. Because of the limitations of using safe local anesthetic infusion rates, it is crucial in infants and young children to place epidural catheter tips in the correct surgical dermatome. When placing epidural catheters directly in a thoracic dermatome or when advancing epidural catheters cephalad to the thoracic region, our practice is to obtain confirmation of proper placement, either radiographically, through ultrasound, or by electrical stimulation. "Blind" advancement of catheters from lumbar to thoracic levels has a failure rate of approximately 30%. One method of radiographic confirmation of proper epidural catheter tip placement is an epidurogram where a small amount (0.5–1 mL) of radiocontrast dye is injected through the epidural catheter that can be detected on a plain radiograph (Fig. 37.6).

Catheters can also be advanced from lumbar or caudal routes under fluoroscopic guidance, and catheter tip positions can be confirmed by a contrast epidurogram. In our experience, lumbar-to-thoracic placement of catheters is more successful if placement occurs at L1–2 rather than lower levels, and with the epidural needle angled in a cephalad direction, rather than perpendicular to the spine. It is important to note that the distance from skin to epidural space is much shorter at the T12–L1 and L1–2 interspaces than at L3–4 or L4–5 which may predispose to inadvertent dural puncture. In our own practice, we make extensive use of electrical stimulation of epidural catheters [126], for confirming placement in the epidural space, for advancing lumbar and caudal catheters to thoracic dermatomes, and for confirming that the catheter is not wrong-sided (directed contralateral to the side of surgery). In this method, a small amount of electric current is applied to a saline-filled, wire-wrapped epidural catheter as it is advanced cephalad in the epidural space. Twitches can be observed at the myotomal level of the catheter tip in a current range

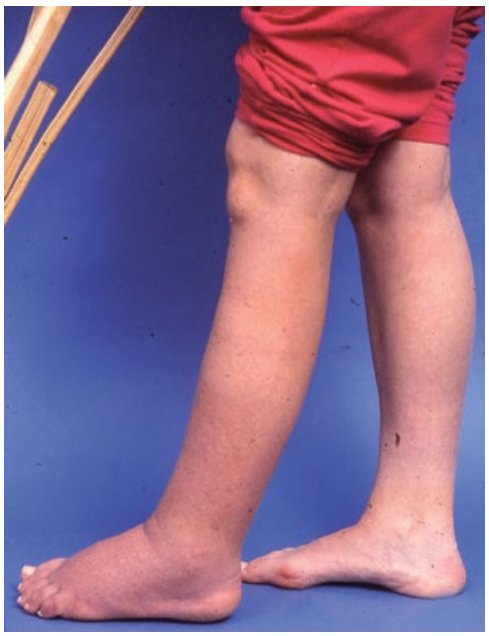

Figure 37.5 Complex regional pain syndrome presentation.

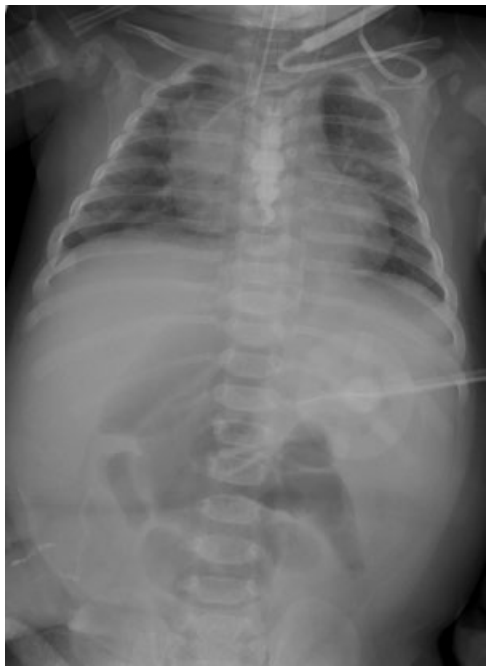

Figure 37.6 Epidurogram following placement of an epidural catheter. Note dye in the thoracic area.

usually between 2 and 15 mA. Characteristic response patterns indicating epidural, vascular, intrathecal, or dural placement can be observed as the catheter is advanced. This technique can also provide information on the sidedness of the epidural catheter so that for a unilateral surgical procedure predominant myotomal twitching on the non-operative side can be detected and the catheter repositioned. Technical success rates of 98% and analgesic success rates of 85% have been described using this method. Even in older adolescent and adults who may undergo regional anesthesia awake or under light sedation, we find that nerve stimulation is tolerated with minimal distress, provided the current is increased gradually.

It is sometimes necessary to confirm proper position of an epidural catheter postoperatively, for example, in the setting of continued pain despite adequate dosing of epidural infusions. Our common practice is to use a "chloroprocaine loading dose," particularly for infants and non-verbal children. Chloroprocaine is an ester local anesthetic that is metabolized by plasma cholinesterases. Although infants have reduced levels of plasma cholinesterases, chloroprocaine is nevertheless rapidly metabolized. Because of concerns of toxicity due to accumulation of amide local anesthetics in infants and young children, we prefer to use chloroprocaine in place of lidocaine or other amide local anesthetics to check epidural catheter placement. Since most patients will have received infusions of amide local anesthetics intraoperatively, administering a bolus of chloroprocaine avoids the possibility of reaching toxic plasma levels through additional boluses of amide local anesthetics. We inject a loading dose of 3% chloroprocaine incrementally over roughly 2 min through the epidural catheter. For this loading dose, infants receive larger weight-scaled volumes than adolescents. For example, an 8 kg infant might receive a total loading volume of 5 mL (0.62 mL/kg), while a 30 kg 7-year-old might receive a total loading volume of 12 mL (0.4 mL/kg), and patients >50 kg get a total loading volume of 15 mL. With these loading volumes, there should be clear clinical signs of sensory and motor block if the catheter is correctly positioned within the epidural space. Behavioral measures of pain relief, such as relaxed posture and ceasing of crying, are helpful in determining whether preverbal patients are experiencing relief, but objectives measures should also be present, such as a motor block and a return of vital signs to baseline values.

The selection of drugs for epidural injection should be individualized and will vary with site of surgery, location of epidural catheter tip, and patient-specific risk factors. For most postoperative children, we recommend infusions of local anesthetics in combination with opioids, clonidine, or both rather than local anesthetics alone because of the synergistic effect of combining local anesthetics with adjuvants. Bupivacaine is a commonly used amide local anesthetic in epidural local anesthetic infusions because it has a prolonged duration of action and produces more sensory than motor block. As previously discussed, the clearance of bupivacaine and other amide local anesthetics is reduced in neonates and young infants. Pharmacokinetic studies measuring unbound: pharmacologically active bupivacaine in infants receiving continuous epidural bupivacaine infusions showed plasma bupivacaine levels rise after the first 48 h and some infants will have plasma bupivacaine levels nearing or exceeding safe levels. Although most infants had an increase in their serum α1-acid glycoprotein concentrations after surgery, the increase did not fully buffer the unbound bupivacaine fraction. Based on these studies, epidural bupivacaine infusion rates in neonates and infants younger than 4 months of age should be limited to 0.2 mg/kg/h. Even at this low infusion rate, accumulation and drug toxicity are possible for infusions lasting more than 72 h [127]. Epidural bupivacaine infusion rates of 0.4 mg/kg/h appear to be safe for children over the age of 6 months.

Ropivacaine is an amide local anesthetic that in adult studies was found to be safer and more sensory selective than bupivacaine. Studies of IV ropivacaine in adult volunteers showed less central nervous system and cardiovascular toxicity than bupivacaine. In double-blind comparisons, ropivacaine and levobupivacaine both produced similar analgesic effects as racemic bupivacaine but less extensive motor block [128]. Pharmacokinetic data in infants and children show that the clearance of bupivacaine is slightly more than the clearance for ropivacaine in all ages but, as with bupivacaine, clearance of ropivacaine is reduced in neonates and young infants compared to older children [129–131]. Our practice is to use ropivacaine infusion rates up to 0.3 mg/kg/h in infants younger than 6 months and up to 0.5 mg/kg/h for older children.

Lidocaine is used as an epidural local anesthetic for neonates and infants in some centers because of the relative ease of monitoring lidocaine blood concentrations and because of reduced cardiotoxicity relative to bupivacaine. Note that even with lidocaine concentrations in a safe range, there is the potential for seizures due to an accumulation of MEGX [132].

Epidural infusions rates of amide local anesthetics are limited in young infants because of the increased risk of toxicity, as detailed earlier. Chloroprocaine infusions have been used as an alternative to continuous amide local anesthetic infusions to allow for sufficient epidural infusion rates without the associated toxicity concerns of amide local anesthetics. Studies of continuous epidural infusions of chloroprocaine showed good surgical anesthesia without neurotoxicity [109]. Higher weight-scaled infusion rates of chloroprocaine are necessary to achieve a similar extent of sensory block that is seen with bupivacaine and ropivacaine. Our practice is to use 1.5% chloroprocaine at a rate of 0.5 mL/kg/h for midthoracic epidural catheters and 0.6–0.8 mL/kg/h for lumbar and low thoracic catheters in neonates and young infants who are monitored in the intensive care unit.

Because of weight-based scaling constraints of local anesthetic infusion rates, one rationale for combining opioids, clonidine, or both along with epidural local anesthetic infusions is to provide a stronger analgesic effect while remaining in a safe local anesthetic dosing range. The addition of opioids, either neuraxially or systemically, will intensity the analgesia, but will increase the frequency of side-effects. Hydromorphone and fentanyl are the most commonly used epidurally administered opioids. In studies in adults, hydromorphone produces analgesia similar to morphine, but with less pruritus. The hydrophilic property of hydromorphone results in more cephalad spread, which can be effective for extensive surgeries that cover multiple dermatomes. The cephalad spread of hydromorphone increases the risk of respiratory depression and we tend to restrict the use of hydromorphone in epidural infusions for infants older than 4 months, infants who are opioid tolerant, or infants who require ventilatory support for a period of time postoperatively. For older children, we favor hydromorphone over other additives especially for extensive

and painful surgery, for patients who have pre-existing chronic pain and hyperalgesia, and for most cancer surgeries. Fentanyl is used in epidural infusions in infants less than 4 months of age and in children whose surgery does not involve multiple dermatomes or is associated with relatively less pain intensity. In general, slightly lower starting infusion rates should be used when epidural catheter tips are located in the thoracic region or when using hydrophilic opioids. All neuraxial opioids cause similar opioid side-effects, which are treated in much the same way as side-effects caused by systemically administered opioids. Pruritus is one of the most common side-effects of neuraxial opioids. It is most likely the result of modulation of neurotransmission in the dorsal horn and the trigeminal nucleus caudalis. Low-dose naloxone infusions in doses of 0.25 μg/kg/h are effective at treating opioid-induced pruritus and nausea without reversing analgesia or precipitating withdrawal symptoms.

Clonidine enhances and prolongs the analgesic effect of local anesthetics without contributing to respiratory depression, nausea, urinary retention, pruritus, and other opioid-related side-effects. We tend to employ clonidine most commonly for patients who have persistent epidural opioid side-effects despite standard treatments. Hypotension can occur, particularly in adolescents or in patients with inadequate blood and volume replacement.

Table 37.7 details recommended epidural infusion rates.

KEY POINTS: LOCAL ANESTHETICS AND EPIDURAL ANALGESIA

- Bupivacaine, levobupivacaine, ropivacaine, or lidocaine dose should scale with bodyweight, and hourly maximum infusion rates in infants less than 3–5 months of age should be reduced by 50%
- Topical anesthetic combinations of lidocaine, tetracaine, and prilocaine are effective but need adequate time to be effective; prilocaine is associated with methemoglobinemia
- Epidural analgesia is a versatile technique for perioperative pain; placement of the tip of the catheter at the dermatome of pain, and infusing dilute local anesthetics with opioids and clonidine, is effective

Peripheral nerve blocks and plexus blocks

The use of peripheral nerve blocks in the pediatric population has increased dramatically over the past 15 years to provide acute postoperative and chronic pain management with relative opioid sparing. Large databases have shown very low rates of complications, establishing the safety of performing peripheral nerve blocks in anesthetized pediatric patients [122,133]. In a recent meta-analysis, there was good evidence that the use of ultrasound guidance increases success rates and block duration in children [134]. Our practice has shifted in the past 10 years to largely placing peripheral nerve catheters for extremity and unilateral thoracic procedures and epidural catheters for extensive bilateral thoracic procedures or for procedures involving multiple sites where safe local anesthetic infusion volumes would prevent use of multiple peripheral nerve catheters. Chapter 20 presents an extensive discussion of peripheral nerve and plexus blocks.

Acute pain services

Over the past 30 years, there has been much focus on the development of acute pain services, in part because of the recognition of the undertreatment of postoperative pain, particularly in children. The Joint Commission has mandated specific hospital-wide standards for the treatment of pain and related symptoms in healthcare settings. There is evidence that acute pain services reduce patient reports of pain intensity and reduce delays in relieving severe pain, however the effect on other outcomes, such as incidence of side-effects, critical events, and length of hospital stay are equivocal. Other studies, however, did not consistently show similar outcomes. The specific organization of pain management programs varies depending on numerous factors including the average number of postoperative patients, the type of surgical procedures performed, and availability of subspecialists. Although the particular model of pain management program is unique to each hospital, there are common features that should be considered in the organization of acute pain services.

- Multidisciplinary group of clinicians dedicated to pain management, including anesthesiologists, nurses, surgeons, pediatricians, and pharmacists

Table 37.7 Recommended epidural infusion rates*

Solution	<1 month	1–4 months	>4 months†
Bupivacaine 0.1% ± fentanyl 2 μg/mL ± clonidine 0.4 μg/mL	Rarely used	0.2 mL/kg/h	0.4 mL/kg/h
Ropivacaine 0.1% ± fentanyl 2 μg/mL ± clonidine 0.4 μg/mL	Rarely used	0.3 mL/kg/h	0.4–0.5 mL/kg/h
Bupivacaine 0.1% + hydromorphone 10 μg/mL	Rarely used	Rarely used	0.3–0.4 mL/kg/h
Ropivacaine 0.1% + hydromorphone 10 μg/mL	Rarely used	Rarely used	0.3–0.4 mL/kg/h
Chloroprocaine 1.5% + fentanyl 0.2 μg/ml ± clonidine 0.04 μg/mL	0.5 mL/kg/h (mid-thoracic) 0.6–0.7 mL/kg/h (lumbar and low thoracic)	0.5 mL/kg/h (mid-thoracic) 0.6–0.7 mL/kg/h (lumbar and low thoracic)	Rarely used Rarely used

* Infusion rates and solutions should be modified according to clinical circumstances. Little information is available on how best to adjust these rates based on degrees of prematurity. Rates shown reflect the upper end of the usual infusion rates, based largely on both systemic accumulation of local anesthetics and on expected extent of sensory and/or motor blockade. Solutions containing hydrophilic opioids such as hydromorphone may pose a higher risk for delayed respiratory depression, so appropriate frequency of observation and continuous electronic monitoring is recommended. Higher concentrations of opioids may be considered for selected patients who are opioid tolerant.

† Weight-scaled infusion rates should plateau at values recommended for patients weighing around 45 kg, i.e. maximum infusion rates for larger patients should rarely exceed 15 mL/h.

- Designated personnel to provide 24h pain management services
- Hospital-wide protocols or algorithms for pain assessment, analgesic therapy, monitoring of pain and vital signs, treatment of side-effects, and documentation of pain-related information
- Hospital-wide standards for management of more specialized analgesic treatments such as epidural catheters, patient-controlled epidural analgesia, spinal catheters, peripheral nerve catheters, baclofen pumps, and implanted spinal/epidural ports
- Education program for clinicians (including pre- and post-tests)
- Education program for parents and children about risks, benefits, and treatment options
- Quality assurance program and outcome tracking system
- Ongoing review of pain management practices.

Formal measures of pain intensity should be assessed at regular intervals and recorded as is routine for vital signs measurement. Specific pain assessment tools are chosen based on the patient's age and cognitive and emotional ability as is detailed above in the section on pain assessment in infants and children. In general, a visual analog scale or numerical rating scale is generally used for children ages 7 years and older. Faces scales such as the Bieri or Wong–Baker faces, are appropriate for younger children aged 3–7 years. Ideally, education regarding the use of appropriate pain assessment tools should be reviewed with children and their parents at the preoperative visit. Composite pain scales that include behavioral observations, such the FLACC scale, are used for toddlers and non-verbal children. The FLACC and PIPP scales are commonly used pain scales for infants and for preterm newborns, respectively.

Protocols for pain and symptom management are the foundation to a comprehensive pain management program. Depending on the type of surgery, patients' medical condition, and the degree of postoperative pain, most postoperative pain is treated by combinations of NSAIDs, opioids, and regional analgesia. For mild postoperative pain, short-acting opioids such as oxycodone, alternating with doses of NSAIDs, generally provides good pain relief. Oral dosing is preferred when patients are able to tolerate oral intake postoperatively. Parenteral opioids are used in patients with more severe pain or when patients are restricted in their oral intake. PCA or NCA is widely used for infants and children with acute postoperative pain who require parenteral opioids. Regional analgesia including peripheral nerve catheter infusions and epidural infusions can provide excellent postoperative analgesia with opioid sparing and a subsequent decrease in opioid side-effects. Protocols for analgesic administration include standardized PCA, epidurals, and peripheral nerve catheter order sets so that range-dosing of opioids and local anesthetics solutions are standardized and somewhat independent of prescriber. Nevertheless, dosing parameters and choice of specific opioid or combined local anesthetic/opioid solutions should be individualized and based on the patient's prior opioid use and side-effect profile, severity of pain, location of surgical pain, medical condition, and psychological state. Inherent in pain management protocols are algorithms and order sets for treatment of side-effects so that patients do not experience delays in receiving treatment for common side-effects, such as pruritus, nausea, and vomiting.

All patients receiving opioids, either systemically or through regional catheters combined with local anesthetics, should be assessed for signs of respiratory depression. Protocols for monitoring level of consciousness and respiratory depression should involve nursing assessment and documentation of levels of sedation at regular intervals. Our practice is to provide electronic cardiorespiratory monitoring for all patients who have a basal rate added to their PCA, patients with risk factors for respiratory depression with opioids, such as those with certain airway diseases or neurological impairments, and young infants who are at risk for apnea with opioids. There have been reports of hypoventilation and critical events among healthy patients receiving epidural analgesia postoperatively, even when fentanyl was used as the opioid in the epidural infusion. We routinely place all patients receiving epidural infusions on cardiorespiratory monitors. While oximetry may be imperfect in detecting hypoventilation, especially when supplemental oxygen is administered, it probably facilitates rescue before serious harm occurs in many cases [135]. Other routine nursing assessment and documentation should include regular assessment of side-effects, extent of sensory and motor block for patients with regional catheters, and total daily amounts of opioids administered so that day-to-day comparisons can be made.

Hospitals with acute pain services need to have available an immediate response system to critical events. The structure of the immediate response system varies among hospitals but it is essential to have clinicians involved who have expertise in pediatric airway management and who are knowledgeable in the pharmacology of local anesthetics, opioids, and sedatives.

Quality assurance programs should analyze data pertaining to clinical practice, including general outcome measures of PCA, epidural, and other regional techniques. Data concerning adverse events should also be analyzed at regular intervals. Based on analyses of data, quality assurance programs can review institutional policies and practices and make practice guideline recommendations for improvement in safety and patient satisfaction.

Painful conditions in infants and children

Cancer pain

Children with cancer experience a variety of types of pain related to their disease process and resulting from the cancer treatments [136]. Studies of cancer pain in children have shown that as successful treatment protocols evolve, pain related to cancer treatments are the more predominant source of pain and suffering, including painful mucositis, postamputation pain, and peripheral neuropathies [137]. Repeated needle procedures, such as bone marrow biopsies, lumbar punctures, and repeated venous access, are particularly distressing for children. Tumor-related pain is often present at the time of the initial diagnosis and also results from disease progression with tumor spread to bone, spinal cord, and nerves plexuses. Children with hematological malignancies often present with bone pain from bone marrow infiltration and abdominal pain from capsular stretch of liver and spleen; those who show a good response to induction chemotherapy generally experience resolution of pain. However, a subgroup

of children will continue to experience somatic, visceral, and neuropathic pain.

Children undergoing treatment of cancer frequently need diagnostic imaging studies, radiotherapy, and brief needle procedures. Aggressive and proactive management will help decrease pain and anxiety associated with these procedures. Cognitive behavioral therapies, such as guided imagery, are useful for children with procedural pain. Topical analgesics should be routinely used for minor needle procedures such as accessing implanted vascular ports or intravenous line insertions. Depending on age, associated medical problems, and severity of pain and other symptoms, general anesthesia or moderate sedation is generally used for more invasive needle procedures, such as bone marrow biopsies and lumbar punctures. Safe sedation protocols have been established by the American Academy of Pediatrics and serve as guidelines for procedural sedation by oncologists and other subspecialists. Children with risk factors for conscious sedation or those who failed prior attempts at conscious sedation require consultation by pediatric anesthesiologists. Daily radiotherapy or diagnostic imaging, such as magnetic resonance imaging (MRI), is not typically painful but does require children to be immobile and brief general anesthesia is usually required.

Mucositis is painful inflammation of the mucosa caused by chemotherapy or radiation. It is a common side-effect in children receiving chemotherapy and is especially intense and prolonged with bone marrow transplantation. Topical agents are often used for symptomatic relief in mild mucositis, but there are limited data showing efficacy. Parenteral opioids through PCA or NCA are generally used for moderate to severe pain from mucositis. Oral opioids are not typically used initially since most children experience painful swallowing from mouth and esophageal involvement. Since many children experience significant pain from mucositis for weeks, our practice is to provide approximately 60% of the total daily opioid dose through a basal rate to provide sustained analgesia without requiring the patient to use the PCA button repeatedly throughout the day and night. For patients with mucositis whose pain is poorly controlled with standard PCA or NCA opioids, a recent trial supports the addition of low-dose ketamine to the mixture [138].

Nearly all children who have had amputations experience phantom sensations and many experience phantom pain [139]. Postamputation pain occurs more often in children who have had amputations due to cancer rather than trauma, and administration of chemotherapy may be a risk factor in the development of phantom pain. Regional analgesia, including epidural and peripheral nerve catheters can provide very effective postoperative analgesia after limb amputations. Although severity of early postop amputation pain correlates with likelihood of longer term pain, studies of pre-emptive actions of several regional anesthetic approaches have yielded mixed outcomes. Treatment with antidepressants, anticonvulsants, NMDA-antagonistic drugs, gabapentin, opioids, and clonidine has shown some success; however, there are limited data from large, controlled clinical trials. Mirror box therapy and other forms of visual feedback therapies have been used with some success in the treatment of postamputation pain [140]. A mirror is positioned so that the reflection and movement of their limb appears as if the amputated limb is intact.

A stepwise program of analgesic therapy proposed by the World Health Organization can provide good treatment of pain in adults with advanced cancer without intolerable side-effects in a large majority of patients. A similar stepwise analgesic approach has been advocated for the treatment of children with cancer pain where NSAIDs, acetaminophen, and low-dose opioids, such as oxycodone, are initially used for the treatment of mild pain. Morphine, hydromorphone, and other opioids are titrated to effect as pain escalates. The use of oral opioids is recommended when possible. For patients with persistent pain, an effective opioid regimen includes the use of long-acting opioids, such as methadone or sustained-release formulations of morphine or oxycodone. Short-acting morphine, oxycodone, hydromorphone, or other opioids are added for breakthrough pain. Oral methadone is useful as a long-acting elixir for children who are unable to swallow pills. Conversion from morphine and other short-acting opioids to methadone requires individualization and close observation because of the incomplete cross-tolerance mentioned earlier. A rough guide for conversion can be found at www.globalrph.net/narcoticconverter. Several sustained-release opioid preparations contain microbeads and it is common practice to open the capsule and sprinkle the microbeads into food just prior to use. However, if the microbeads are chewed or left in contact with food for an extended period of time, they release their contents. Not only does this reverse the sustained-release property, it can also increase the risk of overdose. Parenteral opioids are used when pain is rapidly escalating and oral opioids are not effective or when patients are unable to tolerate oral opioids due to nausea, vomiting, gastrointestinal processes, or the inability to swallow. In this setting, PCA or NCA is used, generally with a basal rate. Opioid side-effects should be aggressively treated and in cases of intolerable side-effects, opioid rotation can be helpful.

Although standard dosing of opioids adequately treats cancer pain in most children, a subgroup of children with cancer will have persistent, severe pain despite an enormous escalation of opioid dosing (e.g. 500 mg/kg/h) [141]. Refractory pain despite massive opioid doses is typically seen with tumor metastases to the spinal cord and major nerves, causing unrelenting neuropathic pain. For some of these patients, low-dose ketamine infusions and intravenous lidocaine infusions may provide an improved therapeutic window [142–144].

Many children with severe cancer pain who are resistant to opioids can be made comfortable through the use of regional anesthetic techniques, such as implanted intrathecal or epidural catheters or ports [145,146]. The choice of drugs should be individualized and depends on a number of factors, such as location and nature of pain, bowel and bladder function, and level of alertness. In most cases, dilute solutions of local anesthetics and opioids provide good pain relief, although other agents are sometimes added, such as clonidine or ketamine. Our general preference is use intrathecal rather than epidural placement in most cases, because this permits versatile dosing as pain escalates over time, and because over time epidural dosing of local anesthetics is limited by tachyphylaxis and systemic toxicity. We generally prefer placement of ports to facilitate skin care, reduce the risk of infection, and reduce the chance of catheter dislodgment at home. These procedures are performed under general anesthesia and with

fluoroscopic guidance. There are a number of technical and management issues involved, and clinicians are encouraged to consult with the authors or with others with experience in this area, since many aspects are not readily extrapolated from either perioperative regional anesthesia or adult chronic pain management. For a very small percentage of children with advanced disease and refractory pain or terminal dyspnea, there may be a role for administration of sedative infusions. However, in our view, use of sedatives near the end of life should never become routine, and efforts should be made whenever possible to preserve clarity of sensorium and interactiveness [147]. The ethical principle of double effect is commonly invoked to guide prescribing of opioids and sedatives at the end of life. While this principle has become nearly universally accepted, critics have pointed out some difficulties with its justification and application [148].

In addition to pain, children with cancer experience a range of other symptoms, such as fatigue, somnolence, and depressed mood. Some data suggest that the prevalence of symptoms is higher among children who are undergoing chemotherapy, who are hospitalized, and who have solid tumors compared with those with hematological malignancies. One study suggested that, as pain is treated more aggressively with opioids, the likelihood of fatigue and somnolence are increased [107]. Studies in adults support the use of stimulants, such as methylphenidate, to counteract somnolence from opioids.

KEY POINTS: CANCER PAIN

- Children with cancer undergo frequent needle and diagnostic imaging procedures and radiotherapy; cognitive behavioral therapies, topical analgesia, and moderate sedation/general anesthesia are used to prevent and treat pain
- Mucositis often requires parenteral opioids via PCA, and phantom limb pain can be treated with regional analgesia, analgesics, or visual feedback therapies
- Severe cancer pain resistant to opioids can be improved through implanted regional anesthetic techniques

Sickle cell vaso-occlusive episodes

Painful vaso-occlusive episodes are the most common cause of pain in children with sickle hemoglobinopathies [149]. Other acute processes can also present with pain, such as pneumonia, stroke, priapism, acute cholecystitis, splenic sequestration, and avascular necrosis. Fever can be associated with an uncomplicated pain episode or may be a sign of pneumonia, appendicitis, or other infection. The pain from vaso-occlusive crises can be unpredictable in severity, location, and frequency – ranging from occasional, mild episodes to frequent, severe, and prolonged episodes requiring repeated hospitalizations. Approximately 5% of children with sickle cell disease account for over 30% of hospitalizations and those patients with the highest rate of painful episodes and hospitalizations have the highest mortality rates [150]. Painful vaso-occlusive crises can occur in children as young as 6 months of age as the protective effects of fetal hemoglobin decreases. Dactylitis is a painful episode involving the hands and feet and is more common in younger children. Adolescents tend to experience back, limb, and chest pain, although the location can be variable. Priapism is caused by sickling of hemoglobin in the sinusoids of the penis and causes prolonged, painful erection.

Children with occasional mild to moderate painful episodes are typically managed at home with NSAIDs and oral opioids. Severe, escalating pain is generally managed in the hospital with NSAIDs and PCA with basal infusions. Opioids should be titrated to effect with close observation for hypoventilation and signs of excessive sedation. Surveys suggest that even with generous PCA dosing, pain scores remain quite high and a considerable percentage of hospitalized patients with vaso-occlusive episodes experience pain on a regular basis [151]. For some patients with severe chest pain, the high doses of opioids necessary to treat pain can result in somnolence, hypoventilation, and inability for effective coughing and incentive spirometry, leading to worsening hypoxemia and further pulmonary decline. There is some evidence that low-dose ketamine infusions may provide analgesic and opioid-sparing effects [152,153]. In selected cases, continuous epidural analgesia or peripheral nerve infusions may provide improved analgesia and reduce the need for further systemic opioids and reduce opioid-induced somnolence.

Cystic fibrosis

Patients with cystic fibrosis (CF) experience a spectrum of recurrent or persistent pain, particularly chest pain and headaches in the final year of life [154]. Other commons sites of pain include abdominal pain, recurrent limb pains that are sometimes associated with arthritis, and back pain, which is multifactorial [155,156]. Chest pain is typically the most commonly reported pain in patients with CF, regardless of severity of lung disease. Coughing and chest wall muscle strain from increased work of breathing leads to chronic musculoskeletal chest pain. Severe coughing can result in rib fractures or periosteal tears that produce pinpoint tenderness on exam and severe pleuritic chest pain.

Headaches may be due to a range of causes, including musculoskeletal strain, chronic sinusitis, migraine, hypoxia, and hypercarbia. Over 50% of patients with CF report chronic headaches. Headaches due to muscular contraction and strain are very common and are worsened by excessive coughing and increased use of accessory muscles of respiration. Sinus disease is found in the majority of patients with CF and can contribute to headache pain. In some cases, surgery can reduce pain from sinus-associated headaches. Migraines can be intractable and particularly difficult to treat in patients with CF; many patients do not experience good relief with typical abortive migraine treatments, such as NSAIDs or 5-HT1 receptor-specific agonists. With disease progression and worsening of pulmonary function, hypercarbia and hypoxia play a more predominant causative role.

Patients with CF experience a number of other musculoskeletal chronic pain conditions. Chronic back pain is generally a result of chronic muscle strain from severe coughing; however thoracic and lumbar compression fractures can

occur and are often under-recognized. The incidence of CF-associated episodic arthritis in children seems to be similar to that seen in older patients with CF, while hypertrophic pulmonary osteoarthropathy is more prevalent in adult patients.

Treatment of children with chronic pain from CF depends in part on location and severity of pain, severity of lung disease, the degree to which pain interferes with good pulmonary toilet, and response to opioids. There are no controlled clinical trials of non-pharmacological therapies in children with CF, although many patients find acupuncture, biofeedback, and other cognitive behavioral therapies helpful [157]. NSAIDs are often used either alone or combined with opioids without contributing to respiratory depression, somnolence, or constipation and may allow for opioid-sparing effects. There may be a role for COX-2 inhibitors for patients who experience gastrointesinal side-effects with traditional NSAIDs and they may be less likely to contribute to hemoptysis. If patients with CF receive opioids postoperatively, there is a very high incidence of constipation; aggressive and pre-emptive use of stimulant laxatives should be considered. The indications for chronic opioid therapy for children and adults with CF is a subject of controversy. CF is now associated with a median survival that exceeds 40 years of age in many centers, so chronic opioid administration should be undertaken with consideration of long-term consequences. We commonly employ thoracic epidural analgesia or paravertebral infusions for major thoracic and abdominal surgery in patients with CF, especially those undergoing lung transplantation. Patients with CF may benefit from thoracic epidural analgesia or paravertebral infusions for (1) severe chest pain due to rib fractures or a chest tube, and (2) impending bowel obstruction associated with meconium ileus equivalent [158]. For CF patients with meconium ileus, a thoracic epidural infusion of local anesthetic has several benefits: it relieves pain and reduces the requirement for opioids, which further slow the bowel, and it provides thoracic sympathectomy, which directly accelerates bowel motility. Many patients undergoing lung transplantation have had chronic, severe chest pain prior to transplantation, and we have found that infusing higher concentrations of local anesthetics (e.g. ropivacaine 0.2%) in combination with hydromorphone is sometimes necessary to achieve adequate analgesia.

KEY POINTS: SICKLE CELL AND CYSTIC FIBROSIS PAIN

- Painful vaso-occlusive crises in sickle cell disease often include back, limb, and chest pain, and can be treated with oral NSAIDs or opioids
- Opioid PCA and low-dose ketamine infusions are effective for severe sickle cell pain; epidural or nerve block catheters may also be used
- Chest pain, headaches, and sinus pain are common in cystic fibrosis; NSAIDs and COX-2 inhibitors are often effective

Neuropathic pain

Neuropathic pain refers to pain associated with injury or altered excitability within the peripheral or central nervous system. Unlike nociceptive pain, neuropathic pain can persist independently of ongoing tissue injury or inflammation. Aδ- and C-fibers can become activated through a range of mechanisms, including infection, inflammation, ischemia, and transection. Other causes include tumor involvement of nerves, metabolic disorders, and chemotherapeutic drugs such as vincristine. Neuronal reorganization and central sensitization occur through sustained C-fiber discharge and "wind-up" in the dorsal horn. An array of complex mechanisms induce central neural changes, including ectopic firing of dorsal root ganglion, decreases in magnesium blockade of NMDA receptors, and changes in afferent Aδ-fibers that facilitate pain [159]. Pathways containing opioid receptors and endogenous opioids, serotonin, and norepinephrine project to the rostral ventromedial medulla and spinal dorsal horn. Input from the hypothalamus, amygdala, anterior cingulate area, and insular cortex modulates the pathways and can facilitate or inhibit the transmission of pain signals.

Many adult neuropathic pain conditions such as diabetic neuropathy, central poststroke pain, and trigeminal neuralgia are quite rare in children. There may be an age dependence to the nervous system's responses to several types of nerve injury. For example, while traumatic brachial plexus injury commonly produces severe pain in adults, perinatal brachial plexus injury in human neonates rarely appears painful, except for a subset of infants who subsequently undergo nerve grafting procedures [160]. In two models of painful peripheral nerve injury, infant rats show markedly reduced allodynia and other pain behaviors compared with older rats [161]. The age dependence of neuropathic pain may be related in part to the ontogeny of microglial inflammatory responses to nerve injury [162–164].

The classic description of neuropathic pain in adults of burning, shooting, or pins and needles pain is sometimes seen in children, but younger children often have difficulty describing their pain. A thorough neurological examination should help detect underlying disease and should assess the whether there are dermatomal deficits. Characteristic physical exam findings include allodynia and hyperalgesia. Allodynia refers to previously non-painful stimuli, such as light touch of the skin, causing pain. The presence of allodynia implies abnormal sensory processing and is an important clinical sign of neuropathic pain. Hyperalgesia refers to normally noxious stimuli, such as a light pinprick, producing abnormally exaggerated pain. The history and physical examination should guide any additional studies such as testing for thyroid dysfunction, vitamin B12 deficiency, or heavy metal toxicity. Electromyography can detect signs of denervation in muscles, and nerve conduction studies are useful for objectively assessing function of myelinated large nerve fibers, but these do not measure function of smaller C- and A-δ-fibers commonly involved in neuropathic pain. Neuropathic pain may occur in a range of static or progressive neurological disorders in childhood, including mitochondrial disorders. Heterozygous Fabry disease can produce painful small-fiber neuropathies that may begin during late childhood or adolescence [165,166]. Quantitative sensory testing is a non-invasive method of assessing the function of

small as well as large sensory nerve fibers. Unlike nerve conduction studies, quantitative sensory testing is well tolerated by children and does not require sedation.

Adults with neuropathic pain are commonly treated with anticonvulsants and antidepressants. While randomized trials show efficacy for conditions such as postherpetic neuralgia and diabetic neuropathy, it should be noted that effect sizes (based on changes in pain scores) are comparatively small, and benefit is often achieved at doses that would be expected to cause significant somnolence or impaired cognition in many patients [167].

The use of drugs for the treatment of neuropathic pain in children is extrapolated from adult studies since there are very few pediatric prospective trials [168,169]. Tricyclic antidepressants are among the most established analgesics in the treatment of diabetic neuropathy, postherpetic neuralgia, and central poststroke pain in adult patients. Tricyclics can also be helpful in promoting sleep in patients with sleep disorders due to pain. For children and adolescents with neuropathic pain, we generally use tricylics and anticonvulsants as first-line drugs. Gabapentin, oxcarbazepine, nortriptyline, and amitriptyline are most commonly used. In a randomized controlled study comparing gabapentin with amitriptyline in 34 children and adolescents with neuropathic pain, both drugs had similar effects on reducing pain intensity and improving sleep without significant side-effects [170]. Tricyclics are often prescribed in twice daily dosing with a larger portion of the dose give at bedtime. A baseline electrocardiogram is recommended prior to initiation. A typical starting dose for nortriptyline is 0.2 mg/kg with dose titration every 3–5 days. Common side-effects are related to anticholinergic effects including dry mouth, sedation, tachycardia, constipation, and urinary retention. There is less robust evidence for the use of selective serotonin reuptake inhibitors (SSRIs) in the treatment of neuropathic pain in children, but they are often used as an adjuvant in the treatment of associated mood disorders. Overall, antidepressants, including SSRIs, appear less effective for treatment of major depressive disorders in children compared with adults. In randomized trials, placebo responses are common and substantial; effect sizes relative to placebo are relatively small, and numbers needed to treat (NNTs) average 8 or greater [171]. NNTs are somewhat better (lower) for the treatment of anxiety disorders in children [171,172]. Gabapentin and pregabalin are widely prescribed, in part because of historical concerns about risks of antidepressants exacerbating suicidal ideation or attempts. However, meta-analyses of clinical trials of anticonvulsants suggest that multiple anticonvulsants also may increase these risks, even in patients without epilepsy or known severe mood disorders [173]. Parenthetically, anesthesiologists should note that lipid emulsions, which are used to treat bupivacaine cardiotoxicity, also appear to be effective in reversing cardiotoxic effects of several classes of antidepressants and anticonvulsants [174]. While the overall excess risk of severe mood or behavioral changes from antidepressants or anticonvulsants appears relatively low, in our view clinicians should titrate these medications gradually, should alert parents to report any concerning changes in behavior or affect, and should employ a system of phone and clinic-based follow-up to detect adverse effects of these medications.

Lidocaine 5% transdermal patches are widely prescribed for neuropathic pain and for other forms of pain. Plasma concentrations of lidocaine are quite low. While these formulations appear quite safe, and there are studies supporting efficacy for several types of neuropathic pain in adults, in our view there is a high likelihood that placebo responses contribute substantially to their reported benefits for many patients [175].

The use of opioids in the treatment of chronic pain not associated with a life-limiting condition remains controversial. Opioid prescribing for chronic pain in adults increased enormously over the past 30 years, with a concomitant increase in overdose deaths in adults and adolescents due to apparent non-medical use or diversion of prescribed opioids. Diversion of prescribed opioids has increased rapidly as a problem among adolescents, however most recent data indicate a downward trend in medical and non-medical use of prescription opioids among adolescents [176,177]. In recent years, heroin and street fentanyl have increased more than prescribed opioids as causes of fatal overdoses. In adult studies for chronic non-cancer pain, evidence for long-term benefit of opioids on pain scores is limited, and most studies show no benefit for measures of functioning or disability. As a result, Centers for Disease Control and Prevention guidelines for the treatment of chronic pain emphasize non-opioid therapies [178]. For children and adolescents with non-life-limiting chronic pain conditions there are additional concerns. First, as noted above, opioid tolerance is probably more rapid in childhood compared to in adults. Secondly, adolescence appears to be a time of unique vulnerability to addiction to multiple classes of substances. Long-term opioid prescribing for children is relatively infrequent [179]. Methadone and buprenorphine may play a role for a very small subgroup of patients with refractory neuropathic pain in the context of a multidisciplinary treatment approach.

KEY POINTS: NEUROPATHIC PAIN

- Neuropathic pain can persist independently of tissue injury or inflammation
- Allodynia and hyperalgesia are components of neuropathic pain
- Tricyclic antidepressants, anticonvulsants, gabapentin, opioids, and transdermal lidocaine are all frequently utilized for neuropathic pain

Complex regional pain syndromes

Complex regional pain syndrome type 1 (CRPS1) is characterized by neuropathic limb pain with associated sensory characteristics and neurovascular and sudomotor findings. The term CRPS1 overlaps with what was previously called reflex sympathetic dystrophy or reflex neurovascular dystrophy [180]. Diagnostic criteria for clinical and research purposes have undergone refinement [181]. The classic clinical presentation is burning pain in an arm or leg with allodynia, hyperalgesia, mottling, coolness, swelling, and abnormal sweating, although the clinical presentation can vary widely. Various motor findings can also occur such as tremors, fasciculations,

and dystonia. CRPS2 refers to this pattern of clinical findings with signs of specific peripheral nerve injury; this is similar to what was traditionally called causalgia. In our view, although there may be important roles for peripheral and autonomic mechanisms, it is useful to view CRPS as being maintained at least in part by abnormal information processing in the brain. These functional brain abnormalities are not purely sensory, but also involve pain modulation [182] and motor representation [183,184].

CRPS has unique epidemiological features in children. Multiple cases series have found a high female to male ratio (approximately 5–8:1) and a preponderance of lower extremity involvement (75–90%) [180,185,186]. The peak age of onset is 10–12 years of age. It is rarely seen in children less than the age of 6 years. Twenty percent of children have a remote or contralateral limb affected. About 90% of patients recall an inciting trauma but it is usually vague and minor. Some children can present as extremely disabled, have significant school absences, and are unable to ambulate independently, however the degree of disability seems to vary widely. fMRI has been used to study CNS activation in children with CRPS [187,188]. Some functional and structural changes normalize after the pain from CRPS resolved, while other changes are persistent [187–190].

Retrospective case series and prospective studies in children have indicated that the majority of children with CRPS will have improvement in both function and pain through an aggressive rehabilitative approach without the use of nerve blocks or pharmacological agents [191,192]. The frequency of recurrent episodes may range from 20% to 50% of cases, although most recurrences of symptoms appear to be milder than the initial episode and more readily responsive to reinstitution of aggressive physical therapy, occupational therapy, and cognitive-behavioral therapies. Our practice in treating children with CRPS involves a rehabilitation program with these therapies. A significant aspect of the approach involves patient and parent education about the non-protective nature of neuropathic pain and recognizing factors that reinforce disability and fear of pain. Physical and occupational therapies are directed at active mobilization of the affected limb, resuming independent weight-bearing, and aggressive desensitization techniques [172,192]. For some children, this program can be accomplished as an outpatient but those who continue to have severe pain and limb dysfunction may need an inpatient or partial hospitalization program. Results of an interdisciplinary day hospital treatment program comprised of physical, occupational, and cognitive-behavioral therapies with medical and nursing services for pediatric CRPS showed significant improvements in pain, functional disability, emotional functioning, and use of assistive devices [192]. Functional gains were maintained or further improved at follow-up at 10 months postdischarge [192]. Continuous epidural or peripheral nerve local anesthetic infusions are used for a comparatively small subgroup of patients who fail to make good progress with good rehabilitation efforts or for those with severe limb swelling or dystonia that persists after an active multidisciplinary treatment program [193]. If the distribution of pain, allodynia, and autonomic abnormality is appropriately limited, there are advantages to the use of peripheral or plexus catheters. Our practice is to use an indwelling catheter technique for several days rather than repeated single injections. We tend to place continuous popliteal–sciatic catheters for lower extremity CRPS and either supraclavicular or infraclavicular catheters for upper extremity CRPS [194]. Patients are then hospitalized and receive continuous local anesthetic infusions of ropivacaine. During their 3–5-day hospital stay, they receive intense rehabilitation with twice daily physical therapy and cognitive-behavioral therapy. In a review of 102 children who received continuous regional analgesia and inpatient pain rehabilitation for CRPS, 75% had significant benefit, including pain reduction and improved function [193].

KEY POINTS: COMPLEX REGIONAL PAIN SYNDROMES

- CRPS presentation includes burning pain in an arm or leg with allodynia, hyperalgesia, mottling, coolness, swelling, and abnormal sweating
- CRPS1 occurs without antecedent peripheral nerve injury (reflex sympathetic dystrophy); CRPS2 occurs in association with peripheral nerve injury (causalgia)
- CRPS treatment incudes an aggressive rehabilitation approach; continuous epidural or peripheral nerve local anesthetic infusions are used for a small subgroup of patients

Back pain

Back pain in adults is a major cause of suffering as well as economic loss due to work-related disability. Non-disabling episodic back pain is relatively common in children and adolescents, but daily persistent back pain is overall much less common than in adults [195]. Since persistent severe back pain is relatively less common in younger children, it is appropriate to evaluate for specific serious causes including infections (osteomyelitis, diskitis, pyelonephritis), tumors, benign abnormalities such as osteoid osteoma, and congenital abnormalities, such as tethered cord and diastematomyelia.

Back pain in our referral practice is more commonly seen in adolescents who are competitive athletes, such as gymnasts, dancers, and cheerleaders. A thorough neurological and musculoskeletal exam is necessary to determine likelihood of conditions such as lumbar disk disease, spondylolysis, spondylolisthesis, sacroiliitis, and muscular strain. Patients with muscular pain without evidence of radiculopathy are treated with an exercise program of core strengthening and reducing repetitive stress and trauma to the spine. With proper patient selection, fluoroscopically guided epidural steroid injections appear to provide intermediate-term benefit in adults with lumbar radiculopathy. Our recent review of experience with fluoroscopically guided epidural steroid injections for children and adolescents with lumbar radiculopathy showed that the majority of patients reported significant reductions in pain with an excellent safety profile. In 2–5 years of follow-up, fewer than 40% of patients required diskectomy [196]. In adults, extension-related back pain is commonly associated with facet arthropathy. In adolescents, this pattern of pain is commonly seen with spondylolysis and spondylolisthesis. These conditions are commonly treated with a trial of bracing. Adults with

cervical or lumbar facet disease commonly receive median branch blocks and, if they provide short-term benefit, with radiofrequency denervation procedures [197]. In our practice, we perform some of these injections using local anesthetic and low doses of steroids. To date, we have been reluctant to perform radiofrequency denervation procedures on patients with a developing spine except in extraordinary circumstances.

Functional gastrointestinal pain

Functional gastrointestinal disorders are common in pediatric populations and include a range of symptoms such as nausea, vomiting, constipation, and pain [198,199]. Functional abdominal pain disorders refers to persistent or episodic abdominal pain occurring among children and adolescents for whom symptoms cannot be attributed to another medical condition [198,200]. Functional abdominal pain disorders present in distinct patterns, as codified most recently by the Rome IV classifications, and include functional dyspepsia, irritable bowel syndrome, abdominal migraine, and functional abdominal pain not otherwise specified [198]. These conditions account for a high frequency of pediatric office visits, and may account for up to 20% of school days missed due to illness in the USA. Most children who present in this manner remain medically well and few eventually are found to have an identifiable structural or inflammatory disorder.

There are common features of functional abdominal pain with respect to clinical characteristics. Most children are between the ages of 4 and 16 years and report episodic, diffuse, or periumbilical pain. Children younger than 4 years should prompt further investigation into underlying causes. Children are otherwise generally medically well without systemic signs of disease. Rarely do children report that pain awakens them at night. The diagnostic approach in primary care should be guided by a careful history and physical examination and should avoid unfocused laboratory testing beyond basic studies, such as a complete blood count and urinalysis, and as appropriate, such as testing for gluten sensitivity, lactose intolerance, amylase, lipase, and stool examination [201]. A psychosocial history is important for identifying reinforcing pain behaviors and other behaviors that suggest disability. In general, extensive testing, routine radiographic studies, and unfocused laboratory testing are not helpful and may heighten parental and patient anxiety. For children who have fevers, weight loss, or poor growth, a family history of inflammatory bowel disease, and localized pain that is not periumbilical, these are concerning signs and warrant further evaluation. Abnormalities on physical examination should also guide additional investigation.

Treatment of functional abdominal pain disorders depends in part on the pattern of clinical presentation and the degree of distress or disability involved. As guided by the history and examination, some clinicians favor empirical trials of treatment of constipation, lactose avoidance, or lactose enzyme supplementation, dietary alterations such as the FODMAP (fermentable oligo-, di-, and monosaccharides, and polyols) diet, or acid suppression [202–204]. Education of parents and patients should include discussion about the non-protective character of the pain, and should discourage catastrophizing and overmedicalizing. Cognitive-behavioral interventions are supported by evidence, and should be used early in the course of treatment [205]. In our view, medications form only a part of the management and should not be used in lieu of lifestyle change, rehabilitative interventions, and cognitive-behavioral interventions. Controlled trials of medications such as amitriptyline have yielded both positive and negative results [206]. Many medications are commonly prescribed based on uncontrolled pediatric case series or extrapolation from adult studies [207,208].

Headache

Episodic headaches are also common in children and adolescents. The frequency of both migraine and tension-type headaches increases through childhood. Prior to adolescence, boys and girls are similarly affected. With the onset of adolescence, the prevalence increases more in girls than in boys, particularly with migraine. Patients and parents are often worried that headache is associated with serious conditions, such as tumors. As with abdominal pain and chest pain, diagnostic evaluation should emphasize the history, including a psychosocial history, and physical examination, including a systematic neurological examination. Practice parameters on imaging for recurrent headaches in childhood have been published. In the absence of features of the clinical presentation that suggest higher risk, imaging studies are generally of low yield [209], or they identify incidental findings [210] that further increase worry but are of generally limited clinical significance.

While recurrent tension-type headaches or episodic migraine are common, for the majority of children in the general population they do not dramatically impair daily functioning. The subgroup of children who may be referred to pediatric neurologists or pediatric pain physicians tends to be those with more frequent or more severe headaches, or those who have pathological but not readily "fixable" headaches. Examples of the latter include headaches following head trauma or following multiple ventricular shunt procedures with slit ventricles. The occurrence of more disabling recurrent headaches [211] or chronic daily [212] headaches is more prevalent with certain lifestyles, including obesity, smoking, and lack of physical exercise, with some psychological comorbidities, including anxiety and depression, and with overuse of analgesic medications.

For children with relatively infrequent migraine episodes, there is evidence to support episodic use of NSAIDs and several triptans for abortive treatment [213]. For children and adolescents with disabling recurrent or chronic daily headaches, in our view, treatment should begin with identification of triggering factors, lifestyle modifications, and avoidance of overly frequent use of acetaminophen and NSAIDs. A number of approaches to cognitive-behavioral therapy show strong evidence of efficacy for both migraine and tension-type headaches, and they should be used widely [214].

The use of prophylactic medications for pediatric migraine is often based on custom and on extrapolation from adult studies. For example, cyproheptidine is widely used, despite absence of controlled trials. While several anticonvulsants are widely used, evidence for efficacy is sparse for most anticonvulsants [215]. There is some support for topiramate in recent placebo-controlled pediatric migraine prophylaxis trials [216]. There are positive trials for amitriptyline, trazodone, and several calcium channel blockers, and trials of propranolol have yielded mixed

results [213]. A double-blinded, placebo-controlled trial of amitriptyline and topiramate for pediatric migraine prophylaxis showed no significant differences in headache frequency or related disability compared with placebo [217]. Patients receiving amitriptyline and topiramate had higher rates of adverse events. Nerve blocks such as occipital blocks and trigger point injections are commonly used in the management of pediatric headaches, however there is limited evidence on efficacy [218]. In young adults with persistent transformed migraine, we occasionally do scalp injections of botulinum toxin, based on adult studies [219].

KEY POINTS: BACK, FUNCTIONAL GASTROINTESTINAL, AND HEADACHE PAIN

- Back pain in adolescents is commonly seen with spondylolysis and spondylolisthesis; fluoroscopically guided epidural steroid injections are effective for patients with lumbar radiculopathy
- Functional gastrointestinal pain is primarily treated with cognitive-behavioral interventions
- Muscle tension headaches are treated with cognitive-behavioral interventions and mild analgesics; migraines may require avoidance of triggers, triptans, and other preventive drug strategies, and occasionally scalp injections of botulinum toxin

Summary

The management of acute, recurrent, and chronic pain in children has made considerable progress over the past 30 years. While pain assessment is more challenging in infants and preverbal children, pragmatic measures are now available for all age groups. Treatment should be individualized and may involve combinations of pharmacological, regional, rehabilitative, and cognitive-behavioral interventions. Multicenter clinical trials will be helpful for conducting adequately powered clinical trials for many forms of acute and chronic pain in pediatrics.

CASE STUDY

You are working in a pediatric chronic pain clinic when you are paged by one of the emergency room physicians who asks if you would urgently evaluate a patient who has severe foot pain and is currently being seen in the ER. You agree to see the patient who then shortly arrives in your office. The patient is an 11-year-old competitive gymnast who is accompanied by her mother. The child has an 8-week history of left foot pain, which she attributes to tripping over a gymnastic mat; this event produced a small laceration of her foot and a sprain. An orthopedic surgeon evaluated her after the fall. Her plain radiographs did not show an obvious fracture, but she did wear an aircast boot for 4 weeks without significant improvement. A recent bone scan showed osteopenia of the affected limb. An MRI showed no significant findings. Her pain is significantly worse this morning since falling last night after her left foot "gave out" as she was walking up stairs. She reports that her foot often "gives out" and feels like she has no strength in it. She is otherwise medically well. She describes her pain as a numb, burning sensation over her entire left foot with shooting pains into her lower calf. She has noticed occasional swelling and redness of her foot and has also noticed that her foot seems to shake involuntarily. She has difficulty falling asleep due to pain and is unable to have the blankets touch her painful foot. She and her mother are tearful as she explains how she will miss the state competitions in 1 month if she cannot participate fully. Her mother explains how difficult this has been for the entire family and how she has had to take a leave of absence from her job since the onset of her daughter's pain 2 months ago. She does describe how supportive the teachers at her child's school have been by allowing her to attend classes only when she is able to make it.

On examination, she is a small-appearing female who is ambulating with the use of crutches. The lateral aspect of her left foot has a 3 × 3 cm area of slight ecchymosis and edema, which the patient reports comes and goes. Her foot has a mottled appearance. When you lightly touch her foot, she withdraws, begins to cry, and explains that it feels like an intense burning and pins and needles sensation. Her foot and lower leg feel cool to touch up to the lower calf. She has noticeable atrophy of her gastrocnemius. She refuses to bear weight on her foot during the examination or to place her left foot on the floor. You explain to the patient and her mother that her history and physical examination findings are most consistent with a diagnosis of complex regional pain syndrome (CRPS). Her allodynia and pain in a nondermatomal distribution are typically seen in CRPS. Neurovascular and motor findings such as edema, intermittent color, and temperature changes, and involuntary spasms and tremors are also consistent with CRPS. A bone scan and MRI have ruled out other worrisome conditions such as osteomyelitis or an occult fracture.

Your discussion with the patient and her mother involves extensive education about CRPS and treatment options. CRPS is rare before the age of 8 years and peaks around the age of 12–13 years. Girls are six times more likely than boys to have CRPS and the lower extremity is much more commonly involved than an upper extremity by a ratio of 8:1. Twenty percent of children experience spread of their symptoms to a contralateral or remote limb, which is presumably due to central sensitization. The majority of children report an antecedent injury, although in most cases the injury seems vague and minor, such as the injury that occurred in this patient. Studies have shown that children with CRPS have similar scores on depression and anxiety testing compared with other children with chronic pain conditions. Plain radiograph findings in children with CRPS are variable and can show diffuse osteopenia or can appear normal,

even with long-standing CRPS. Bone scans also show variable results and have little to no predictive value in CRPS but, as in our patient, can exclude other pathology such as infection. Although CRPS is a clinical diagnosis, quantitative sensory testing has been used in children to provide more objective evidence of sensory abnormalities. It is used to assess function of cutaneous somatic small fibers and is particularly applicable to children since it is painless and does not require sedation.

In discussing various treatment options, you explain that studies of children with CRPS show that the majority will show a good improvement with respect to function and pain intensity through a multidisciplinary approach of active physical therapy, occupational therapy, and cognitive-behavioral therapy. You explain that in some cases a nerve block is indicated so that patients are able to participate in physical therapy or if you are concerned about limb perfusion. The patient's mother asks for a medication such as oxycodone that will alleviate her daughter's pain quickly so that she can participate in the state gymnastics competition. You explain that data showing efficacy of medications are lacking and there is no "quick fix." However, since the patient is having difficulty with sleep, you do prescribe 10 mg of nortriptyline at night. You order a baseline ECG to detect any underlying dysrhythmia that would place her at additional risk in taking a tricyclic antidepressant. You explain that in most cases, you do not prescribe opioids for patients with CRPS. You emphasize to the patient and her mother that cognitive-behavioral techniques such as biofeedback are important to her overall recovery and that therapy will be directed at improving her coping skills, maintaining regular school attendance, and normalizing behavioral responses to pain. She will need to have active participation in physical therapy, particularly to regain strength, to ambulate without the use of assistive devices and for desensitization techniques. You discuss the non-protective nature of neuropathic pain in that, unlike nociceptive pain which is protective, neuropathic pain is abnormal processing of nerves and pain does not imply tissue injury. If outpatient therapy is not effective, you discuss the possibility of an inpatient or partial hospitalization program for intense rehabilitation.

The patient and her mother return for a follow-up visit in 3 weeks after an outpatient trial of physical therapy and cognitive-behavioral therapy. She has made very little progress. She refuses to participate in physical therapy because of her severe pain. In fact, she is using a wheelchair almost exclusively now and will not allow anyone or anything to touch her foot, even to examine it. She is tearful throughout the evaluation and keeps her knee flexed to protect her foot. Her foot and lower calf have a duskier and diffusely mottled appearance with significant worsening of muscle atrophy. Because of her refusal to participate in physical therapy and her severe neurovascular findings, you offer the patient an admission to a partial hospital pain rehabilitation program which is available to her in 3 weeks. In addition, you offer her a nerve block with an inpatient rehabilitative hospital stay prior to her admission to the pain rehabilitation program to which the patient and her mother agree. Since her pain is unilateral and involves the foot and ankle, you recommend placing a popliteal–sciatic peripheral nerve catheter.

Under general anesthesia, she has a left popliteal–sciatic catheter placed using ultrasound guidance. You inject 7 mL of 0.2% ropivacaine which results in a motor and sensory response. She is taken to the recovery room where a continuous sciatic catheter infusion of 0.1% ropivacaine is started at 8 mL/h; she is then admitted for an anticipated 4–5-day hospital stay. During her hospitalization, she will receive twice daily physical therapy and daily cognitive-behavioral therapy. She will have a strict schedule each day consisting of physical therapy, psychology therapy, "home" exercises, and school tutoring. She will have to dress each morning in regular clothes and wear her shoes and socks. She progresses well during the hospitalization and shows increasing participation in her therapies and activities. No new medications are started. During the course of her psychology sessions in the hospital, it becomes apparent that the demands of school and competitive gymnastics have been very stressful for her, particularly given her perfectionistic tendencies. On hospital day 5, the catheter is removed. She continues to experience intense allodynia and neurovascular symptoms, but feels that overall her symptoms have improved. She is discharged home with physical therapy and psychology follow-up with a planned admission to the partial pain rehabilitation program when an opening is available.

In 2 weeks she is admitted to the partial hospital pain rehabilitation program. During her stay, she receives intense multidisciplinary treatment consisting of 8 h per day of physical therapy, occupational therapy, and psychological therapy with nursing and physician involvement. There is a significant focus on learning active coping skills, family and individual education, desensitization, independent ambulation, and regaining full function despite the presence of pain. By the end of her first week in the partial program, she is able to tolerate shoes, socks, and partial weight bearing on her left leg. By the end of week 2, she is fully weight bearing with no crutches and is able to walk on a treadmill. Sleep is greatly improved through the use of cognitive-behavioral sleep strategies. She has discontinued nortriptyline. Desensitization techniques are still very painful although she is compliant with all aspects of the program. She stays an additional 2 weeks in the partial program. She makes good progress in regaining muscle strength and bulk. Her foot and ankle appear pink and well perfused. Through family therapy with the psychologist, it has been decided that she will still participate in gymnastics but not at a competitive level. Results of neuropsychological testing indicate that she has a mild learning disability and appropriate accommodations will be provided to her when she returns to school. A school reintegration plan is made with her school and her team at the partial program prior to discharge. At discharge, she is able to run, dance, and participate in a full school day, although continues to report some pain in her left foot and ankle.

At her 4-week follow-up appointment, she walks into the office without the use of assistive devices, wearing her shoes

and socks. She and her mother report she is back to school full time with no absences or early dismissals due to pain. She is socially active and involved in an upcoming school play. She reports having no functional limitations.

Teaching points

1. In evaluating children with painful conditions, it is important to perform a thorough history and physical examination to detect underlying or sometimes overlooked causes of pain. For example, other causes of pain in this patient include an isolated nerve injury resulting from her fall or osteomyelitis, since she had erythema, pain, and swelling associated with an open laceration and a presumed fracture. Most children with allodynia in a non-dermatomal pattern associated with motor and neurovascular changes will have CRPS. However, an underlying malignant tumor causing nerve compression can also cause exquisite neuropathic pain and a careful history and physical examination with attention to neurological signs, lymphadenopathy, and distribution of pain will help to clarify possible etiologies.
2. There are numerous classes of drugs used in the treatment of chronic pain, including tricyclic antidepressants, anticonvulsants, and serotonin reuptake inhibitors. It is necessary to understand the wide range of side-effects of these medications and possible interactions as different classes are combined. Our practice is not to use opioids for chronic pain not due to a life-limiting illness.
3. Evidence shows that the majority of children with CRPS will show good response to a conservative approach of intense physical therapy and cognitive-behavioral therapy and many children will never require a nerve block. Nevertheless, treatment must be individualized for each patient. The 11-year-old girl described in this case had a brief trial of outpatient physical therapy and cognitive-behavioral therapy. It was apparent at her initial follow-up visit that she was unable to actively engage in the physical therapy and cognitive-behavioral therapy necessary to recover. It was therefore decided to provide more intense treatment in a partial hospital pain rehabilitative program. Prior to her admission to the program, it was decided to pursue a nerve block and initiate aggressive physical therapy and cognitive-behavioral therapy in the hospital. Because she still had significant functional deficits at discharge, it was necessary for her to continue treatment in a partial hospital pain rehabilitation program.

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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169 Cooper TE, Wiffen PJ, Heathcote LC, et al. Antiepileptic drugs for chronic non-cancer pain in children and adolescents. Cochrane Database Syst Rev 2017; 8: CD012536. A combined analysis of two studies with 141 participants. Similar to the antidepressant study [168], although some adult data exist, insufficient data from children exist for antiepilectics like pregabalin.

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183 Shokouhi M, Clarke C, Morley-Forster P, et al. Structural and functional brain changes at early and late stages of complex regional pain syndrome. J Pain 2018; 19(2): 146–57. Using functional MRI techniques, CRPS patients had changes in gray matter volume and perfusion in areas associated with pain processing; connectivity to sensorimotor cortex showed disruptions in regions associated with motor control and planning.

191 Lee BH, Scharff L, Sethna N, et al. Physical therapy and cognitive-behavioral treatment for complex regional pain syndromes. J Pediatr 2002; 141: 135–40. This prospective, randomized trial of physical therapy and cognitive-behavioral therapy for children and adolescents with complex regional pain syndrome (CRPS) demonstrated that most patients experienced reduced pain and improved function with a non-invasive rehabilitative treatment approach.

200 Apley J, Naish N. Recurrent abdominal pains: a field survey of 1,000 school children. Arch Dis Child 1958; 33(168): 165–70. This meta-analysis of randomized controlled trials demonstrated improvement in pain relief in children with headache, abdominal pain, and fibromyalgia through the use of psychological therapies.

CHAPTER 38
Outpatient Anesthesia

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Introduction

One of the most significant changes in medical practice over the past two decades has been the rapid and enormous expansion of outpatient surgery. For the purposes of this chapter, this includes only day case surgery or other procedures, where the procedure and the discharge home are on the same calendar day, and does not include so-called short stay, i.e. "23-hour admission" surgery where an overnight stay in a medical setting, with nursing care, is included. This growth has been largely fueled by escalating healthcare costs and an imperative need for efficient utilization of shrinking healthcare resources. Recognition of the numerous benefits of outpatient surgery including less disruption of family schedules, decreased inconvenience to patients, fewer psychological disturbances, decreased exposure to nosocomial infections, and greater patient satisfaction have further driven the shift toward performing surgery in the ambulatory setting. This change in practice has affected both adults and children. Indeed, in the year 2006, over 2.3 million ambulatory anesthetic procedures were performed in children under 15 years of age in the United States alone which translates to 38 procedures per 1000 children and represents an approximately 50% increase over procedures performed in 1996 [1]. By 2010, this number had increased to 2.9 million procedures, and of these, approximately half were performed in hospital outpatient settings, and half in ambulatory surgery centers (Table 38.1) [2]. A breakdown of surgical procedures by outpatient versus inpatient status at Texas Children's Hospital in 2017 is shown in Figure 38.1. Of 45,663 total anesthetics, 33,786 (74%) were outpatients.

Historically, the practice of outpatient surgery was first reported in 1909 more than a century ago [3] and the first outpatient surgical center was established in Sioux City, Iowa in 1918 [4]. However, it was not until 1984 that outpatient anesthesia became recognized as a specialty and the Society of Ambulatory Anesthesia was formed. The growth of the specialty of ambulatory anesthesia was accompanied by significant advances in anesthetic techniques including the availability of better anesthetic agents that enabled patients to recover faster. Improved analgesic agents and the practice of regional analgesia techniques allowed patients to be discharged home in reasonable comfort, or with mild to moderate pain that could be adequately managed at home. Such advances coupled with improvements in surgical techniques including minimally invasive procedures made it possible to move procedures from the inpatient to the ambulatory setting. These developments have also resulted in patients with more complex co-morbidities being considered for ambulatory surgery. The ongoing challenge is the provision of efficient, high-quality, and safe perioperative care to patients with complex medical histories for a large variety of surgical procedures in diverse venues. Continuous scrutiny of existing systems along with critical ongoing evaluation of outcomes is necessary to provide a framework that will guide care that is safe, effective, patient centered, and efficient in the ambulatory surgery setting.

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

Design and setting for outpatient surgery

Outpatient surgery in the pediatric population may be performed safely and efficiently in a variety of settings. Such environments include hospital-associated ambulatory care facilities such as operating room suites within hospitals or satellite surgery centers, unaffiliated freestanding facilities, as well as individual physician's offices. One of the most significant reasons for implementing outpatient or day surgery is to maximize efficiencies while decreasing costs. Previous investigators have suggested that the ambulatory surgery center (ASC) model by virtue of its bias toward high volume provides more efficient, higher quality care at a lower cost as compared with hospital-based facilities [5].

Table 38.1 Estimates for outpatient surgery and other outpatient procedures in the USA in children 0–15 years of age, 2010

Procedure	Number
All procedures	2,916,000
Operations on the eye	93,000
Operations on the ear	847,000
Myringotomy with insertion of tube	699,000
Operations on the nose, mouth, and pharynx	903,000
Tonsillectomy with or without adenoidectomy	289,000
Adenoidectomy without tonsillectomy	69,000
Operations on the urinary system	67,000
Operations on the musculoskeletal system	173,000
Reduction of fracture	52,000
Operations on the integumentary system	131,000
Miscellaneous diagnostic and therapeutic procedures	228,000

Estimates are for both ambulatory surgery centers and outpatient procedures in hospital settings.
Source: Data from US Centers for Disease Control Ambulatory Surgery Data [2].

The Institute of Medicine has described high-quality care as care that is safe, effective, patient-centered, timely, efficient, and equitable [6]. These goals may be achieved by focusing on a select population with as few complicating factors as possible.

To ensure the most efficient operation, facilities and personnel should be dedicated solely to pediatric patients as well as outpatient or day surgery. Administrative and medical personnel at such a center are able to provide a uniquely effective care plan that is perhaps hindered, disadvantaged, or even unobtainable when such children are mixed with adults or a more complicated inpatient pediatric patient population. Resource and space constraints may nevertheless force the comingling of various patient groups in a single surgical environment. In such cases, special consideration should be given to the needs of pediatric patients and parents. The separation of inpatient (hospital setting) and outpatient waiting and recovery areas is highly desirable. Likewise, where children and adult patients are mixed, special attention should include the incorporation of child life experts, playroom facilities, changing stations, feeding considerations, and progressive care into the pre- and postoperative setting.

Generally speaking, outpatient surgery requires the same anesthetic and recovery equipment that would be required for any hospital patient. At autonomous surgical sites or physicians' offices, certain other minimal capabilities should be available on site: basic laboratory functions, processing facilities for equipment sterility and maintenance, and an informatics system to accommodate medical record utilization. Standard resuscitation equipment specific to pediatric patients of all ages must be available. A fully stocked cart addressing difficult airway scenarios should also be available, and should minimally include some form of video or fiberoptic assist as well as materials for an emergent cricothyrotomy. Finally, clearly delineated plans and prearrangements must be conceived and implemented to accommodate any patient who

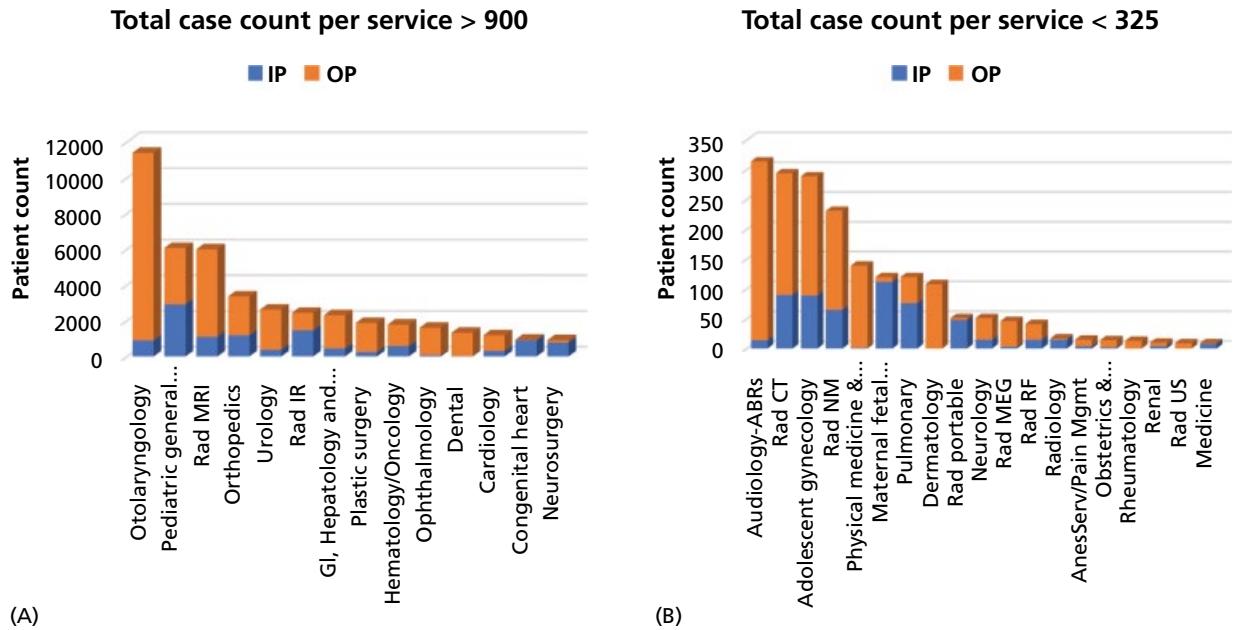

Figure 38.1 Inpatient (IP, blue bars) versus outpatient (OP, orange bars) anesthetics at Texas Children's Hospital in 2017. (A) Services with >900 cases, and (B) services with <325 cases. ABRs, auditory brainstem response; CT, computed tomography; IR, interventional radiology; GI, gastroenterology; MEG, magneto-encephalography; MRI, magnetic resonance imaging; NM, nuclear medicine; Rad, radiology; RF, radiology fluoroscopy; US, ultrasound.

Table 38.2 Summary of the American College of Surgeons Childrens' Surgery Verification Program scope of practice

Level	I	II	III
Age	Any	Any	>6 months
ASA	1–5	1–3*	1–2
Multidisciplinary management of co-morbidities	Multiple medical and surgical specialties; pediatric anesthesiology	Typically single surgical specialties; neonatology; pediatric anesthesiology	None
Operations†	Major congenital anomalies and complex disease, including those that are uncommon or require significant multidisciplinary coordination	Common anomalies and diseases typically treated by most pediatric surgical specialists and that do not require significant multispecialty coordination	Common, low-risk procedures typically performed by a single specialty
Ambulatory‡	ASA 1–3 Full-term infants and preterm infants may be cared for as ambulatory patients based on written guidelines established by the pediatric anesthesiologist in charge of perioperative care. Institutional guidelines generally require full-term infants <44 weeks or preterm infants <50 weeks PMA to be monitored for at least 12 h postoperatively	ASA 1–3 Full-term and preterm infants may be cared for as ambulatory patients based on written guidelines established by the pediatric anesthesiologist in charge of perioperative care. Institutional guidelines generally require full-term infants <44 weeks or preterm infants <50 weeks PMA to be monitored for at least 12 h postoperatively	Otherwise healthy (ASA 1–2) Age >6 months

* Emergent procedures in some patients >ASA 3 may be appropriate in neonatal patients such as those with necrotizing enterocolitis.
† Depending on patient age, co-morbidities, and need for multidisciplinary surgical approach, these may be appropriate for either level I or level II centers.
‡ Ambulatory sites of care are included in these recommended levels of institutional designation when the on-site provider team possesses the requisite pediatrie training and experience. The site of care may be physically attached/integrated into the hospital or may be a component of a demonstrably integrated healthcare delivery system that provides these defined resources.
ASA, American Society of Anesthesiologists; PMA, postmenstrual age.
Source: Reproduced from Brooks Peterson et al [8] with permission of Wolters Kluwer.

develops complications requiring more extensive care including emergent transportation and hospital admission [7].

The American Academy of Pediatrics Section on Pediatric Anesthesiology has published recommendations for the perioperative environment for anesthesia and surgery in children [7]. The facilities should include a separate preoperative unit or an area within a general preoperative unit that is available and designated to accommodate pediatric patients and caregivers. It should have age- and size-appropriate pediatric equipment required for the preoperative evaluation and preparation of the infant or child. In the operating and procedure rooms, a full selection of pediatric-sized equipment for all phases of anesthesia care, including airway and monitoring equipment, and drug dosing and resuscitation carts, should be available for pediatric patients of all sizes. A pediatric difficult airway cart with devices of all sizes needs to be available. Warming devices, i.e. forced-air warming systems and heat lamps, also need to be available. The postanesthesia care unit (PACU) environment similarly should be equipped with pediatric devices of all sizes and appropriate recovery beds for the pediatric population, i.e. high-top cribs for patient safety. There needs to be a set of written pediatric guidelines for treatment, and drug dosing information specific to pediatric patients. Anesthesiologists caring for pediatric patients should have significant training and experience in the care of pediatric patients; and patients of higher risk should have the services of an Accreditation Council for Graduate Medical Education (ACGME) trained, and preferably American Board of Anesthesiology (ABA) certified pediatric anesthesiologist. Minimum case volume standards for pediatric anesthetics should be in place for anesthesiologists. Similarly, nursing staff in all phases of care should have specific training and experience caring for pediatric patients. In the case of freestanding ASCs, detailed, specific transfer agreements to an inpatient hospital with pediatric capabilities must be in place.

The American College of Surgeons, in conjunction with the Society for Pediatric Anesthesia and American Academy of Pediatrics, has recently instituted a voluntary Children's Surgery Verification (CSV) program, with the goal of improving pediatric surgical, procedural, and perioperative care [8]. Included in this program are standards for the delivery of pediatric anesthesia care across a variety of practice settings. The scope of practice requirements are summarized in Table 38.2. The definition of a "pediatric anesthesiologist" is one who is certified or eligible for the ABA pediatric anesthesiology certification or equivalent, i.e. ACGME fellowship trained (Table 38.3). An alternative pathway for this designation requires significant ongoing pediatric anesthesia practice and additional continuing medical education requirements. An "anesthesiologist with pediatric expertise" is defined as certified or eligible for basic ABA certification, and is performing at least 25 anesthetics per year on patients <24 months of age. Of note, in level III of this program, only patients >6 months of age, and of American Society of Anethesiologists (ASA) physical status (PS) 1 or 2 should be cared for in the institutions with this designation. This verification program requires an extensive application and a site visit for inclusion. As of this writing, there were only seven ACS CSV centers in the USA, and all were level I. It remains to be seen whether this program will be widely adopted, especially by potential level II and III centers. This program may have significant implications for pediatric anesthesia practice in the outpatient setting in the USA.

Table 38.3 Summary of classifications of pediatric anesthesiologists in the American College of Surgeons Childrens' Surgery Verification Program

Type of anesthesiologist	Board certification and licensing requirements	Pediatric cases/year	Other requirements
Pediatric anesthesiologist	Certified or eligible for certification in pediatric anesthesiology (prerequisite is ABA certification)		
Anesthesiologist with pediatric expertise	Certified or eligible for certification by the ABA	25 patients per anesthesiologist per year (patients <24 months old)	Ongoing care of patients <18 years ≥10 pediatric CME credits annually (category 1)
Alternative pathway for pediatric anesthesiologist designation	Completion of residency in anesthesiology with letter detailing the pediatric component Licensed to practice medicine and credentialed by hospital to care for children <2 years of age	30% or more of practice averaged over past 5 years devoted to pediatric cases including neonates, children <2 years, high-risk patients	PALS certified 48 h in 3 years of pediatric anesthesia-related CME Membership or attendance at children's anesthesia meetings Case list of patients <2 years of age during reporting period

ABA, American Board of Anesthesiology; CME, continuing medical education; PALS, Pediatric Advanced Life Support.
Source: Reproduced from Brooks Peterson et al [8] with permission of Wolters Kluwer.

Appropriate procedures

Outpatient or day surgery should be restricted to procedures that combine expeditious and efficient throughput with patient safety that obviates the need for lengthy observation or involved inpatient care. Such procedures must meet minimal criteria [9–11] that would:

- Include a relatively limited duration (usually less than 4 h, however this may vary from state to state or institution to institution)
- Comprise a low hazard of surgical or anesthetic complication
- Encompass minimal or easily regulated physiological derangements (including minimal blood loss)
- Involve minimal or moderate postoperative pain that may be easily treated and finally managed with oral analgesics (necessitating the ability to resume oral fluids or nutrition in the immediate postoperative period).

By and large, the majority of common pediatric surgeries fit the described ambulatory surgery parameters (Box 38.1). It should be noted that whereas most adults do not, children do often require significant sedation or anesthesia along with comprehensive monitoring for certain brief exams and minor or rather superficial procedures. As such, myringotomies, circumcisions, cystoscopies, biopsies, and ophthalmological exams, among others, are often scheduled as outpatient procedures. The fact that the most recent data regarding free-standing ASCs reveal the top three pediatric procedures to be. myringotomy (699,000), tonsillectomy with/without adenoidectomy (289,999), and adenoidectomy (69,000) (see Table 38.1) only confirms the shift in thought when considering appropriate procedures for the ambulatory setting [8].

Ear, nose, and throat procedures

Historically, pediatric ear, nose, and throat (ENT) surgery (most commonly adenotonsillectomy) required overnight admission due to concerns for hemorrhage and airway compromise. Hence day surgery was previously practiced on a relatively limited population of older, healthy ASA PS1 and 2 patients without obstructive sleep apnea (OSA). Today, despite the fact that OSA has become a primary indicator for these procedures, the push to attain advantages in efficiency, cost containment, and better resource utilization has made outpatient surgery much more appealing [12,13].

Recent studies have substantiated the general safety of adenotonsillar procedures in children 4 years and older [13,14]. An analysis of national data for pediatric ambulatory ENT surgery confirms the relative safety of such procedures, with minor complications occurring at rates of approximately 1%; however, complication rates for patients younger than 4 years were significantly higher with 2.5% of patients ($p < 0.001$) returning to the surgery center and 9.3% ($p < 0.011$) having an unplanned admission [15]. Likewise, a systematic review noted a statistically significant increase in both complication rates (odds ratio 1.64) as well as unplanned admissions (odds ratio 1.71) in children younger than 3 years of age [13].

Children with OSA encompass a growing portion of the ENT practice, and these patients present augmented risks (see section "Obstructive sleep apnea"). For the predisposed patient, tonsil or adenoid surgery inherently creates the potential for worsened airway obstruction or pulmonary complication in the postoperative period. Data suggest that OSA may markedly accentuate risk; however, it is difficult to independently separate this effect from the more clearly substantiated age effects. Regardless, the literature supports hospital admission for children aged 3 years and younger in whom tonsillectomy and adenoidectomy (T&A) is indicated for OSA [16]. Indeed, outpatient T&A is less cost effective than planned hospital admission for children in this age range [17].

Presenting indications for scheduled ENT surgery may include pathologies that increase risks. Whether suffering from OSA, obesity, central sleep apnea, facial or oral dysmorphism, or even recurrent or continual upper respiratory tract infections (URIs), each patient must be evaluated individually when considering their selection for day surgery, especially in a free-standing ASC. Those patients under 4 years old or possessing multiple co-morbidities should be seen at a hospital centered practice allowing for the possibility of lengthier observation or admission.

Box 38.1: Commonly performed outpatient surgical procedures

Otolaryngology
- Myringotomy and insertion of tubes
- Adenoidectomy
- Tonsillectomy and adenoidectomy (unless contraindicated)
- Frenulectomy
- Laryngoscopy
- Closed reduction of nasal fracture
- Foreign body removal
- Brachial cleft cysts
- Endoscopic sinus surgery
- EUA including some DL/bronchoscopies

Ophthalmology
- EUA
- Eye muscle surgery (strabismus)
- Nasolacrimal duct probing
- Excision of chalazion
- Insertion of lens or prosthesis
- Trabeculectomy

Dentistry
- Extraction
- Restoration

Orthopedics
- Cast change
- Arthroscopy
- Closed reduction of fracture
- Manipulation
- Hardware removal
- Percutaneous tenotomies
- Arthrograms

Urology
- Cystoscopy
- Meatotomy
- Orchiopexy
- Circumcision
- Hydrocelectomy
- Testicular biopsy
- Hypospadias repair

General surgery
- Hernia repair
- Excision of cyst
- Ganglion
- Skin lesion
- Suture of lacerations
- Removal of sutures
- Dressing change
- Muscle biopsy
- Sigmoidoscopy
- Bronchoscopy
- Esophagoscopy
- Incision and drainage of abscess
- Proctological and vaginal procedures

Plastic surgery
- Otoplasty
- Septorhinoplasty
- Scar revision
- Cleft lip and some cleft palate repairs
- Placement of tissue expanders

DL, direct laryngoscopy; EUA, examination under anesthesia.

Continuing the trend toward outpatient surgery for an increasing number of ENT patients, a recent combined review concluded that tympanomastoidectomy, and even cochlear implantation in children older than 2 years, could be done safely as outpatient surgery [18].

KEY POINTS: DESIGN, SETTING, AND APPROPRIATE PROCEDURES

- Ideally, facilities should be dedicated solely to pediatric patients and outpatient surgery
- Appropriate procedures are generally <4 h, have a low risk of surgical or anesthetic complication, have minimal blood loss and physiological derangements, and have easily managed pain
- ENT surgery comprises about one-third of outpatient surgical procedures

Patient selection

In order to accomplish the workflow goals implicit in the outpatient surgery process, patient selection (and preparation) is paramount. Generally healthy ASA class 1 and 2 children are excellent surgical candidates who can go home soon after surgery. Initial ambulatory practices focused on these patients. However, with the evolution of healthcare practice (medications, equipment, interventions), ASA 3-classified children with stable systemic disease may also now be seen in the ambulatory setting. Even more than other patients, these children should be rigorously screened and ought to have prior approval from their surgeon specialist and anesthesiologist.

Congenital heart disease

The recent increase in survival after congenital heart disease (CHD) surgery means that these patients are increasingly presenting for outpatient anesthesia. With a population incidence of about one in 100, there are approximately 1 million children in the USA with CHD. Outpatient surgery can be done safely in these patients, but in general they should be surgically anatomically corrected two-ventricle patients with no or minimal residual defects [19]. These patients would be considered ASA 2 and do not have an increased risk over other ASA 2 patients without CHD. When a patient has a single functional ventricle at any stage of repair, or has unrepaired two-ventricle defects or significant residual cardiac disease after surgery, great care must be taken with evaluation, and the patient's cardiologist must be contacted, and echocardiography and other studies must be reviewed [20]. Most of these patients will be considered ASA 3 and should not have outpatient procedures, particularly in a freestanding ASC. The well-documented increased risk of anesthetic complications,

especially cardiac arrest, in CHD patients warrants extreme caution, and procedures are best done in a tertiary hospital setting where appropriate expertise and back-up are available. If the decision to proceed with outpatient anesthesia is made, consideration for infective endocarditis prophylaxis is needed. See Chapters 27 and 28 for more information on CHD.

Resource management

The focal point of the outpatient or ambulatory facility centers on resource allocation. Even a single patient requiring increased attention or unplanned efforts may compromise the overall flow or function of the unit. Such a patient might be a normally healthy child with a history of asthma and a new URI who is more prone to laryngospasm and postoperative bronchospasm; or an otherwise healthy child with micrognathia and previously difficult intubation; or an obese child with known OSA who might need prolonged postoperative monitoring or even positive pressure ventilation. It is not that such patients cannot be safely cared for, it is that their care may be more easily accommodated at a larger center possessing greater resources and readily available admission. As such, it is crucial to recognize and triage these patients before they arrive at an ambulatory practice setting.

A surgical scheduling system for ENT cases in a large tertiary children's hospital is displayed in Table 38.4 [21]. Category I patients could be scheduled at an outlying ambulatory surgery center, and of 8478 procedures in a 12-month period, 3454 (48%) were deemed suitable for category I ASC scheduling. Of these, 93% were actually performed in an ASC. Unfortunately, outcomes were not reported in this publication [21].

Table 38.4 Surgical scheduling categorization system for ear, nose, and throat procedures

Category	ASA*	Description
I	1 or 2	Full-term infant 4 months of age or older Must be acceptable based on anesthesia criteria†
II	1 or 2	Category I patients that must be done in main OR due to family/social issue
III	1 or 2	Category I patients that must be done in main OR due to coordinated case
IV	2–4	Patients that do not qualify for satellite based on anesthesia criteria† or fit exclusion criteria‡

* American Society of Anesthesiologists (ASA) physical status classification: ASA 1, no systemic disease; ASA 2, single systemic disease (mild or well controlled); ASA 3, two or more systemic diseases or single moderately controlled systemic disease; ASA 4, poorly controlled systemic disease(s).
† Well-controlled gastroesophageal reflux disease, developmental delay, or mild cerebral palsy without coexisting medical conditions; well-controlled asthma; cardiac lesions with minimal hemodynamic effects (atrial septal defect, ventricular septal defect, patent ductus arteriosus); well-controlled or resolved seizures; malignancy in remission; simple uncomplicated diabetes mellitus; and von Willebrand disease considered on an individual basis.
‡ Known or anticipated difficult airway; immediate or one-degree relative with history of malignant hyperthermia; bleeding disorder requiring possible transfusion; less than 1 year of age and former prematurity less than 35 weeks' gestation; and corrected complex cardiac disease.
OR, operating room.
Source: Reproduced from Gantwerker et al [21] with permission of Elsevier.

KEY POINTS: PATIENT SELECTION

- Generally, outpatients should be of ASA 1 or 2; occasionally ASA 3 patients with stable systemic disease can be anesthetized in the outpatient setting
- Patients with CHD can be anesthetized as outpatients, but generally they must be ASA I or II, and have repaired or minimal two-ventricle disease
- Patients with a known risk of increased intervention such as new URI with asthma, a difficult airway, or known significant OSA should be cared for in a hospital setting

Preoperative evaluation/screening

While there are specific conditions or pathologies that would seemingly be in conflict with ambulatory procedures, creating a definitive list is debatable. Much depends on the specific environment of the surgical suite – ASC or physician office versus hospital or tertiary care setting. Likewise, such decisions must be informed by the comfort level of the assigned staff or anesthesia provider. The conditions listed in Box 38.2 warrant careful preoperative evaluation and screening in order to determine appropriateness for ambulatory surgery. They provide a framework from which medical directors may develop guidelines appropriate for their site.

There are clearly conditions that should generally be avoided in such centers – a patient with a previously difficult airway, or with a coagulopathy previously requiring considerable blood products, or with an unstable congenital heart defect. However, even patients with such conditions may appear on a spectrum. There are two basic areas of concern when evaluating such cases. The first and most important is patient safety. For example, if the ASC or outpatient site does not possess the capability to procure or administer blood products, then the hemophiliac or brittle sickle cell anemia patient should probably not be a surgical candidate there.

As noted above, after patient safety, the goal of the ambulatory practice is to optimize throughput and efficiency. Any patient condition that increases the probable perioperative complexity also increases the potential drain on the ambulatory unit's resources. A severely autistic or developmentally delayed child often requires greater resources or attention in

Box 38.2: Patient co-morbidities that require special considerations for ambulatory surgery

- Prematurity/exprematurity
- Obstructive sleep apnea
- Obesity
- Uncorrected or hemodynamically significant congenital heart disease
- Known difficult intubation, airway obstruction
- Myopathy
- Inborn errors of metabolism
- History of malignant hyperthermia
- Down syndrome
- Known coagulation disorders
- Sickle cell disease
- Diabetes mellitus

the pre- and postoperative setting and thus impedes unit throughput. The difficulty is deciding at what point the potential for unanticipated problems outweighs the benefit of caring for such a patient in the ambulatory setting.

Apnea in the infant

Patient age is not regarded as the limiting factor for outpatient procedures; however, full-term neonates in the first 4–6 weeks of life require special consideration due to concerns stemming from the transition from fetal and neonatal physiology to a more mature homeostatic state. Most significantly, these infants, whose brainstem breathing regulation remains immature, are at increased risk of apnea after anesthesia.

With improvements in neonatal intensive care, a greater number of premature infants (less than 37 weeks' gestation) now survive through the neonatal period, and a proportionally larger number present for surgery in early infancy. Regarding these infants, studies clearly demonstrate an increased risk of postanesthetic apnea in ex-premature babies with hazard stratified by postconceptual age. In the most significant analysis (combining eight prospective studies) a postconceptual age of 56 weeks was required to reduce the postanesthetic risk of apnea to less than 1% (95% statistical confidence) in infants with a gestational age of 32 weeks. For those with a gestational age of 35 weeks, the required postconceptual age was 54 weeks [22]. Despite the suggestion that regional techniques might reduce or eliminate this risk [23–25], there have been published case reports of apnea after spinal anesthesia [26,27] and a Cochrane Review of this topic determined that there was no reliable evidence to demonstrate a reduction in postoperative risk of apnea with spinal versus general anesthesia in former premature infants [28,29].

As noted, even the healthy full-term infant may be prone to periods of apnea and hence it is prudent to delay outpatient procedures in such patients. Most institutions set a 4–6-week age requirement for term infants [30]. Alternatively, scheduling such patients earlier in the day also allows for an extended observation period if indicated. Regarding former premature infants, the recommended cut-off postconceptual age for outpatient consideration varies from 46 to 60 weeks [9,31,32]. Of course any complicating medical conditions must be considered, and the more premature the infant, the lower the threshold for admission. Likewise, if apnea is documented during the recovery period, the patient should be admitted for observation. These patients are not candidates for surgery at freestanding centers due to their need for admission and continuous cardiorespiratory monitoring for apnea.

Obstructive sleep apnea

Beyond its significance as the primary indication for T&A, OSA and its associated risks must be appreciated and understood in the greater context of all pediatric procedures. Peak prevalence occurs in 3–6-year-olds, but rates are on the rise due to the rapid rise in pediatric obesity. OSA is also more prevalent in children with respiratory disease, prematurity, craniofacial anomalies, hypotonia, myelomeningocoele, cerebral palsy, and other disorders such as Down syndrome and Arnold–Chiari malformation. Among its most significant manifestations are neurocognitive and behavioral dysfunction as well as cardiopulmonary sequelae including pulmonary hypertension and cor pulmonale [33].

Children with OSA are clearly at increased risk during the perioperative period and those with severe OSA must be assessed closely before proceeding [34,35]. Clinical practice guidelines released by the American Academy of Pediatrics describe risk factors for respiratory complications in children with OSA undergoing T&A including: age <3 years, severe OSA on polysomnography, cardiac complications of OSA such as right ventricular hypertrophy, failure to thrive, obesity, prematurity, recent respiratory infection, craniofacial anomalies, and neuromuscular disorders [36]. These guidelines also recommend T&A as the first-line treatment for children with severe OSA although they do not define the exact polysomnography criteria that are indicative of high risk. Finally, these guidelines recommend that patients deemed as high risk be monitored as inpatients following T&A.

Polysomnography is the recognized gold standard to diagnose and quantify the severity of OSA; however, it cannot predict postoperative clinical outcomes. In one study, its positive predictive value for respiratory complications was only 25% [37]. Postoperative complications in children with OSA include laryngospasm, apnea, pulmonary edema, pulmonary hypertension, and pneumonia [38]. Even the incidence of respiratory complications in such children is significantly higher than in the general pediatric population (21% versus 1–2%) [37].

Studies also show that children with moderatet o severe OSA (SpO_2 nadir <85%) have increased sensitivity to opioids and are more prone to postoperative apnea [39]. While these patients should be considered on a case-by-case basis, significant or severe OSA should be considered a contraindication to the outpatient management of all procedures, not just ENT cases.

Obesity

With a prevalence of 16%, representing a threefold increase in the past 30 years, obesity is a growing concern in the pediatric population and a significant risk factor in pediatric ambulatory procedures [40,41]. Compared with the non-obese population, these children are significantly more predisposed to complicating co-morbidities including asthma, hypertension, gastric reflux, type 2 diabetes, and OSA. More importantly, obesity has been associated with an increased incidence of adverse perioperative respiratory events including difficult mask ventilation, airway obstruction, bronchospasm, significant oxygen desaturation, and overall critical events [42]. Various studies have demonstrated similar perioperative risks and obesity has been identified as an independent predictor for the likelihood of admission after T&A [43]. Keeping these concerns in mind then, the obese patient with any comorbidity must be evaluated carefully before scheduling for outpatient surgery. Indeed, before being considered for procedures at freestanding ambulatory centers, such patients should be evaluated and approved by the anesthesiologist or the medical director of the center.

Malignant hyperthermia

Children with suspected or confirmed malignant hyperthermia (MH) susceptibility present special challenges for outpatient anesthesia [44]. Undoubtedly these children should

receive a trigger-free anesthetic with the use of continuous temperature and end-tidal carbon dioxide monitoring. Arterial blood gas monitoring and dantrolene must be available for the management of a rare case of MH. Additionally, children with MH susceptibility may require extended monitoring of temperature and heart rate in the PACU. In the ambulatory setting, an important question is whether the MH-susceptible child should be routinely admitted for overnight monitoring following a trigger-free anesthetic. A retrospective study of 285 MH-susceptible children undergoing 406 procedures reported no cases of intraoperative pyrexia [44]. The sample included 25 children with biopsy proven MH and none of them developed pyrexia; however, six of these children had received routine preoperative dantrolene. Of 10 children who developed postoperative pyrexia, none were believed to be experiencing an MH reaction and none were treated with dantrolene, although four of them had received dantrolene prophylactically. These data suggest that it may be safe to discharge children with MH susceptibility home following a trigger-free anesthetic. However, the facility must be prepared to monitor them for an extended period of time (4 h or more) and have the ability to transfer the child to an inpatient setting in the rare but unexpected case of an MH reaction. It remains questionable whether the surgical care of these patients is best handled in a hospital-based facility rather than a freestanding ASC, given the throughput goals at the latter site.

Upper respiratory infection

Among the most difficult scenarios confronting the anesthesia provider in the ambulatory setting is the otherwise healthy child who presents with a new URI. Rather benign, recurrent viral illnesses may be ubiquitous in the preschool and primary school population and should not necessarily delay surgery. However, more severe symptoms, including fever, lethargy, purulent secretions, a productive cough, or pulmonary involvement, should mandate procedure postponement for a minimum of 4 weeks. Likewise for a suspected bacterial infection where an antibiotic may be prescribed; the patient can then be assessed by their primary care physician before returning for surgery. The difficulty resides in those URI cases that fall in between the toxic appearing child and the bright, interactive child.

These infections, whether viral or bacterial, may increase airway inflammation, irritability, and respiratory tract secretions to a degree that may persist up to 6 weeks. This airway hyper-reactivity during anesthesia can lead to adverse respiratory events, a protracted recovery time, or even hospital admission. Indeed, much of the literature on this topic confirms that an active or recent URI increases the risk of perioperative complications including atelectasis, hypoxemia, laryngospasm, and bronchospasm in the pediatric population [45–49]. Furthermore, certain factors raise the perioperative risk when combined with a URI: endotracheal intubation, history of prematurity, history of reactive airway disease, airway surgery, the presence of copious secretions, nasal congestion, and passive smoking [48]. Despite such increased risk, there is little evidence of long-term sequelae; the vast majority of adverse events are manageable under the judicious care of experienced practitioners [50].

Decisions regarding whether to proceed with elective surgery in a child harboring a URI should be based on findings from a detailed history and physical examination. Parents are often clear in differentiating their child's condition from their "typical runny nose" or "allergic symptoms." They should be able to provide lucid differentiation between a chronic symptomology and an acute illness exacerbation. Indeed, previous investigators have found that confirmation of a URI by the parent was a more reliable predictor of laryngospasm than symptom criteria alone [51]. A 3-year-old with recurrent ear infections presenting for myringotomy and tube placement may exhibit symptoms such as fever and congestion. Waiting for an asymptomatic window in such a child may be unrealistic given the waxing/waning course of the patient's pathology (e.g. otitis media). With a detailed history regarding the frequency of the symptoms and in the absence of findings on auscultation, it may be reasonable to proceed with the surgery in this case. If persistent concerns remain, such patients should be referred to a hospital-based center with greater flexibility for observation and admission.

Preoperative evaluations or phone interviews may help identify patients with URI in whom it is prudent to delay elective surgery. Postponement of such cases before they arrive in the hospital or ASC will avoid a wasted trip for the family and prevent interruptions in the surgical schedule at the ambulatory facility. Elective surgery is usually delayed 2–4 weeks for simple nasopharyngitis; 4 weeks for more severe infections including antibiotic prescription; and a minimum of 4–6 weeks, including a follow-up with a primary care physician before rescheduling, for any URI including a lower respiratory tract component (bronchitis, pneumonia, asthma exacerbation, etc.). Ultimately, each of these patients must be evaluated on an individual basis keeping in mind the severity of their symptoms, the urgency of the scheduled procedure, the presence of identifiable risk factors, and finally the comfort level and experience of the involved anesthesia provider. For children difficult to diagnose due to the ambiguity of their presentation or the existence of multiple risk factors, a more conservative approach should be taken when considering proceeding at a freestanding surgery site or physician's office.

Asthma

Asthma, afflicting approximately 9% of children in the USA, is the commonest serious childhood illness and the leading cause of school absenteeism. In its severe form, it carries substantial morbidity and mortality. Asthma accounts for about 3% of all pediatric hospital admissions and emergency department (ED) visits [52]. Despite its associated hazards, in the absence of active wheezing and with appropriate patient evaluation, preparation, and perioperative management, children with asthma may be safely anesthetized in an ambulatory setting.

Patient history is crucial when evaluating a child with asthma. The severity of their condition must be assessed on a spectrum. How frequent and/or severe are their wheezing episodes or exacerbations? How often must they visit the ED? Have they ever required admission to the intensive care unit? What is their current medication regimen? Only patients with well-controlled mild to moderate reactive airway disease should be considered for outpatient surgery.

Children with mild or intermittent symptoms who do not require continuous medications and who may only require sporadic rescue treatments are usually excellent candidates for surgery. The moderate asthmatic requiring regular medications to manage their symptoms must continue these medications or treatments through the morning of their procedure. Inhaled steroids and other treatments (e.g. leukotriene inhibitors or cromolyn) necessitate continual use in order to be effective. A short course of systemic steroids starting the day before the planned procedure may be appropriate for those patients who have required systemic steroids previously. Preoperative prophylactic treatment with a β-agonist may attenuate increase in airway resistance with intubation.

Due to the isolated nature of the freestanding ASC or physician office, a conservative approach is advocated for those patients who appear well but have evidence of suboptimal disease control: hospitalization for asthma within 3 months of scheduled procedure; an exacerbation within 1 month; wheezing during exercise; more than three wheezing episodes in the past 12 months; the need for systemic steroids within 1 month; or a room air O_2 saturation of <96% [9,49]. Caution should be practiced for those patients who are actively wheezing, especially in conjunction with a URI or other respiratory symptoms (e.g. cough or tachypnea). Elective surgery in these patients should be postponed and rescheduled for a time when they are symptom free and fully optimized. Severe asthmatics (baseline wheezing) are at increased risk despite optimization through consultant care and assertive preoperative treatments including systemic steroids and increased bronchodilator therapy. Even with aggressive perioperative management, they should only be scheduled at a hospital-based practice in the event that an exacerbation requires admission.

KEY POINTS: PREOPERATIVE EVALUATION/ SCREENING

- Risk of apnea limits outpatient anesthesia to full-term infants who are 4–6 weeks of age or older; and former premature infants of 46–60 weeks' postconceptional age
- Significant or severe OSA should be a contraindication to outpatient anesthesia
- URI is frequent; an acute infection with fever should result in cancellation of elective surgery; an improving URI without fever should be considered for anesthesia

Preoperative preparation

The prospect and actual process of any surgical procedure is inherently stressful and anxiety provoking. The potential trauma experienced by a child may be transmitted to the caregivers or family. Ambulatory surgery may in fact diminish this trauma by minimizing the separation time between parents and child as well as avoiding a disruptive hospital stay. Yet, the ambulatory model's very emphasis on efficiency and throughput may end up limiting the time and effort allowed for preparation, understanding, and acceptance of the prospective perioperative experience. Fast tracking patients through outpatient surgical settings restricts the ability to address each patient's psychological needs, which may be pronounced in younger children. Ultimately, consideration of these varying child/family requirements (the basis for family-centered care) is integral to the success of the ambulatory model. Ignorance, anxiety, and uncertainty in the preoperative holding area may lead to confusion, patient agitation, delays, and/or staff interventions that strain the surgery center's resources. Moreover, there is evidence that preoperative pediatric patient anxiety is related to emergence delirium (agitation), increased pain (hence, opioid requirements with attendant side-effects), and postoperative behavioral problems [53,54]. These outcomes may postpone discharge and further stress the ASC's timetable and resources.

Among the most cited methods for ameliorating surgery's attendant anxieties are the use of sedative premedications, parental presence at induction, and specific presurgery preparation programs for children as well as their parents.

Premedication

Sedative premedication, in most circumstances, effectively reduces preoperative anxiety, and may reduce perioperative recall and postoperative agitation or maladaptive behavior. Oral midazolam is the most commonly used agent and benefits from a relatively rapid onset and reliable effect. A dose of 0.25–0.5 mg/kg should be administered 20–30 min prior to taking the child to the operating room (the lower dosing requires a longer interval to achieve effect). Establishing protocols and maintaining communication between the preoperative area and the operating room should allow for timely medication administration and mitigate possible delays in anesthetic induction due to premedication. A particular concern in the ambulatory setting is the possibility of an extended sedative effect delaying patient discharge. While there are studies indicating protracted sedation at the higher dosing regimen, most studies have failed to demonstrate a prolonged effect that delays patient discharge [55,56]. In any case, most parents and anesthesia providers will accept the infrequent short delay in order to moderate any psychological trauma.

Alternative agents are available. Oral ketamine (5 mg/kg) or fentanyl (15–20 μg/kg) may be given although these are sometimes associated with prolonged recovery (ketamine) and nausea, vomiting, and pruritis (fentanyl). For those patients unable to cooperate with oral administration, midazolam (0.2 mg/kg) may be given via intranasal or intramuscular routes where the onset of action is more rapid (5–10 min). In the exceptionally uncooperative patient, ketamine (3–4 mg/kg), often combined with midazolam and glycopyrrolate, may be given via intramuscular injection. The resultant nystagmus of the latter method may not be a good option in strabismus surgeries. The intramuscular route, however, should be reserved for situations when all other measures have failed since most children have an inherent phobia for needles. Dexmedetomidine, given intranasally at a dose of 0.5–2 μg/kg 30 min before induction, is an effective technique for patients who will not take an oral premedication [57]. Involvement of a child life specialist and use of distraction techniques may permit children with a high degree of anxiety to cooperate.

Parental presence at induction

Much of the parents' and child's anxiety centers on the separation that occurs at the time the child departs to the operating room. Indeed, sedative premedication is administered in part to facilitate this separation. Intuitively, allowing parents to be present during their child's induction should help to calm the child while simultaneously allaying parental uncertainty and fear. It may also increase cooperation and parental satisfaction with the entire perioperative experience. This approach, while still somewhat controversial, has garnered a great deal of support and has been implemented in many institutions and surgery centers. Nevertheless, most current evidence does not support parental presence at induction [55,58] and in most cases, has not reliably alleviated children's or parents' anxiety. Indeed, for those instances where parental presence did seem to benefit the involved participants, sedative premedication is shown to be a viable alternative and similarly efficacious.

There are clearly cases where parental presence can and does afford benefit; however, this depends on an accurate assessment of individual personalities as well as interpersonal dynamics between patient and parents/caregivers. Experienced anesthesia providers quickly evaluate and build rapport with the patient and parents, but the limited preoperative interaction necessitated by day surgery scheduling militates against clearly or effectively appraising such complex interactions and advocating for or against parental presence. Notwithstanding, children who may benefit are older, less impulsive or active in temperament, and typically have calmer parents who value preparation and coping skills in stressful situations [59].

Preoperative preparation programs

The increased focus on family-centered care often includes preoperative preparation programs incorporating a variety of techniques and activities designed to allay child anxiety and assuage parental concern. Among those activities for the children are non-medical play, medical play, tours of the operating rooms and PACU, videos or movies relating to the perioperative course, and teaching of relaxation or coping techniques. Parental involvement is encouraged throughout and may additionally involve parental tours, presence at induction, and early admittance to the PACU to be with their child.

Feeling inadequately prepared leads to increased parental anxiety [60], and there appears to be a relationship between parental anxiety and an increased risk for the child to manifest anxiety, postoperative agitation, and maladaptive behavior [53]. Hence, methods to mitigate parental concerns such as preoperative preparation programs may expedite and facilitate patient care and the ambulatory process. Furthermore, ancillary benefits may be attained by integrating such programs into an ambulatory process that already requires preoperative evaluation and education as well as the administrative procurement of records and financial/insurance information.

Due to the increased interest in the family-centered care model, many institutions and pediatric-centered facilities have initiated varying forms of these preparation programs. While there are indications that such programs can make a substantive difference in the overall experience of patients and families, and by association the workflow ease and productivity of the ASC, it is still unclear how effective they are in specifically addressing patient anxiety and subsequent sequelae. Study results are mixed when assessing the efficacy of various measures; yet even when patient anxiety is reduced, there is evidence that preoperative benefits fail to translate to the induction or postoperative recovery period [61]. This may be due to the unstructured and piecemeal implementation of many plans that rely on specific or uncoordinated measures.

Recent evidence has demonstrated that a highly integrated and evolved preoperative program can successfully reduce preoperative anxiety (significantly reduced when compared to control and parental presence cohorts; similar when compared to a premedication cohort) and improve postoperative outcomes (decreased analgesic consumption, decreased emergence delirium, decreased time to discharge) [54]. Such a fully developed program, however, requires significant resources in staffing and expertise and thus would be very expensive to implement and run. Likewise, to be effective it would require parental enrollment and a large commitment of time. These constraints may limit the application of such programs to larger, hospital-centered practices that have more resources and can benefit from economies of scale. Chapter 14 presents additional discussion of preoperative preparation.

KEY POINTS: PREOPERATIVE PREPARATION

- Premedication may delay emergence for short cases, but, if needed, oral midazolam is preferred; intranasal dexmedetomidine is an alternative
- Parental presence at induction does not reliably reduce anxiety in the patient or improve induction quality
- Preanesthetic education programs can be effective in reducing anxiety in selected children

Preoperative fasting

Standard nil per os (NPO) guidelines are followed for outpatient surgery [62]. The ASA guidelines were updated in 2017 for patients of all ages and allow ingestion of clear liquids (water, fruit juices without pulp, carbonated beverages, carbohydrate-rich nutritional drinks, clear tea, and black coffee) up to 2 h before procedures requiring general or regional anesthesia, or procedural sedation (Table 38.5) [62]. Breast milk may be ingested up to 4 h before the procedure, and infant formula or non-human milk or a light meal up to 6 h before the procedure. Additional fasting time, i.e. 8 h, may be needed for intake of fatty foods, fried foods, or meat. Gastrointestinal stimulants (e.g. metoclopramide), histamine-2 receptor antagonists to block gastric acid secretion (e.g. famotidine), and antacids (e.g. sodium citrate), and proton pump inhibitors (e.g. omeprazole) are only indicated in patients at significant risk of pulmonary aspiration. If patients are taking these medications, they should continue to take them as usual preoperatively. In general, obese children and teenagers who do not have symptoms of gastrointestinal

Table 38.5 Fasting guidelines for all ages in healthy patients undergoing elective procedures*

Ingested material	Minimum fasting period†
Clear liquids‡:	2 h
Breast milk	4 h
Infant formula	6 h
Non-human milk§	6 h
Light meal**	6 h
Fried foods, fatty foods, or meat	Additional fasting time (e.g. 8 or more hours) may be needed

* These recommendations apply to healthy patients who are undergoing elective procedures. Following the guidelines does not guarantee complete gastric emptying.
† The fasting periods apply to all ages.
‡ Examples of clear liquids include water, fruit juices without pulp, carbonated beverages, clear tea, and black coffee.
§ Since non-human milk is similar to solids in gastric emptying time, the amount ingested must be considered when determining an appropriate fasting period.
** A light meal typically consists of toast and clear liquids. Meals that include fried or fatty foods or meat may prolong gastric emptying time.
Source: Reproduced from American Society of Anesthesiologists Task Force [62] with permission of Wolters Kluwer.

reflux are not treated prophylactically with agents to decrease pulmonary aspiration risk.

In actual practice, although patients can and should ingest clear liquids until 2 h before the induction of anesthesia, because of scheduling considerations – i.e. the possibility that preceding cases could cancel or be completed ahead of schedule – this period may be extended to 3–4 h so that a case can start earlier if needed. Under no circumstances should infants and young children undergoing outpatient anesthesia be fasted for long periods of time, i.e. more than 4 h. Although healthy patients will tolerate this, it is very uncomfortable for the patient and upsetting for the caregivers. If a procedure is significantly delayed, clear liquids are offered to infants and young children while awaiting the start of the procedure.

Anesthetic agents and techniques

Apart from the economic advantages of ambulatory surgery and anesthesia, there are psychosocial benefits to a child recuperating at home following surgery. Hospital admission is associated with behavioral problems possibly due to separation from parents and disruption of family life [63]. To this end, rapid and short-acting drugs for induction and maintenance of anesthesia have been developed to facilitate early recovery following day case surgery. The ideal anesthetic agent for ambulatory surgery should provide smooth and rapid induction of general anesthesia, allow prompt recovery, have minimal side-effects, have analgesic properties, and be free of postoperative nausea and vomiting (PONV). Such an agent does not exist. Since induction of anesthesia is a very important component of the overall ambulatory surgery experience, it is important to use the most acceptable and least distressing technique for the child. While induction of anesthesia is most commonly achieved via the inhaled or the intravenous routes, maintenance is often exclusively by the inhalational method. In some centers outside the USA, rectal administration is sometimes used for sedation or induction of anesthesia [64].

Monitoring

The ASA monitoring standards must be applied to all children undergoing an anesthetic regardless of the setting in which the surgery is performed including office-based settings.

Induction technique

Inhalational induction of general anesthesia is arguably the most common technique used by pediatric anesthesia providers in North America. However, what constitutes the "gentlest" induction method for children remains unclear [65]. Very often, induction method is guided by personal preference of anesthesia providers, institutional practice, and cultural factors. For example, because of prevailing "needle phobia" in many children, anesthesia practitioners in the USA often avoid IV induction [66]. However, in many other parts of the world, including Europe, IV induction appears to be more favored [67]. Very few investigators have compared the induction characteristics of intravenous and inhalational techniques. Some investigators contend that because inhalational induction is not always "smooth," it may be associated with long-term negative memories for children and may be a source of severe stress for parents [65]. Still others claim that IV induction can be a pleasant experience for the child provided topical anesthetic cream is applied to the venepuncture site and the cannulation is performed by a skilled practitioner [63].

Inhalational agents

The ideal inhalational agent should have many of the following desirable characteristics: it should be pleasant to inhale (permitting a smooth induction and emergence), potent (allowing the concomitant administration of high fractional oxygen concentration), produce rapid induction and emergence (low solubility), and it should be easy to administer and analyze (infrared). Such an agent should also be stable in storage, should have minimal to no reaction with soda lime, and should not be significantly biotransformed in the body. It should have little or no cardiac or respiratory irritant or depressant effects and should possess some analgesic properties. With the almost total withdrawal of halothane from clinical anesthesia in developed countries, sevoflurane has become the prototype inhalational agent.

Sevoflurane

Sevoflurane, by virtue of its non-pungent smell and relative lack of airway irritant properties, has become the agent of choice for induction of anesthesia via the inhaled route in children. Due to its low blood gas solubility, sevoflurane causes rapid induction of anesthesia and recovery making it particularly suitable for the ambulatory setting. Other advantages of sevoflurane include its lack of major side-effects, the ability to induce and maintain anesthesia with one drug, better conditions for laryngeal mask airway (LMA) insertion, and ability to induce anesthesia without IV access. Notable

disadvantages of sevoflurane-based anesthesia, however, include possible increased pollution of the operating room with anesthetics and excitatory movements during anesthetic induction [68]. A recent meta-analysis comparing the induction characteristics of sevoflurane with propofol concluded that the two drugs had similar efficacy for anesthetic induction but sevoflurane use was associated with a higher incidence of PONV [68]. Sevoflurane induction and maintenance of anesthesia is also associated with excitatory motor movements on induction and emergence agitation [69]. These side-effects may be distressing to parents and may potentially delay discharge from the PACU. The practice at the University of Michigan is to induce anesthesia with sevoflurane and change to isoflurane for the maintenance of anesthesia. In many cases, we begin inhalational induction with a N_2O/O_2 mixture and gradually introduce sevoflurane into the gas mixture. This practice has been shown to dampen the fairly strong odor of sevoflurane and may reduce some of the anxiety and excitement associated with inhalational induction [70].

Isoflurane

Isoflurane has a pungent odor and causes considerable airway irritation making it a poor choice for induction via the inhaled route. Indeed previous investigators have reported a higher incidence of coughing, breath holding, excessive salivation, and laryngospasm in children who underwent induction of anesthesia with isoflurane compared to those who were induced with halothane for myringotomy and tube placement [71]. Isoflurane is excreted predominantly in the lungs with very little hepatic biotransformation. It is possibly the most popular inhalational agent for anesthesia maintenance due to its lower cost compared with sevoflurane.

Desflurane

Due to its low blood gas solubility (about 0.42 lower than all currently available volatile anesthetics, and slightly lower than nitrous oxide), induction of and recovery from desflurane anesthesia is rapid with a prompt return of protective airway reflexes [72]. The rapid emergence and recovery from general anesthesia provided by desflurane has been associated with a frequent incidence of emergence agitation in children [73,74]. In some patients emergence agitation may be severe enough to require treatment with supplemental analgesic or sedative medications in the PACU. The use of these medications and the need for additional observation prolong and complicate PACU care and delay discharge. Some investigators have determined that the administration of 2.5 μg/kg of fentanyl, given after induction, successfully reduced the incidence of severe agitation associated with desflurane anesthesia in children without delaying emergence [75].

Desflurane may prove useful in overweight and obese patients. Recent data indicate that desflurane use is associated with faster return of protective airway reflexes in otherwise healthy overweight and obese adults [76]. Similar data indicating rapid wash-out of desflurane compared with sevoflurane in morbidly obese patients have also been published [77]. The rising prevalence of childhood obesity in the general and pediatric surgical population may indicate that desflurane is the agent of choice for obese children undergoing prolonged anesthesia. Studies comparing the emergence characteristics of desflurane between obese and normal weight children are warranted.

Due to its pungent odor and associated airway irritability, however, desflurane is unsuitable for inhalational induction. Several pediatric studies [78–80] have demonstrated a high incidence of airway irritation and/or reactivity, including breath holding, coughing, excessive secretions, and laryngospasm.

Intravenous agents

Although inhalational induction is more popular with outpatient anesthesia, IV induction and (less commonly) maintenance of anesthesia is sometimes preferred or indicated. There is a smooth, rapid loss of consciousness and emergence is rapid with currently available agents.

Propofol

This has rapidly become the most popular IV induction agent because it has many of the properties of an ideal intravenous agent. Induction of anesthesia is smooth and recovery is rapid even after prolonged infusion making it suitable for total intravenous anesthesia (TIVA). Propofol is also becoming the agent of choice for most procedural sedation, especially with recurrent procedures such as radiotherapy or chemotherapy. It is a good antiemetic agent (another desirable characteristic in ambulatory anesthesia) and very often some clinicians may opt for propofol TIVA in patients with a compelling history of PONV. It is important to keep in mind that due to their large central volume of distribution and rapid clearance of propofol, children have a higher dose requirement for induction and TIVA than adults. The typical induction dose of propofol in children is 2.5–3.5 mg/kg.

Perhaps the biggest drawback to the use of propofol is pain on injection. The incidence is as high as 70% [81] and various techniques have been tried to reduce this rather distressing side-effect. These authors commonly co-administer lidocaine (1 mg to 1 mL of propofol) and inject the mixture very slowly.

A recent systematic review of propofol-based TIVA versus sevoflurane for outpatient pediatric anesthesia reported a total of 16 trials involving 900 children [82]. Propofol TIVA was associated with a significantly lower risk of PONV (16.1% versus 32.6%), and postoperative behavioral disturbances (11.5% versus 24.7%). There was no difference in incidence of respiratory or cardiovascular complications, time to anesthesia recovery, or discharge from hospital.

Dexmedetomidine

Dexmedetomidine is a presynaptic α2-agonist that binds to the locus ceruleus in the brain and to receptors in the spinal cord to provide sedation, anxiolysis, and some analgesia, while preserving normal respiratory patterns and reducing doses of opioids and inhalational agents when utilized as an adjunct to general anesthesia [57]. In the outpatient surgery setting, dexmedetomidine can be utilized as a single loading dose of 0.25–1 μg/kg at the start of the anesthetic, and the anesthesia can then be maintained with inhaled agents or propofol. This approach has been effective at reducing opioid requirements for pediatric patients undergoing T&A [83]. Other intraoperative applications in the outpatient setting

include airway procedures such as direct laryngoscopy and bronchoscopy, magnetic resonance imaging sedation as a sole agent or combined with propofol for bone marrow biopsy/intrathecal chemotherapy.

KEY POINTS: ANESTHETIC AGENTS AND TECHNIQUES

- Inhaled induction and maintenance with sevoflurane is by far the most common technique for outpatient anesthesia; a high risk of emergence delirium in young children is seen if mitigation strategies are not used
- Propofol as a component of TIVA is associated with smooth emergence and low risk of PONV
- Dexmedetomidine as an adjunct in outpatient anesthesia can reduce opioid requirement and risk of emergence delirium

Emergence agitation and delirium

Rapid-acting anesthetics and an emphasis on avoiding opioids, and providing analgesia with non-steroidal anti-inflammatory drugs (NSAIDs) and regional anesthesia (see section "Regional blockade"), often translates into a significant incidence of emergence agitation and possibly delirium for outpatient surgery [84]. Emergence agitation and delirium are a continuum, with agitation in the early recovery period, and delirium persisting after about 30 min of recovery; both terms are frequently used interchangeably. Emergence delirium is a state of dissociated consciousness in a child who is crying inconsolably, and thrashing about after anesthesia, who typically does not recognize parents or caregivers, or familiar objects like their favorite stuffed animal. The patient is typically preschool aged and is disoriented and does not seem to be aware of their environment. He/she is difficult or impossible to console. The time course is normally early in recovery, usually in the first 5–15 min, and resolves spontaneously in most cases. Emergence agitation lasting longer than 30 min is referred to as emergence delirium. Needless to say this is very upsetting to parents and caregivers, and with an emphasis on smooth recovery and discharge from anesthesia, and parent and family satisfaction of the perioperative care process, minimizing delirium is an important outcome for outpatient surgery programs to strive for.

It is very important to rule out pain or physiological disturbance (e.g. hypoxia) as a cause of emergence delirium. Factors associated with such delirium include age 2–5 years, preoperative anxiety and anxious temperament, pain, and anesthetic technique. A comprehensive review of 158 studies involving 14,045 children clearly associated sevoflurane with a higher incidence of emergence delirium than a halothane or propofol-based anesthetic [85]. No clear difference was found in the use of desflurane or isoflurane versus sevoflurane. Effective pharmacological adjuncts to reduce the incidence of delirium include dexmedetomidine, clonidine, opioids (fentanyl), a propofol bolus at the end of the anesthetic, ketamine, or midazolam. Parental presence on induction and midazolam premedication did not reduce the risk of emergence delirium. A later systematic review and meta-analysis of delirium incidence with desflurane versus sevoflurane identified 14 randomized studies in 1194 patients [86]. The incidence and severity of delirium was the same in both groups, but the emergence and awakening times were shorter with desflurane by 2–3 minutes. See Chapters 14 and 17 for further discussion of emergence delirium.

Pain management

The strategy for postoperative pain management is an integral part of any anesthetic plan; however it becomes particularly important in children undergoing outpatient surgery in order to ensure that parents are able to manage their child's analgesia effectively at home. The intraoperative analgesic regimen should under ideal circumstances allow the child to emerge from anesthesia in reasonable comfort since it is easier to maintain analgesia in a pain-free child than to achieve analgesia in one with severe pain. Effective analgesia is best achieved using multimodal therapies including non-opioid and opioid analgesics, as well as appropriate regional techniques based on the surgical procedure and the child's comorbidities. Education of parents and caregivers regarding assessment of their child's pain and analgesic needs following discharge in addition to detailed instructions regarding the timing and dosage of prescribed analgesics are other important facets of care for children undergoing outpatient surgery.

Non-opioid analgesics

Non-opioid analgesics may be used alone for the treatment of mild pain or as important adjuncts in combination with opioids or regional techniques for the multimodal treatment of moderate to severe pain. Non-opioid analgesics produce dose-dependent responses, but are limited by a ceiling effect, i.e. a concentration is reached above which no additional analgesia is achieved. Therefore, moderate to severe pain is rarely managed with these drugs alone.

Acetaminophen

Acetaminophen is the commonest analgesic and antipyretic used in children. The recommended dose for oral administration is 10–15 mg/kg every 4 h. An oral loading dose of 30 mg/kg followed by a maintenance dose of 10–15 mg/kg may result in an earlier onset of action. Rectal administration results in unpredictable absorption with variable peak blood concentrations being achieved in 60–180 min [87–89]. One study reported a greater morphine-sparing effect with a less frequent need for additional rescue analgesics for 24 h in children who received 40 or 60 mg/kg of rectal acetaminophen compared with those who received 20 mg/kg or placebo during outpatient surgery [90]. Intravenous formulations of paracetamol (acetaminophen) and its prodrug propacetamol have been available in Europe and Australia for many years. Intravenous administration of paracetamol results in an onset of analgesia in 15 min and of antipyresis in 30 min [91,92]. One controlled randomized trial reported good analgesia for the first 6 h after surgery in children undergoing T&A who

received either rectal acetaminophen 40 mg/kg or IV acetaminophen 15 mg/kg after induction of general anesthesia [93]. However, children who received acetaminophen rectally required rescue analgesics later than those in the intravenous group. The intravenous formulation of acetaminophen has been approved by the US Food and Drug Administration (FDA) for use for analgesia and fever in patients 2–18 years of age, and for fever in infants 0–2 years of age since 2010. The maximum daily dose of acetaminophen via any route should not exceed 75 mg/kg for children and 60 mg/kg for infants. Oral acetaminophen is available in a wide variety of over-the-counter and prescription formulations. These include cold remedies and opioid combination products that place children who may inadvertently receive more than one such formulation at risk of an overdose. A careful review of medications and parental education is needed to minimize this risk. In addition, if IV acetaminophen has been administered intraoperatively it is important to communicate this to the PACU staff so that postoperative acetaminophen-containing products are not given too early or in doses exceeding recommended limits.

Non-steroidal anti-inflammatory drugs

NSAIDs provide excellent analgesia for mild to moderate pain due to surgery, injury, and disease. *Ibuprofen*, one of the oldest orally administered NSAIDs, has been used extensively for the treatment of fever and pain derived from a variety of etiologies including surgery, trauma, and arthritis. The recommended dose of ibuprofen is 10–15 mg/kg PO every 6 h. IV ibuprofen is now FDA labeled in the USA for patients older than 6 months for treatment of pain and fever. In a randomized, placebo-controlled trial of a single 10 mg/kg IV dose versus saline placebo for T&A in 161 pediatric patients, ibuprofen demonstrated a significant reduction in the total fentanyl dose and number of doses in the postoperative period [94]. Surgical complications, including bleeding, were not different than with placebo. Ibuprofen may prove to be an attractive choice because of a lower risk of bleeding and gastrointestinal and renal effects.

Diclofenac in a dose of 1 mg/kg every 8 h PO, PR, or IV also provides effective analgesia after minor surgical procedures in children. In the USA it is only available as an oral tablet; however, rectal and injectable formulations are available in other countries. Previous studies have reported that children who received diclofenac during inguinal hernia repair experienced comparable analgesia to those who received caudal bupivacaine or IV ketorolac [95–97]. Diclofenac also yielded better analgesia with a reduced need for supplemental opioids, less nausea and vomiting and earlier resumption of oral intake compared with acetaminophen in children undergoing tonsillectomy and/or adenoidectomy [98,99]. However, diclofenac use has been associated with above average bleeding in children during tonsillectomy [100].

Ketorolac provides postoperative analgesia comparable to opioids in children of all ages. Its lack of opioid side-effects including respiratory depression, sedation, nausea, and pruritis make it a very attractive choice for the treatment of postoperative pain, especially in the ambulatory setting. However, like other NSAIDs, it does carry the risks of platelet dysfunction, gastrointestinal bleeding, and renal dysfunction. Some studies that evaluated the safety and benefits of ketorolac in children undergoing tonsillectomy reported a 2–5-fold increase in bleeding complications including measured blood loss, ease of achieving hemostasis, and bleeding episodes in the PACU necessitating re-exploration and hospital admission in some cases [29,101–103]. Two studies were terminated early when preliminary analysis found an unacceptably greater risk of bleeding in children who had received ketorolac [29,103].

A systematic review of the literature included 25 studies related to the use of NSAIDs for T&A and found that compared with opioids, NSAIDs were equianalgesic, caused significantly less nausea and vomiting, but were associated with more frequent reoperation for bleeding [104]. This study found that the use of NSAIDs avoided PONV and its attendant complications in 11/100 patients, but 2/100 were exposed to the risk of postoperative bleeding requiring reoperation. A Cochrane review involving 13 studies related to the use of NSAIDs and peritonsillectomy bleeding found no statistically significant increase in the risk of bleeding but reported a significant decrease in the incidence of PONV in children who received NSAIDs compared to other analgesics [105]. A follow-up to this review, with 15 studies and 1101 children, confirmed these findings [106]. Taken together, this suggests that until further data become available, it may be prudent to avoid the use of NSAIDs during or after tonsillectomy, and alternative analgesics such as acetaminophen and tramadol should be considered as adjuncts in order to reduce opioid requirements.

Corticosteroids

The role of dexamethasone as a co-analgesic is becoming increasingly recognized in both adults and children [107]. The use of dexamethasone provides the added benefit of antiemesis, which is highly desirable in ambulatory surgery. The mechanism of steroid-based analgesia appears to be related to their powerful anti-inflammatory effect and reduction of prostaglandins at sites of tissue injuries [108]. Recent studies raising concern over the possibility that dexamethasone increased post-tonsillectomy bleeding were assessed in a systematic review and meta-analysis of 61 pediatric studies, and no increased risk of post-tonsillectomy hemorrhage, with or without concomitant NSAID administration, was identified [109].

Opioid analgesics

Opioids play a fundamental role in the management of postoperative pain. Unfortunately, their use is associated with a number of side-effects, including nausea, vomiting, pruritus, sedation, and respiratory depression (particularly undesirable in ambulatory surgery). The high incidence of PONV and concern for respiratory depression often prompts many clinicians to avoid opioids or to use them sparingly [110].

Oral opioids are suitable for children experiencing mild to moderate pain, those who undergo outpatient surgery, or as adjuncts to a regional anesthetic technique. In fact, administration of an oral opioid dose upon awakening in the PACU prior to a regional block wearing off may provide a virtually pain-free recovery period. If dosed appropriately and at regular intervals, reasonably constant blood levels can be achieved with oral opioids. In most cases, oral opioids are better

tolerated after the resumption of oral intake. Codeine now has a US FDA "black box" warning, and is contraindicated in children after T&A. Codeine formerly was the commonest opioid prescribed for pediatric outpatients. It is a weak analgesic and, being a prodrug, it requires conversion to morphine to be effective. Because of polymorphisms in the hepatic metabolizing enzyme CYP2D6, a large percentage of children either have no analgesia from codeine or are at risk of respiratory depression from rapid metabolism to morphine. Codeine has been removed from many children's hospital formularies. *Oxycodone*, with or without acetaminophen, is now one of the most commonly prescribed oral opioids available in liquid form making it easy to prescribe for infants and young children. Oxycodone causes significantly less nausea and vomiting than codeine and appears to be better tolerated by the postoperative child just resuming oral intake.

Children who wake up in moderate to severe pain may require IV opioids such as fentanyl or morphine to achieve rapid and effective pain relief. However, careful titration of dosing and frequent assessment of the child are required to ensure adequate analgesia without excessive opioid side-effects such as respiratory depression, excessive sedation, or PONV that may prolong the PACU stay and delay discharge. Children with obstructive sleep apnea have documented increased sensitivity to opioids and investigators have recommended a 50% reduction in morphine doses for children undergoing T&A who experienced a pulse oximetry nadir to <85% on preoperative sleep studies [39]. See Chapter 37 for additional information about opioids and pain management.

Regional blockade

Regional blocks with long-acting local anesthetics provide excellent postoperative analgesia, particularly for genitourinary and orthopedic procedures performed in the outpatient setting. Both peripheral nerve blocks and central neuraxial blocks (caudal or lumbar epidural) may be used. The techniques are discussed in detail in Chapter 20. Peripheral nerve and plexus blocks provide relatively long periods of analgesia lasting for 8–12 h in most cases and sometimes exceeding 24 h. Depending on the nature of the surgery, this may permit the child to transition to non-opioid analgesics at the time the block wears off, thereby eliminating or reducing the use of opioids and their potential untoward effects. However, appropriate analgesic plans must be made for the parents to follow at home to ensure the comfort of the child once the block wears off.

The optimal time to place the block remains a subject of debate; however, there are several purported advantages to placing the block before the onset of surgery [111]. In addition to the potential benefit of pre-emptive analgesia, the effectiveness of a block placed after induction of anesthesia can be assessed during the procedure so that the block can be repeated at the end of the procedure if ineffective. An effective block may decrease general anesthetic requirements, facilitating a faster recovery. On the other hand, placing the block at the end of the procedure requires a deeper level of anesthesia to be maintained for block placement, resulting in delayed awakening. Lastly, a block placed at the end of surgery may require some time to become effective causing the patient to wake up in pain. A single caudal injection of local anesthetic prior to incision does not shorten the duration of postoperative analgesia after procedures lasting 1 h or less. Investigators have reported similar times from recovery until the first request for analgesics in children undergoing inguinal herniorrhaphy who had caudal blocks placed before incision or after surgery [112]. For prolonged procedures, a second caudal block using half the original volume of local anesthetic may be placed prior to emergence. For central neuraxial blocks in the setting of outpatient surgery, dilute concentrations of local anesthetic (0.1–0.15%) may be preferable since they provide effective postoperative analgesia while avoiding motor blockade and urinary retention. Additives such as clonidine have also been shown in some studies, but not in others, to prolong the action of "single shot" central neuraxis and some peripheral blocks.

Ilioinguinal-iliohypogastric nerve blocks provide excellent postoperative analgesia for genitourinary procedures such as inguinal herniorrhaphy and orchidopexy. They are technically easy to perform (see Chapter 20) and they appear similar in efficacy to caudal blocks with a duration of analgesia of at least 4 h when bupivacaine with epinephrine is used. A randomized, blinded study found that an ilioinguinal nerve block was as effective as caudal blockade to the T10 level in children undergoing orchidopexy [113]. However, pain following procedures that involve considerable manipulation and traction on the spermatic cord and testis may be better managed with caudal blockade. While a penile block is effective for both circumcision and distal, simple hypospadias repair; a caudal block provides more effective analgesia for more extensive procedures on the penis such as the repair of penile/scrotal hypospadias [114]. Infiltration of the incision site with local anesthetic provides effective analgesia for 4–6 h after surgery and should be used at the end of virtually every operation [115,116].

With the widespread application of ultrasound-guided regional anesthesia and the greater numbers of pediatric anesthesiologists who are skilled in this technique in recent years, the repertoire of nerve blocks for outpatient surgery has expanded considerably [117,118]. This includes upper extremity blocks: all approaches to the brachial plexus, and axillary, musculocutaneous, elbow, and wrist blocks. In addition, lower extremity blocks such as lumbar plexus/psoas compartment blocks, and fascia iliaca, femoral, sciatic, popliteal fossa, and saphenous blocks are feasible in the outpatient setting. Truncal blocks including the transversus abdominus plane, rectus sheath, paravertebral, and quadratus lumborum blocks have all been described in the outpatient setting.

A relatively recent addition to regional analgesia techniques in the outpatient setting has been ambulatory peripheral nerve block (PNB) catheters, which go home with the patient and remain in place for 1–5 days postoperatively, delivering dilute concentrations (e.g. 0.1% ropivacaine or bupivacaine) via a disposable infusion pump (Fig. 38.2) [119]. Several large series demonstrate the effectiveness and safety of this approach. In a series of 1285 outpatient PNB catheters, 35% were discharged home on the day of surgery [120]; 82% of these catheters were femoral or sciatic catheters; most patients were in the 11–18-year age group and had arthroscopic knee surgery for anterior

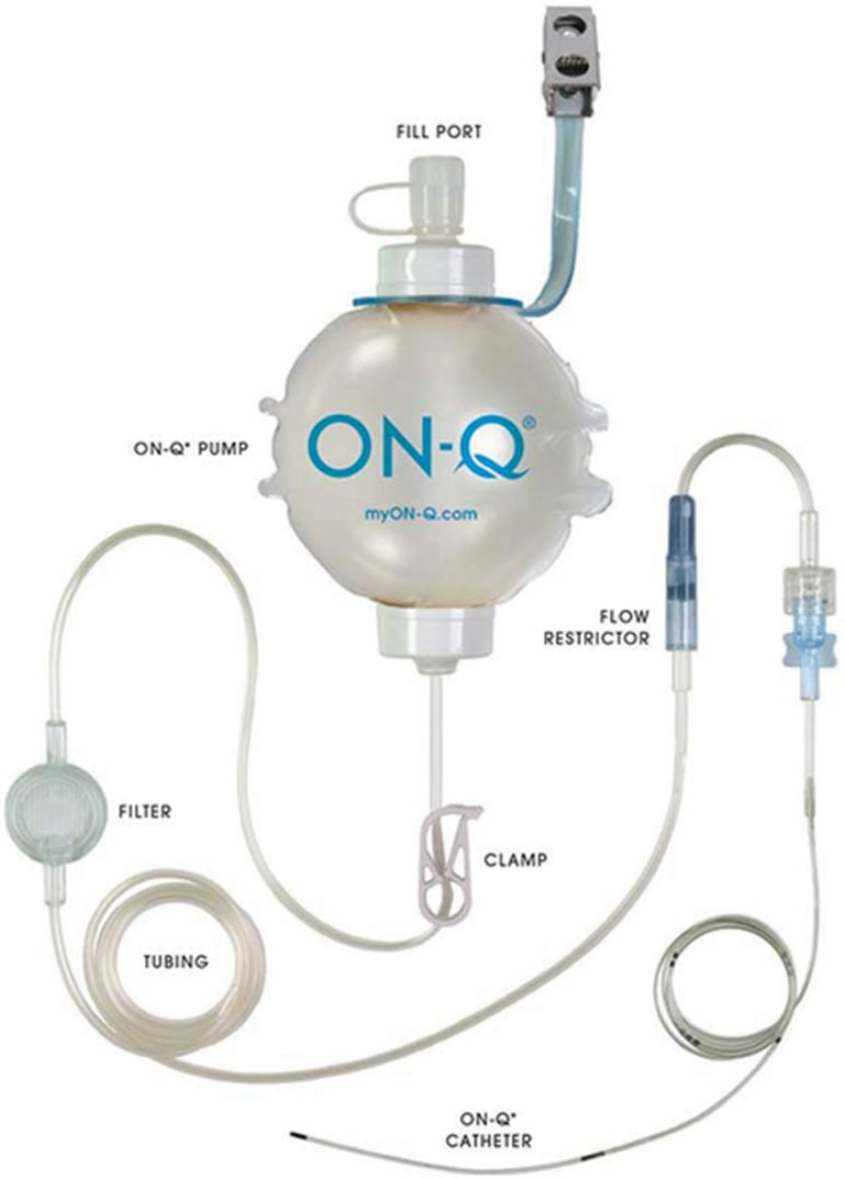

Figure 38.2 Elastomeric pump for local anesthetic infusion. See text for details. Source: Courtesy of Halyard Health; On-Q® Pain Relief System.

cruciate ligament or menisceal repair. The median duration of infusion was 50 h, with a range of 0 to 168 h. Analgesia was good, with 13% of patients requiring no opioid medication, and median time to first opioid dose was 16 h; 5% of patients had complications, most of which were accidental catheter removal or excessive leakage. There were no serious complications, although five patients had local anesthetic-related side-effects. Another series of 403 patients with brachial or lumbar plexus, femoral, sciatic, or paravertebral catheters reported good pain relief and patient/parent satisfaction; 14.4% of patients had complications, the majority were nausea/emesis, with leaking or accidental removal also observed [121]. All authors in this field stress the requirement for a well-organized service, including detailed education and instruction written material for parents, with at least daily telephone follow-up and established procedures for returning to the hospital for problems and for removal of the catheter.

A potential future development in regional anesthesia for outpatients is long-acting local anesthetic drugs, where a single injection could provide many hours, or even days, of local anesthetic blockade. One approach is liposomal bupivacaine, either by local intra-articular infiltration for knee surgery, or as the agent used for a regional block, for example a transversus abdominus plane block. Reports in adults have indicated safety and long-lasting analgesia equivalent to a PNB catheter [122,123]. No reports specific to pediatric patients have been published. A second approach is neosaxitoxin, a site-1 sodium channel blocker that exerts its local anesthetic effects by binding to the outer pore of the voltage-gated sodium channels, blocking impulse generation and propagation [124]. A phase I study of dosing and safety for cutaneous anesthesia reported 30–47 h of duration of action for neosaxitoxin combined with bupivacaine with or without epinephrine. Additional clinical trials in pediatric patients are needed before this approach can be adopted.

KEY POINTS: PAIN MANAGEMENT

- Non-opioid analgesics are a mainstay for outpatient surgery; IV acetaminophen, ibuprofen, and ketorolac are all available
- Opioid analgesics include standard intraoperative drugs; codeine should not be used in children; hydrocodone with or without acetaminophen is a good choice for oral postoperative analgesia
- Regional blockade is increasingly used in outpatient anesthesia; ambulatory peripheral nerve block catheters are effective with low complication rates

Postoperative nausea and vomiting

Postoperative nausea and vomiting is a major concern in pediatric outpatient surgery because it may increase patient discomfort, delay patient discharge, increase the incidence of wound dehiscence, and increase the cost of patient care [125]. PONV, the commonest cause for delayed discharge from the PACU, can be a source of frustration to parents/caregivers and is a frequent cause of unplanned hospital admission or an early postoperative visit to the emergency department secondary to dehydration and electrolyte derangement [126]. Many adult patients rank PONV as the number one complication of surgery they wish to avoid [127].

Young children often have difficulty describing the occurrence or severity of nausea and, for this reason, many investigators use vomiting as a more definite endpoint [128]. Older children may be instructed preoperatively to report any nausea experienced in the postoperative period. It is not clear whether these "suggestions" may increase the reported incidence of nausea in children who may simply answer the way they think the investigators want. Despite these limitations, the incidence of postoperative vomiting in children is between 8.9% and 42%, approximately twice the incidence for both nausea and vomiting after surgery in adults [129]. PONV rates may be as high as 50–89% following tonsillectomy possibly due to swallowed blood, pharyngeal stimulation, and the use of opioids [130]. Risk factors for PONV may be broadly grouped thus: patient factors, surgical factors, and anesthetic factors. Patient factors include age greater than 3 years, gender (female > male), previous history of PONV, and a family history of PONV and motion sickness [129,130]. Commonly described surgical factors include type of surgery (strabismus surgery, tonsillectomy, laparoscopic surgery, and certain urological procedures) and prolonged surgery [131]. Anesthetic factors although well described, are controversial and include the use of nitrous oxide, difficult mask ventilation, use of opioid medications, and reversal of neuromuscular blockade [132]. Many investigators agree that a propofol-based anesthetic technique is associated with the lowest incidence of PONV [68,133]. A simplified risk score for postoperative vomiting in children is presented in Figure 38.3 [134].

Management of PONV is based on primary prevention and pharmacotherapy. Primary prevention includes a careful history to identify risk factors and tailoring the anesthetic technique to patient and surgical risk factors. Ensuring adequate hydration and nasogastric suctioning following tonsillectomy and/or adenoidectomy are other non-pharmacological techniques that have been employed to reduce the incidence of PONV.

Pharmacotherapy

This may be divided into prophylactic or rescue therapy. It is presently unresolved whether routine prophylaxis is warranted in all patients undergoing general anesthesia or whether prophylaxis should be based on risk stratification. Very often economic considerations and risk–benefit analysis determine the choice and use of prophylactic PONV medications [135]. An international panel of experts compiled comprehensive evidence-based guidelines for the management of PONV under the auspices of the Society for Ambulatory Anesthesia [134]. These guidelines suggest that the use of prophylactic antiemetics should be based on valid assessment of risk factors for postoperative vomiting as detailed in the algorithm in Figure 38.4 [134]. These guidelines recommend that children deemed at moderate to high risk for PONV should receive combination therapy with two or three prophylactic

Risk factors	Points
Surgery ≥ 30 min	1
Age ≥ 3 years	1
Strabismus surgery	1
History of POV or PONV in relatives	1
Sum =	0 to 4

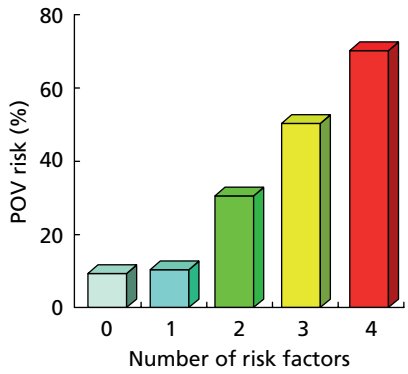

Figure 38.3 Risk factors for postoperative vomiting (POV) in children showing a simplified risk score to predict the risk for POV in children. When 0, 1, 2, 3, or 4 of the depicted independent predictors are present, the corresponding risk for POV is approximately 10%, 10%, 30%, 55%, and 70%. PONV, postoperative nausea and vomiting. *Source*: Reproduced from Gan et al. [134] with permission of Wolters Kluwer.

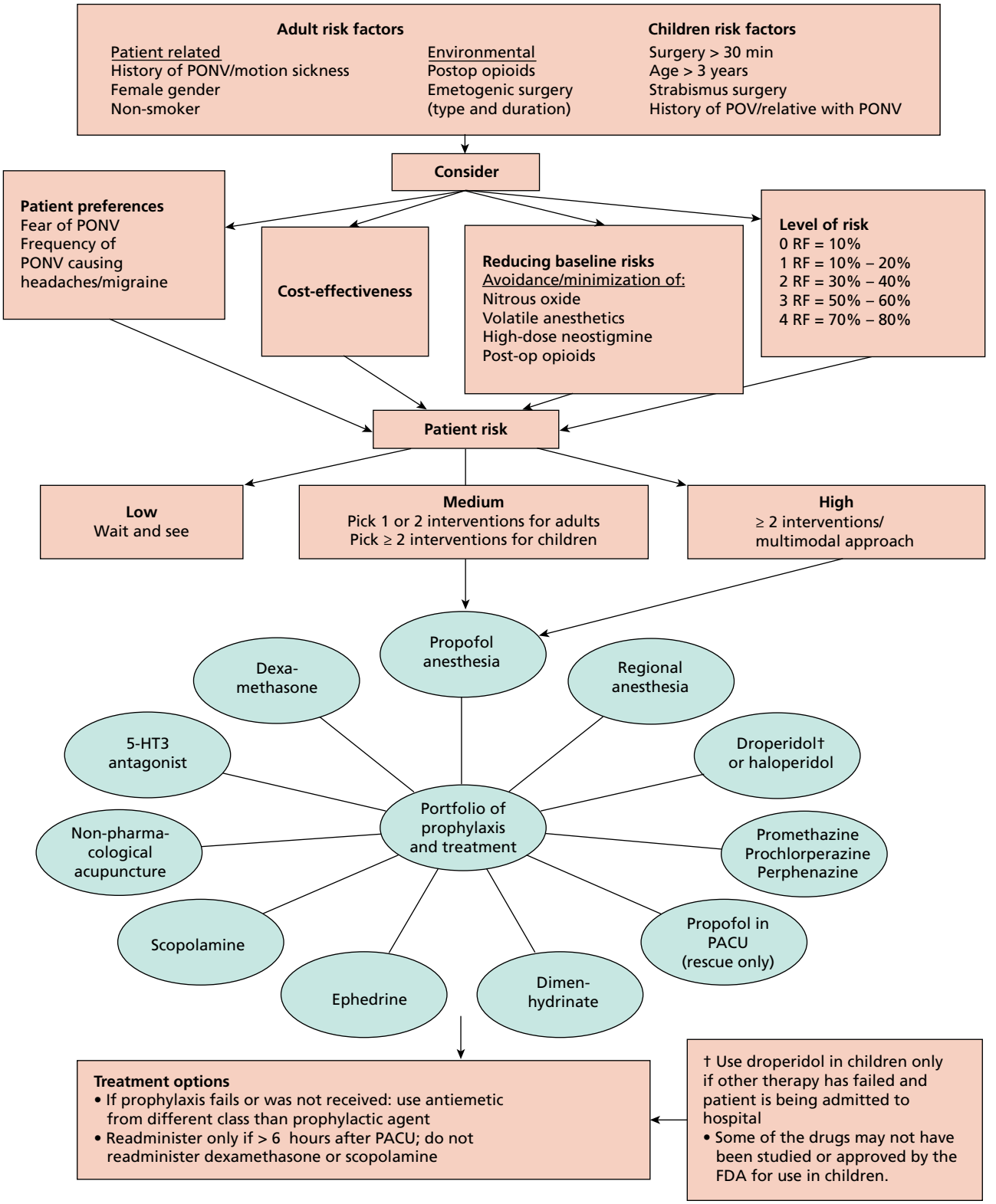

Figure 38.4 Algorhithm for management of postoperative nausea and vomiting (PONV). FDA, Food and Drug Administration; PACE, postanesthesia care unit; POV, postoperative vomiting; RF, risk factor. *Source*: Reproduced from Gan et al [134] with permission of Wolters Kluwer.

drugs from different classes. Additionally, patients who experience PONV despite prophylaxis should receive additional antiemetics from a pharmacological class different to that of the prophylactic drug since repeating the same drug within 6 h of the original dose does not confer any benefit.

Commonly used medications include serotonin (5-hydroxytryptamine-3 or 5-HT3) receptor antagonists (ondansetron, granisetron, dolasetron), steroids (dexamethasone), antihistamines (promethazine, benadryl), metoclopramide, and droperidol. It should be noted that droperidol has a "black box"

warning from the US FDA against its use for PONV due to fatal cases of QT interval prolongation and torsade de points. In addition, promethazine has a similar warning against use in children less than 2 years of age because of cases of fatal respiratory depression, especially when combined with opioids. A systematic review reported good evidence that dexamethasone and the serotonin receptor antagonists ondansetron, granisetron, and tropisetron were clinically effective for PONV prophylaxis in children undergoing tonsillectomy with or without adenoidectomy [136]. Furthermore, this review found that dimenhydrinate, perphenazine, droperidol, gastric aspiration, and acupuncture were not efficacious in reducing PONV in this population. The 5-HT3 receptor antagonists are rapidly becoming the most frequently prescribed agents for both prophylaxis and treatment of PONV [130]. Recent data indicate that ondansetron (0.1 mg/kg, up to 4 mg) was effective in preventing early and delayed PONV in children undergoing various types of surgeries [137]. Due to its efficacy and safety profile, ondansetron has become the most commonly prescribed antiemetic for prophylaxis and treatment of PONV. Despite its established safety record, it is important to be aware of some of the fortunately rare but serious side-effects of ondansetron, which may cause a lethal outcome. Recent data indicate that ondansetron may cause QT prolongation leading to ventricular tachycardia [138]. Rarely, ondansetron may be associated with serotonin syndrome [139] and malignant hyperthermia reaction in patients with muscular dystrophies [140,141].

Two novel antiemetic agents are now available that will likely have an increasing role in the treatment of PONV. Palonosetron, a second generation 5-HT3 antagonist, was approved by the FDA in July 2003. Due to its unique binding properties and greater binding affinity for the receptor, it has a substantially longer half-life of approximately 40 h. A study of adult patients undergoing outpatient laparoscopic surgery with two or more risk factors for PONV found that a single IV dose of 0.075 mg of palonosetron prior to induction significantly increased the complete response rate, i.e. no emetic episodes and no rescue medication, compared with placebo [142]. Furthermore, patients who received palonosetron reported less severity of nausea and less interference in their postoperative function due to PONV. Pediatric data with the use of palonosetron are limited to its use for chemotherapy-induced nausea and vomiting. A study that compared children who received ondansetron before the administration of chemotherapy and every 8 h through the hospitalization with those who received a single dose of palonosetron prior to chemotherapy reported significantly reduced intensity of nausea and a significant reduction of emetic events for 3 days of treatment, with some benefits for up to 7 days in the palonosteron group [143]. Palonesetron has been found to be superior to other agents in preventing nausea and vomiting in highly emetogenic chemotherapy regimens [144,145]. Its long duration of action makes it an excellent choice for patients undergoing outpatient surgery and further studies are needed to evaluate its benefits in this setting.

Aprepitant is a neurokinin-1 receptor antagonist that crosses the blood–brain barrier and blocks the emetic effects of substance P [146]. Studies in adults have reported its efficacy in reducing PONV following joint arthroplasty and abdominal surgery [147,148]. However, no pediatric data are available for this indication. A single oral dose of 40 mg given 1 h prior to surgery has been recommended for adults. An IV formulation is now available but its only indication is for chemotherapy-induced nausea and vomiting. A recent review of the literature in pediatrics revealed no PONV studies, but a number of studies have documented the effectiveness of aprepitant when added to highly emetogenic chemotherapy regimens [149].

KEY POINTS: POSTOPERATIVE NAUSEA AND VOMITING

- Risk factors for PONV include age >3 years, being female, a family history or previous history of PONV and motion sickness, and surgical procedures like ENT, eye, and laparoscopy
- High-risk patients should receive dexamethasone and ondansetron for the prophylaxis of PONV
- Reducing opioid dose and employing regional anesthesia may reduce the risk of PONV

Recovery and discharge

Recovery from anesthesia is a complex process encompassing several outcomes including normalization of physiological end-points, return to baseline sensorium and activity, and emotional and psychological recovery. For the patient undergoing ambulatory surgery, assessment of recovery has largely focused on a return of acceptable physiological parameters, ability to ambulate, and recovery of consciousness such that the patient may be safely discharged home. To that end, a number of simple clinical scoring systems that assess recovery have been developed and tested [150–154]. The scoring system that is perhaps most widely used is the Aldrete score which was first described in 1970 [150]. The original Aldrete score was a 0–10 point scale comprising of five recovery parameters, each of which was scored from 0 to 2, similar to the Apgar score. Subsequently, a number of modifications of this score have been made that incorporate fast-track criteria and oxygen saturation rather than observation of color to identify hypoxemia, in addition to consideration of developmental stages in children [151,153,155]. Table 38.6 describes a version of the Aldrete score suitable for use in children.

Another score that is easy to use and is well suited for use in children is the Steward postanesthetic recovery score which incorporates three recovery parameters scored from 0 to 2 yielding a maximum achievable score of 6 (Table 38.7). In addition to monitoring of physiological variables such as vital signs, oxygen saturation, and level of consciousness, a standardized recovery score should be calculated for each patient on admission, at appropriate intervals during the PACU stay, and on discharge. Each facility must select the recovery score that works best in their setting taking into consideration the psychometric as well as pragmatic qualities of the scoring system to facilitate its repeated use.

Recently, the limitations of such scoring systems in evaluating the broader and potentially long-term impact of anesthesia and surgery have been recognized [156,157]. In attempts to assess early and long-term recovery across multiple domains, including cognition, emotional recovery, and activities of

Table 38.6 Modified Aldrete score for children

Variable		Score*
Airway	Coughing on command or crying	2
	Maintaining good airway	1
	Airway requires maintenance	0
Vital signs	Stable and appropriate for age	2
	Stable but inappropriate for age	1
	Unstable	0
Motor activity	Moving limbs purposefully	2
	Non-purposeful movements	1
	Not moving	0
Consciousness	Awake	2
	Responding to stimuli	1
	Not responding	0
SpO_2 on room air	>95	2
	90–94	1
	<90	0

* A score ≥9 is considered suitable for discharge.
Source: Reproduced from Patel et al [155] with permission of Wolters Kluwer.

Table 38.7 Steward postanesthetic recovery score

Patient sign	Criterion	Score
Consciousness	Awake	2
	Responding to stimuli	1
	Not responding	0
Airway	Coughing on command or crying	2
	Maintaining good airway	1
	Airway requiring maintenance	0
Movement	Moving limbs purposefully	2
	Moving limbs non-purposefully	1
	Not moving	0

Source: Reproduced from Steward [152] with permission of Springer Nature.

Box 38.3: Items included in the post-hospital behavior questionnaire.

I. Does your child need a pacifier?
Does your child seem to be afraid of leaving the house with you?
Is your child uninterested in what goes on around him (or her)?
Does your child bite his (or her) fingernails?
Does your child seem to avoid or be afraid of new things?
Does your child have difficulty making up his (or her) mind?
Is your child irregular in his (or her) bowel movements?
Does your child suck his (or her) fingers or thumbs?

II. Does your child get upset when you leave him (or her) alone for a few minutes?
Does your child seem to get upset when someone mentions doctors or hospitals?
Does your child follow you everywhere around the house?
Does your child spend time trying to get or hold your attention?
Does your child have bad dreams at night or wake up and cry?

III. Does your child make a fuss about going to bed at night?
Is your child afraid of the dark?
Does your child have trouble getting to sleep at night?

IV. Does your child make a fuss about eating?
Does your child spend time just sitting or lying and doing nothing?
Does your child have a poor appetite?

V. Does your child have temper tantrums?
Does your child tend to disobey you?

VI. Does your child wet the bed at night?
Does your child need a lot of help doing things?
Is it difficult to get your child interested in activities (like playing games, with toys, and so on)?
Is it difficult to get your child to talk to you?
Does your child seem to be shy or afraid around strangers?
Does your child break toys or other objects?

Source: Reproduced from Vernon et al [160].

daily living, studies in adults have evaluated the reliability, validity, precision, and pragmatic qualities of instruments that measure postoperative recovery outcomes at various time periods following surgery. [156–159]. These studies evaluated instruments that were designed for use in adults and most would not be suitable for use in children. The post-hospital behavior questionnaire comprises of 27 items across six categories of anxiety including: general anxiety, separation anxiety, sleep anxiety, eating disturbances, aggression against authority, and apathy/withdrawal (Box 38.3) [160]. This instrument was designed specifically to evaluate maladaptive and negative behavioral changes in children and has been widely used to assess postoperative behavior changes in the pediatric surgical population [53,161,162].

Discharge criteria

The ASA practice guidelines recommend that each patient care facility should develop suitable recovery and discharge criteria and provide guidance for the development of such criteria (Box 38.4) [163]. Box 38.5 summarizes the ASA stance on specific discharge criteria that have been traditionally mandated in some settings, such as requiring that patients void or tolerate oral liquids prior to discharge. These practices prolong recovery stay and evidence to support their benefits in reducing adverse outcomes is insufficient. Indeed, a previous study reported a lower incidence of vomiting and a shorter stay in the day surgery unit in children who were allowed to drink electively compared to those who were required to drink prior to discharge [164]. No child in either group required readmission for vomiting or dehydration. However, the intravenous fluid regimen was liberalized to supply a calculated 8 h deficit in addition to maintenance fluids and intraoperative losses. Adequate intravenous hydration and correction of fluid deficits prior to discharge may be prudent in children who refuse oral fluids in the PACU.

Discharge before voiding has also not been found to result in readmission for urinary retention. In one study, 30/1719 ambulatory patients who were unable to void but met other discharge criteria were discharged home and followed by a home care nurse [165]. Three of these patients required catheterization at home and all three had undergone rectal or inguinal surgery under spinal anesthesia, and none required readmittance. Risk factors for postoperative urinary retention in children include a history of urinary retention or urethral surgery. In the absence of these risk factors children may be discharged before voiding with instructions to the caregivers to call if they have not voided within a given timeframe.

Sample PACU discharge criteria are presented in Box 38.6. The responsibility of discharge to inpatient settings when specific discharge criteria are met may be delegated to the PACU

Box 38.4: Summary of recovery and discharge criteria

General principles
- Medical supervision of recovery and discharge is the responsibility of the supervising practitioner
- The recovery area should be equipped with appropriate personnel and monitoring and resuscitation equipment
- Patients should be monitored until appropriate discharge criteria are satisfied
- Level of consciousness, vital signs, and oxygenation should be recorded at regular intervals
- A nurse or other individual trained to monitor patients and recognize complications should be in attendance until discharge criteria are fulfilled
- An individual capable of managing complications should be immediately available until discharge criteria are fulfilled

Guidelines for discharge
- Patients should be alert and oriented. Patients whose mental status was initially abnormal should have returned to their baseline
- Vital signs should be stable and within acceptable limits
- Discharge should occur after patients have met specified criteria
- Use of scoring systems may assist in documentation of fitness for discharge
- Outpatients should be discharged to a responsible adult who will accompany them home and be able to report any postprocedure complications
- Outpatients should be provided with written instructions regarding postprocedure diet, medications, activities, and a phone number to be called in case of emergency

Source: Data from American Society of Anesthesiologists Task Force on Postanesthetic Care [163] with permission of Wolters Kluwer.

Box 38.5: Summary of recommendations for discharge.

Requiring that patients urinate before discharge
- The requirement for urination before discharge should not be part of a routine discharge protocol and may only be necessary for selected patients

Requiring that patients drink clear fluids without vomiting before discharge
- The demonstrated ability to drink and retain clear fluids should not be part of a routine discharge protocol but may be appropriate for selected patients
- Replacement intravenous hydration is recommended

Requiring that patients have a responsible individual accompany them home
- As part of a discharge protocol, patients should routinely be required to have a responsible individual to accompany them home and to monitor for complications

Requiring a minimum mandatory stay in recovery
- A mandatory minimum stay should not be required
- Patients should be observed until they are no longer at increased risk for cardiorespiratory depression
- Discharge criteria should be designed to minimize the risk of central nervous system or cardiorespiratory depression after discharge

Source: Data from American Society of Anesthesiologists Task Force on Postanesthetic Care [163] with permission of Wolters Kluwer.

Box 38.6: Sample postanesthesia care unit (PACU) discharge criteria

Criteria for discharge to general care inpatient units
- Stable respiratory status (patent airway, adequate respiratory function, adequate oxygen saturation)
- Stable vital signs within an acceptable range for patient's age, condition and preoperative status
- Awake or easily arousable. Level of consciousness appropriate for preoperative developmental age/status
- Operative area without evidence of significant bleeding
- Adequate analgesia so that comfort needs can be easily managed by resources available at the discharge location
- Normothermic or core temperature that is minimally 36°C or temperature within an acceptable range of preoperative status
- Patients who have received spinal or epidural anesthesia must demonstrate maximum sensory block at the T12 dermatome level and be free of orthostatic hypotension
- Patients who receive racemic epinephrine will be admitted or monitored for at least 8 h

Criteria for discharge to home
- Tolerate oral fluids with minimal nausea or vomiting or have received adequate intravenous fluid replacement to deter dehydration
- Parents or caregivers have adequate understanding of discharge instructions and are able to provide postoperative care
- Patients who have received spinal or epidural anesthesia must be able to transfer with assistance
- Patients who receive regional anesthesia will be instructed to call the PACU or surgical service if they have not voided within 6 h

nurse. In the USA, all patients who are to be discharged home must be evaluated for discharge readiness by an anesthesiologist in accordance with guidelines from the Centers for Medicare and Medicaid Services [166].

Fast-tracking

Fast-tracking is the process of bypassing the PACU and transferring the patient who has met specific criteria directly to the step-down or phase II recovery unit. The goals of fast-tracking are to improve efficiency without compromising patient safety or satisfaction. Table 38.8 describes suggested criteria for fast-tracking children that take into consideration the adequacy of pain relief [155]. A randomized study found that children who were fast-tracked had a 20 min shorter recovery time compared with those who were sent to PACU even though both groups met fast-track criteria in the operating room [155]. Children in the fast-track group were less likely to be given analgesics postoperatively (41% versus 62%) and were more likely to be restless in the phase II recovery unit (31% versus. 16%) compared with the children who were sent to the PACU. Yet no child experienced a clinically significant adverse event. A previous study that included patients >12 years of age found that ASA PS3 compared with ASA 1, age <60 years, and general surgery compared to orthopedics and ophthalmology were risk factors for fast-track ineligibility [167]. Consideration of such factors in addition to standard criteria may enhance efficient and cost-effective utilization of PACU resources. As stated in the American Society of Perianesthesia Nurses standards, "Phase II is a level of care, not a physical place. The decision to fast-track a patient should

Table 38.8 Criteria for fast-tracking children

Criterion		Score*
Level of consciousness	Awake and oriented	2
	Arousable with minimal stimulation	1
	Responsive only to tactic stimulation	0
Physical activity	Appropriate for age and development	2
	Weak for age and development	1
	Unable to move extremities	0
Hemodynamics	BP <15% of baseline MAP	2
	BP 15–30% of baseline MAP	1
	BP >30% below baseline MAP	0
Respiratory stability	Coughing, crying, deep breaths	2
	Hoarseness with crying or coughing	1
	Stridor, dyspnea, wheezing	0
SpO_2	>95% on room air	2
	90–95% on room air	1
	<90% on room air	0
Pain	None/mild discomfort	2
	Moderate to severe controlled with IV analgesics	1
	Persistent severe pain	0

* A minimum score of 10 (with no score <1 in any individual category) is required for fast-tracking children.
BP, blood pressure; IV, intravenous; MAP, mean arterial pressure.
Source: Reproduced from Patel et al [155] with permission of Wolters Kluwer.

be based on patient needs, clinical assessments, and desired patient outcomes" [168].

KEY POINTS: RECOVERY AND DISCHARGE

- The modified Aldrete score is the most common and reliable assessment of recovery from anesthesia; versions modified for pediatrics are in common use
- Requirements to ingest oral fluids or to void prior to discharge are unnecessary
- Fast-tracking bypasses the standard PACU and admits the petient to a phase II step-down recovery to improve efficiency and discharge the patient home earlier

Complications of outpatient anesthesia

Adverse postoperative outcomes are usually multifactorial in origin and occur due to the patient's underlying comorbidities, due to anesthetic techniques, or due to the surgical procedure itself. Fortunately, major morbidity and mortality are extremely rare following ambulatory anesthesia, with a reported death rate of approximately two per 100,000 procedures [169,170]. However, minor sequelae such as drowsiness, uncontrolled PONV, unrelieved pain, bleeding complications, and respiratory complications may lead to delayed discharge, unplanned hospital admission, or readmission following discharge.

Unrelieved pain is the commonest symptom reported by parents following discharge, with an incidence of 25–91% [171–177]. One study found that tonsillectomy was a predictor for postoperative pain. Pain lasted for 7 days or longer in 33% of children in this study and 12% of the parents believed that postoperative instructions for pain management at home were inadequate [172]. The incidence of PONV following discharge is reportedly 5.9–59% [171–175,178]. Predictors for PONV include emetic symptoms in the hospital, pain at home, age >5years, and administration of postoperative opioids [172]. Other symptoms after discharge include drowsiness, headache, dizziness, fever, hoarseness, mild croup, and difficulty voiding. Adequate preparation of the family/caregivers with individualized discharge education regarding the potential complications and symptoms may alleviate parental anxiety following discharge and promote satisfaction.

Unplanned admission

Unplanned hospital admission for the ambulatory surgery patient increases utilization of resources, poses inconvenience to patients and their families, and has been viewed as a measure of outcome and quality of care. Previous investigators have reported that approximately 2% of children scheduled for outpatient surgery required hospital admission [179–181]. One study found that almost 4% of children undergoing ambulatory surgery required a prolonged PACU stay (>3 h) and 1.9% required hospital admission [179]. Prolonged PACU stay occurred most frequently due to PONV (19%) or respiratory complications (16%) including bronchospasm, oxygen desaturation, stridor, and apnea. Hospital admission was most commonly required due to respiratory complications and surgical reasons including more extensive surgery than was originally planned. Similarly, other investigators reported a 1.8% unplanned admission rate most commonly due to PONV, postoperative bleeding, or unexpected difficulty of the procedure [181]. Another study reported a 2.2% incidence of unplanned hospital admission in children that occurred most commonly due to surgical reasons including uncontrolled pain, surgical complications, need for extensive surgery, and bleeding [180]. In this study, hospital admission also resulted from: anesthesia-related causes including PONV, oxygen desaturation, bronchospasm, and somnolence; social causes including surgery ending late in the day; and medical causes including underlying medical problems or undiagnosed medical disease. Notably, in the latter two studies, orchidopexy was the commonest surgical procedure resulting in unplanned admission. Taken together these data suggest a need for careful and frequent re-evaluation of selection criteria for outpatient surgery and vigilant monitoring for potential complications in the PACU.

A recent study of 21,957 ambulatory surgery cases in children documented a 0.97% hospital admission rate; 47% of the admissions were anesthesia related [182]. Factors associated with admission were age <2 years, ASA 3, surgery duration >1 h, completion of surgery after 3 p.m., orthopedic, dental, or ENT surgery, OSA, and intraoperative events. Leading anesthetic causes for admission were inadequate pain control in 24% and PONV in 21%.

Summary

As we enter an era of healthcare reform, it is inevitable that the pressures to provide low cost, yet efficient and high quality surgical care will become increasingly relentless.

The practice of ambulatory surgery will likely expand further and at a more rapid pace than it has over the past 30 years. The need for development of innovative delivery models that capitalize upon low-cost organizational structures and prudent management of resources will call upon the resourcefulness of healthcare professionals and administrators alike. In the setting of ambulatory surgery, it will become increasingly important to prevent such pressures from constraining clinical judgment regarding the safest and most appropriate patient care.

CASE STUDY

A 22-month-old male child presented for hypospadias repair as an outpatient.

History

The patient had been healthy since birth and had been followed regularly for his well child visits. He was up to date on his immunizations and his growth and development had been normal. The parents reported a history of a "cold" with a runny nose and cough that started 7 days prior to the scheduled surgery. His skin was warm to touch, and he had decreased appetite and activity on the first day of his symptoms. Most of his symptoms had resolved without any treatment but he continued to have an occasional cough. This was his second upper respiratory infection since he started going to daycare 6 months ago. His review of symptoms was otherwise negative. The child was on no medications. He had not undergone any previous surgery.

He was born at 41 weeks' gestation by emergent cesarean section for fetal bradycardia. His neonatal course was complicated by hyperbilirubinemia that was treated with phototherapy and caused him to stay in the newborn nursery for an extra day.

His family history was negative for anesthesia-related problems. His mother received an uneventful epidural anesthetic for his birth and his father had undergone a tonsillectomy as a child that was uneventful to the best of his knowledge.

Physical examination

The child was active and alert, playing with toys in the surgical waiting room but started crying and clinging to his mother when being examined. His vital signs were normal for age and his weight was 13.2 kg. He had no dysmorphic features and while it was impossible to perform a detailed airway examination, he had normal neck mobility and anatomy and his mouth opening was adequate. His breath sounds were initially coarse but cleared when he was distracted and stopped crying. He had normal heart sounds and no murmurs, extra sounds, or clicks.

Anesthetic management

The child was fearful of strangers and resisted changing into the hospital gown. His mother was concerned that he would not cooperate with induction of anesthesia by mask. He was therefore premedicated with 7 mg of midazolam orally. He also received 200 mg of acetaminophen suspension orally for pre-emptive analgesia. Within 15 min, the child appeared visibly calmer but resisted being carried by the anesthesia team. He was wheeled into the operating room in a wagon. Anesthesia was induced by the inhaled route using sevoflurane and intravenous access was secured after induction. Due to the potential airway hyper-reactivity from the recent upper respiratory infection, a laryngeal mask airway was placed and anesthesia was maintained with oxygen, nitrous oxide, and sevoflurane. After induction of anesthesia, a caudal block was placed using 7 mL of 0.125% bupivacaine with 1:200,000 epinephrine. The surgery was completed uneventfully and the LMA was removed in the operating room prior to transfer to the PACU.

Postoperative management

The child was asleep but readily arousable on arrival in the PACU. He had stable vital signs and his oxygen saturation was 98% on blow-by oxygen. The oxygen was discontinued and he maintained saturations >95% on room air. His pain score on awakening was 3/10 by the FLACC (face, legs, activity, crying, consolability) scale and since 4 h had elapsed after his initial acetaminophen dose, he was given an additional 150 mg of oral acetaminophen. He was reunited with his parents in the PACU. The child had two episodes of emesis in the PACU after he drank apple juice. He was given 2 mg of ondansetron and no further emesis occurred. The child refused additional fluids but was able to void in the PACU. He had complete return of motor function and was able to stand prior to discharge. He was discharged home with a prescription for oxycodone suspension when he met institutional discharge criteria. Telephone follow-up the next day revealed that the child had an uneventful recovery at home and had required one dose of oxycodone upon awakening the morning after the surgery.

Conclusion

This case describes the perioperative care of a child undergoing a common urological procedure. It illustrates the effective use of a sedative premedication that facilitated separation from the parent. The use of a regional block allowed the child to awaken in minimal pain and significantly reduced the need for opioids.

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 39
Anesthesia for Trauma

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Introduction

Trauma is the leading cause of death in children older than 1 year of age. In children, trauma accounts for approximately 65% of deaths and more than 35% of all non-fatal injuries (Table 39.1) [1]. Trauma resulting in death is higher in males than in females in all age groups from age 0 to age 18, with fatal trauma rates in males nearly double that of females [2]. Non-fatal injury rates are highest for Native Americans and lowest for Asian and Pacific Islanders; Caucasian and African-American rates of non-fatal injury are similar [3]. Blunt force trauma is significantly more common than penetrating trauma, and traumatic brain injury (TBI) constitutes 80% of pediatric trauma, followed by intra-abdominal and intrathoracic trauma. Motor vehicle trauma and other transportation-related traumas (e.g. cycling, pedestrian) are a leading cause of fatal injury across all age groups and genders, but is most substantial in adolescents 15–18 years of age. According to the Centers for Disease Control and Prevention (CDC), falls are the leading cause of non-fatal injuries in children under the age of 15 years; they occur predominantly in children 4 years of age and younger and are highest in infants less than 1 year in age. Penetrating trauma, occurring largely in the form of animal bites, accounts for a high number of non-fatal injuries in children aged 0–9 years of age, and occurs more commonly in the form of firearm-related injuries in adolescents aged 15–18 years.

Prehospital care

Critically ill children represent approximately 10% of emergency medical service transport cases. However, children utilizing emergency medical services for transport to an emergency department are of higher acuity than adults, require care in the emergency department more promptly, and have significantly higher rates of admission [4][. The "golden hour" represents the early critical period during which crucial managements can directly increase the patient's chance of survival.

While emergency medical service systems have recently undergone fundamental improvements with regards to pediatric trauma care, there still exists a significant gap in quality of prehospital care for pediatric patients compared to that of adults [4]. Vella et al studied 154 pediatric trauma patients who presented at level 1 trauma centers and found that 70% of the patients either did not receive or received inadequate fluid resuscitation. Half of the patients did not have a second intravenous line, as per the Advanced Trauma Life Support (ATLS) guidelines, which may be a result of the perception that the patients did not require significant resuscitation [5]. There is a higher rate of failed tracheal intubation in children receiving prehospital care, even when tracheal intubation is performed by skilled, hospital-based providers [6]. Similarly, intravenous placements by prehospital providers have a higher complication or failure rate in pediatric patients versus adult patients [7]. Prehospital pediatric intubation carries a much higher rate of tube malposition and left lung atelectasis, with less than one-third of tracheal tubes placed in a safe position [8]. Of note, Gausche et al demonstrated that there is no significant difference in survival rate or neurological outcome among pediatric trauma patients who were randomized to bag–mask ventilation verses tracheal intubation in the prehospital setting. Their study raises the question whether prehospital providers should be educated in managing the airways of appropriately selected patients using a bag–mask rather than placing all patients at risk for multiple intubation attempts or incorrectly placed tracheal tubes [9].

Fewer sets of vital signs are obtained in children under the age of 15 years, and children under 4 years of age are significantly less likely to have a complete set of initial vital signs taken than all other age groups combined. Blood pressure and respiratory rate, two principle components of field triage assessment for identifying children needing the resources of a

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

Table 39.1 The five leading causes and number of non-fatal unintentional injuries among children treated in emergency departments, United States, 2009

	Age				
Rank	**<1 year**	**1–4 years**	**5–9 years**	**10–14 years**	**15–19 years**
1	Fall 147,280 (59%)	Fall 955,381 (45%)	Fall 631,381 (37%)	Fall 615,145 (29%)	Struck by motor vehicle 617,631 (24%)
2	Motor vehicle 31,360 (13%)	Motor vehicle 372,402 (18%)	Motor vehicle 406,045 (24%)	Motor vehicle 574,267 (27%)	Fall 468,967 (18%)
3	Bite/sting 10,922 (4%)	Bite/sting 137,352 (7%)	Cut/pierce 104,940 (6%)	Overexertion 276,076 (13%)	Overexertion 372,035 (14%)
4	Foreign body 8,860 (4%)	Foreign body 126,060 (6%)	Bite/sting 92,590 (5%)	Cut/pierce 118,440 (6%)	Motor vehicle occupant 341,257 (13%)
5	Fire/burns 7,846 (3%)	Cut/pierce 84,095 (4%)	Pedal cyclist 84,590 (5%)	Pedal cyclist 118,095 (6%)	Cut/pierce 184,972 (7%)

Source: Center for Disease Control and Prevention, National Action Plan for Child Injury Prevention, 2012. https://www.cdc.gov/safechild/pdf/national_action_plan_for_child_injury_prevention-a.pdf. Data source from the National Electronic Injury Surveillance System-All Injury Program (NEISS-AIP) from the Consumer Product Safety Commission; accessed through WISQARS.

trauma center, are the most frequently missed vital signs by prehospital providers in the pediatric population, leading to the undertriaging of more than half of pediatric trauma patients [10]. The IMPACT prospective randomized trial demonstrated that pediatric trauma patients who had enhanced monitoring during transport had shorter lengths of hospital stay and lower rates of multiorgan dysfunction [11]. These findings underscore the need for focus on pediatric-specific education and skills training, especially in situations where providers do not have regular encounters with pediatric patients. Without the consistent use of these skills in the field, a disparity in the provision of care for injured children is created [12]. In addition to emergency medical services, medical direction and oversight, protocol development, and implementation, education is paramount for continued prehospital process improvement [13]. Baker et al demonstrated that there was a significant increase in vascular skill performance in emergency medical service providers trained in pediatric advanced life support (PALS) versus those not trained in PALS (100% versus 77% for intravenous, 100% versus 55% for intraosseous) [14].

Organization of trauma services

Trauma centers are assigned levels I–III, designated by the American College of Surgeons (ACS) based on capability. Pediatric trauma centers may be present in either level I or II trauma centers. Level I trauma centers require the continued presence of specialized providers with a dedicated trauma operating room (OR) that is available 24 h a day, in concert with the immediate availability of supportive services such as radiology and blood banks. Level II trauma centers require the prompt availability of these services [15]. Advances in prehospital care has been focused on early identification and stabilization of the critically ill patient and rapid prehospital transport during the "golden hour" to specialized centers capable of definitive intervention. The regionalization of trauma centers has permitted early referral of severely injured children to facilities equipped with specialized pediatric-trained providers. Nevertheless, pediatric trauma patients still suffer a relatively increased number of inappropriate delays during transport to definitive care in the current trauma system in the United States [16].

Furthermore, despite the existence of regional referral networks, there is evidence that a significant number of injured children are not treated at pediatric trauma centers, likely due to geographical limitations of such specialized providers and care [17]. Compared with non-pediatric trauma centers, care at pediatric trauma centers increases the percentage of non-operative management of solid organ injuries, and data suggest that children with splenic injuries treated at non-pediatric trauma centers have up to five times the odds ratio of having a splenectomy compared with those treated at pediatric centers [18]. Evidence exists that treatment at pediatric trauma centers improves functional outcomes and mortality of severely injured patients, and, in particular, improves outcomes of patients with severe traumatic brain injury [20,23]. With regard to older children, a recent analysis of the National Trauma Data Bank between 2007 and 2011 revealed that severely injured adolescents have improved outcomes and decreased imaging and invasive procedures when treated at pediatric versus adult trauma centers [23]. However, the data are not entirely unequivocal and remain a topic of controversy.

Primary and secondary evaluation

The ATLS guidelines for the initial assessment of an injured child involves identification and stabilization of the most immediately life-threatening issues. The primary survey consists of immediate management of the patient's airway, breathing, circulation, and disability (ABCD). A sizing, length-based resuscitation tape, such as the Broselow® tape, is used for rapid weight approximation in order to size equipment and work out dose fluids and medications (Fig. 39.1) [24]. If necessary, cardiopulmonary resuscitation should be performed in accordance with the PALS guidelines. Of note, the pediatric Basic Life Support for non-medical professionals advises beginning with an assessment of airway and breathing, and performing ventilation at a rate of one breath every 3–5 s. If the patient has no pulse, or their heart rate is less than 60 beats/min (bpm), chest compressions should be conducted at a rate of 100–120 bpm. However, the modified Advanced Life Support (ALS) algorithm prioritizes circulation or perfusion as the primary step, following a circulation, airway, and breathing sequence. Therefore, the healthcare provider should

Figure 39.1 The Broselow® tape used for rapid estimation of pediatric patient sizing and dosing. *Source*: Broselow, https://commons.wikimedia.org/wiki/File:BTape1.jpg. Licensed under CCBY 3.0.

first determine the presence of a pulse and immediately initiate chest compressions if necessary, prior to establishing an advanced airway. Of note, the survival rate for pediatric trauma victims who have undergone cardiopulmonary resuscitation is low (8–16%), with extraordinarily high morbidity rates for those receiving cardiopulmonary resuscitation on arrival at the emergency room [25].

Management of airway, breathing, and circulation, as described below in greater depth, should aim to maintain age-appropriate normal vital sign values. ATLS guidelines suggest that an approximate systolic blood pressure goal can be calculated using the formula 90 mmHg plus twice the age in years. As soon as possible, monitoring of urine output through placement of a Foley catheter allows for assessment of end-organ perfusion and adequate circulatory resuscitation, as well as serving as an indicator of bladder trauma and increasing the accuracy of an abdominal physical examination. Ensuring that the patient is normothermic is of high priority, especially since infants and children are at significantly higher risk of hypothermia due to their larger surface area to volume ratio, increased metabolic rate, thin skin, and decreased subcutaneous tissue and fat. Temperature should be maintained through warmed fluids and blood, increased ambient temperature, and the use of warmed blankets and heat lamps. Evaluation of disability involves a rapid assessment of neurological function. It is important to emphasize that regular, frequent reassessment of the primary survey be repeated as the patient's condition can change rapidly.

Once the primary survey is completed, the secondary survey involves a head-to-toe evaluation of other injuries. When possible, a more detailed history should be attained and should include the patient's allergies, medications, past medical and surgical history, last oral intake, and events related to injury (mechanism, timing, prior medications, and resuscitative procedures). If the patient remains stable enough for further evaluation, areas with a high index of suspicion for injury, identified by the physical examination, should be radiographically scanned. The primary trauma survey consists of radiographs of the chest and affected extremities. Computed tomography (CT) is the gold standard for the assessment of hemorrhage in the intraabdominal, thoracic, and cranial spaces. Because of the risk of malignancy from childhood CT radiation exposure, approximately 1:10,000 after a single CT scan, ATLS guidelines advise that radiation be as low as reasonably achievable (ALARA), and that CT should be limited to the affected area, with risks weighed against its prognostic value and ability to guide management [26]. During the secondary survey, treatment of pain should not be overlooked, and sequential doses of fentanyl (1 μg/kg) should be administered and redosed to achieve comfort, while ensuring that hemodynamic status and adequate respiratory drive is maintained. It is important to note that the undertreatment of pain can lead to an inability to perform an adequate physical exam, as well as lead to an increased incidence of post-traumatic stress conditions [27].

KEY POINTS: PRIMARY AND SECONDARY EVALUATION

- ALS guidelines mandate that chest compressions be initiated in a pulseless patient, prior to establishing an advanced airway
- The primary survey should be frequently repeated throughout the patient evaluation as the patient's condition can change rapidly
- CT radiation should be as low as reasonably achievable (ALARA) to decrease the risk of malignancy

Airway management

As per ATLS guidelines, an immediate priority of the anesthesiologist is to evaluate and, if necessary, manage the airway of the pediatric trauma patient. Indications for urgent intubation include hypoxia, respiratory distress, hemodynamic instability, airway or pulmonary injury, and decreased cognition leading to an inability to protect the airway [28]. Hypoxemia is detected by a decrease in oxygen saturation on pulse oximeter, but can also be observed by the patient's color, which is most apparent in infants and neonates. Respiratory distress is evident by signs of increased work of breathing, use of accessory and intercostal muscles, chest retractions, grunting, nasal flaring, and tachypnea. If upper airway obstruction exists as a result of airway edema, blood, or decreased pharyngeal tone, suprasternal retractions and stridor will be apparent [29]. Hemodynamic instability, often a result of hypovolemia and bleeding in the trauma patient, is reflected in the blood pressure, heart rate, capillary refill, and moistness of the mucous membranes. Patients with a modified Glasgow coma scale (GCS) score below 8 cannot protect their airways and are at risk for aspiration due to abated airway reflexes.

There are a number of factors that render the airway management of pediatric trauma patients especially challenging. From an anatomical standpoint, compared with adults, smaller children and infants tend to have larger tongues, shorter jaws, longer palates and epiglottises, a narrower cricoid cartilage, and an increased risk for laryngospasm. The relatively larger head to body ratio results in natural neck flexion when an infant is lying flat, making the "sniff position" more difficult. Moreover, as Pouiseuille's law dictates, the naturally smaller diameter of the pediatric airway means that even small decreases in size resulting from edema from

chemical injury or burns, swelling from direct airway injury, or adherent blood or secretions results in large increases in airway resistance. Infants tend to be obligate diaphragmatic breathers, and in the setting of respiratory distress, tire more rapidly. Hypoxia is precipitous even in healthy infants because of their increased oxygen demand and their decreased oxygen reserve (functional reserve capacity). The predisposition for infants to become quickly hypoxic is further exacerbated in cases where there is direct trauma to the lungs or pulmonary compromise from concomitant edema, transfusion-related acute lung injury, or acute respiratory distress syndrome. Furthermore, at baseline, infants have increased chest wall compliance but decreased lung compliance. Direct or indirect trauma can cause sudden decreases in pulmonary compliance and problems with ventilation [30].

Unlike in adults where cardiac problems remain the primary cause of cardiac arrest, in children hypoxia is the most common cause. Positioning of an infant's head and neck is very important, and because of the larger occiput, a small towel roll can be placed under the infant's shoulders in order to extend the neck into an ideal "sniff position" (Fig. 39.2). As many infants will have or be at risk for cervical spine injury, it is recommended that the cervical collar be removed prior to intubation and manual inline stabilization be performed by another provider. Preoxygenation for 3–5 min is imperative if possible, given the decreased oxygen reserve. As with adults, pediatric trauma victims are considered to have full stomachs and are at high risk for aspiration. Therefore, a rapid-sequence intubation should be performed and should include a slight reverse Trendelenberg (head up) position when possible (and provided the patient has a reasonable blood pressure) and cricoid pressure. Cricoid pressure should be reduced compared to that used in adults, as the softer tracheal cartilage of children is more collapsible, and can impede intubation. Succinylcholine (2.0 mg/kg) should be used to deliver intubating conditions as soon as possible. It is also prudent to have atropine readily available in the event that the succinylcholine coupled with vagal stimulation from intubation leads to sudden bradycardia, particularly in infants less than 1 year of age.

Cuffed tracheal tubes should be used instead of uncuffed tubes in the setting of trauma. Uncuffed tubes often lead to large leaks in ventilation, especially since, in children, pulmonary compliance can quickly deteriorate with pulmonary and airway injury in the setting of rapid fluid resuscitation. Studies show that the use of uncuffed tracheal tubes leads to an increased need for reintubation and subsequent airway trauma [31]. To avoid tracheal injury and subsequent tracheal stenosis, when the tracheal tube cuff is inflated, an air leak should be audible at 20–25 cmH_2O. As with any potentially difficult intubation scenario, emergency and back-up equipment should be immediately available. Such equipment includes appropriately sized laryngeal mask airways, oral and nasal airways, bougies, videolaryngoscopes, and fiberoptic bronchoscopes. ATLS guidelines recommends that oral airways should not be placed using a backward, 180° rotation technique as this can cause trauma to the more fragile oral tissue. For the same reason, these guidelines advise against nasotracheal intubation in children.

Videolaryngoscopy has become increasingly popular in both the OR and emergency room settings. Several studies have shown that videolaryngscopes have the potential to improve the view of the glottis in anterior or challenging airways, but generally increase time to intubation compared to direct laryngoscopy [32]. In cases of difficult intubation, fiberoptic scopes can be used. However, depending on the size of the tracheal tube, the smaller size and decreased rigidity of small-caliber or "spaghetti" flexible scopes make it more difficult to navigate past swollen pharyngeal tissue. Secretions and blood in the oral pharynx, common in trauma patients, can obscure or obstruct the view of the glottis, and can block small size tracheal tubes (Fig. 39.3). Smaller scopes do not have suction capability to remove secretions and mucous which can hinder visibility. While airway bougies can be helpful, especially in situations where there is an acute angle or small mouth opening or oropharyngeal space, they can be associated with very rare but devastating complications such as tracheal injury or perforation [33]. The extra fragility of the tracheas of small children means that special caution should be taken when using an airway bougie to ensure that it is not advanced too far past the vocal cords, and that advancement is without resistance. End-tidal CO2 should be continuously monitored to ensure that ventilation achieves normocapnea, and because changes in ventilation is an early indicator of tube malplacement. The tracheal length in infants is approximately 5 cm and grows to 7 cm at 18 months. The shorter tracheal length results in easy malpositioning of the tube. Reassessment and repeat auscultation should be performed after intubation, after the patient is moved or repositioned, or whenever there appears to be a change in the ventilation, as the probability of unrecognized inadvertant dislodgment or mainstem intubation of the tracheal tube is inversely proportional to the size of the child.

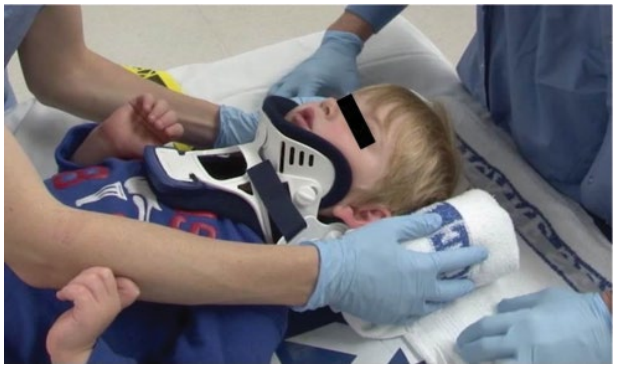

Figure 39.2 Towel rolls used to stabilize the cervical spine prior to intubation. *Source*: Courtesy of Dr Sanjay Bhananker, University of Washington, Harborview Medical Center.

KEY POINTS: AIRWAY MANAGEMENT

- Hypoxia is the most common cause of cardiac arrest in children
- Cuffed tracheal tubes should be used in preference to uncuffed tracheal tubes in pediatric trauma patients
- Reassessment and repeated auscultation should be performed after an airway is secured, when the patient is moved or repositioned, or when an acute change in ventilation manifests; malpositioning of the tracheal tube is increasingly likely in smaller children and infants

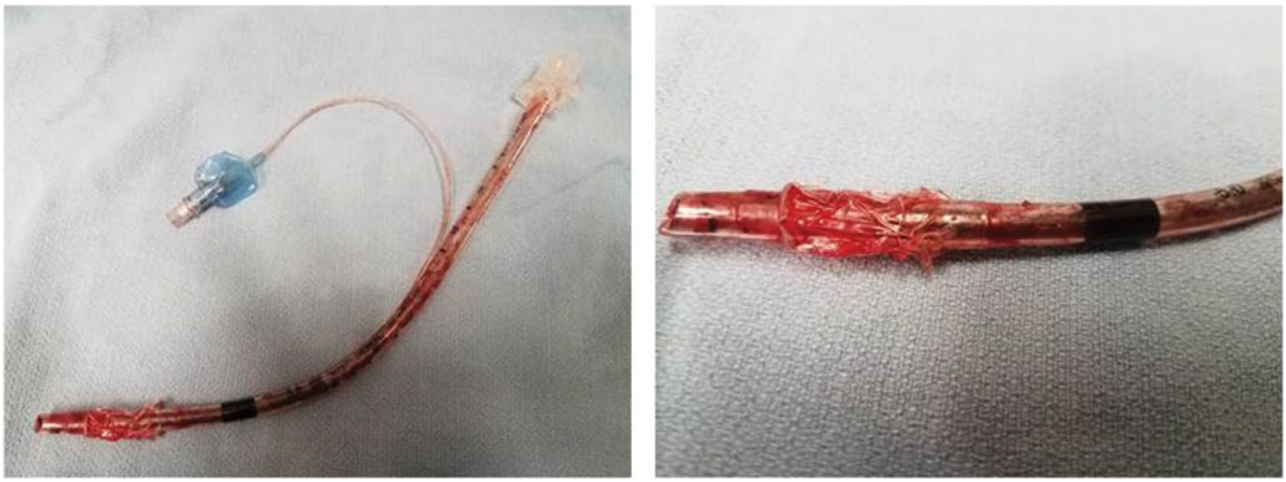

Figure 39.3 A smaller tracheal tube diameter increases the risk of airway obstruction by blood and secretions.

Table 39.2 Flow rates* of peripheral IV catheters [34,124]

Gauge	Flow rate (mL/min) [124]	Flow rate of Level 1 (mL/min) [34]	Flow rate of RIS (mL/min)
24 G	17	Not published	Not published
22 G	35	Not published	Not published
20 G	60	140	144
18 G	105	209	205
16 G	220	368	412
14 G	330	488	584
4 Fr	286	450	516
5 Fr	380	533	667
6 Fr	480	548	702
7 Fr		564	772
8.5 Fr	674	596	857

* Flow rates apply to crystalloid solutions.
Level 1, Level 1® Fast Flow Fluid Infuser, Smiths Medical, Dublin, OH, USA; RIS, Belmont® Rapid Infuser, Belmont Instrument Corporation, Billerica, MA, USA.

Vascular access

Establishing intravenous access is an immediate priority in both the prehospital and hospital settings. The smaller size of pediatric vessels and increased subcutaneous fat on the extremities of infants and toddlers can make intravenous catheter placement challenging. Peripheral access should consist of at least two intravenous lines, and should be placed in the upper extremities (preferably antecubital fossa) in situations when there is likely abdominal or thoracic trauma. Other common sites include the saphenous veins and external jugular veins, although the latter should be avoided in patients who have cervical spine collars or who exhibit signs of airway distress. Small increases in the radius of the intravenous catheter results in large increases in flow rate (by a power of 4). Placement of intravenous catheters as large as is feasible, and no smaller than 20 gauge in size (22 gauge in infants), allows for optimal rapid fluid and blood resuscitation (Table 39.2). There is evidence that rapid transfusion systems confer no significant benefit to flow rates or warming capacities of fluids through IV catheters of size 20 gauge or smaller [34].

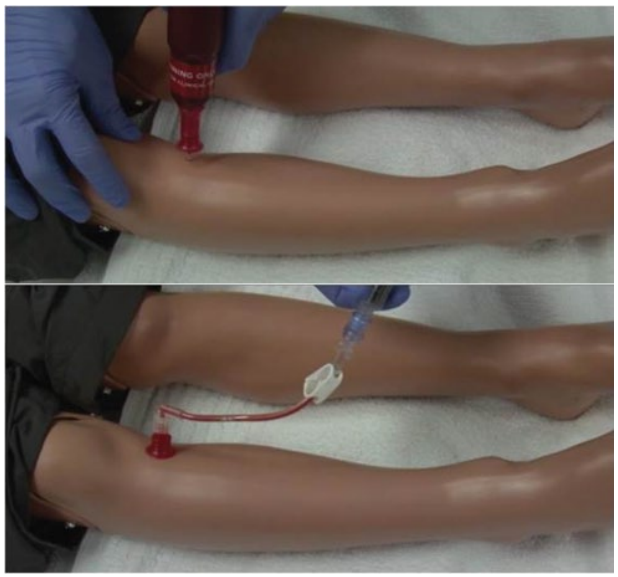

Figure 39.4 Placement of an intraosseous line in the anteromedial tibia and confirmation by line aspiration. *Source*: Courtesy of Dr Sanjay Bhananker, University of Washington, Harborview Medical Center.

Difficult intravenous access may require the use of ultrasonography or the blind saphenous technique. However, the severe hypovolemia and vasoconstriction in patients suffering from shock may render adequately sized intravenous access impossible within minutes of patient arrival. In situations where intravenous access cannot be successfully obtained within three attempts or 90 s, an intraosseous cannula should be placed. According to ATLS guidelines, the intraosseous catheter size should be 18 gauge in infants and 15 gauge in young children. Intraosseous cannulation is possible in long bones, although the most common site is the anteromedial aspect of the tibia, just below the tibial tuberosity (Fig. 39.4), followed by the distal femur. Complications include possible fluid extravasation but studies have shown that the incidence of complications is consistently low, and intraosseous lines offer a fast, safe method of fluid resuscitation, although they are often underutilized [35].

After the initial resuscitation, central venous access (either femoral or internal jugular) may be required as intraosseous access is life saving but temporary. Studies in the critical care setting have assessed techniques and complication rates associated with the placement of central venous lines in children. A recent evaluation of over 5000 patients demonstrated that although complication rates for central venous access was low among anesthesiologists (1.3%), failure was more likely in children <3 kg [36]. The use of ultrasound-guided techniques have improved first-pass success and decrease rates of complications. Evidence from a recent study demonstrated ultrasound-guided subclavian vein cannulization conferred a 98% first-pass success in patients weighing over 5 kg and a 92% first-pass success in neonates weighing under 5 kg, within a median time of 40 s [37]. When possible, confirmation of correct central line catheter placement through visibility by cross-sectional and longitudinal ultrasound, radiography, and pressure transduction should be ascertained prior to use of the central line. Similarly, placement of an arterial line may also prove necessary following initial resuscitation for more vigilant hemodynamic monitoring and for sequential blood draws that will guide further resuscitation and ventilation strategies. For small infants and neonates, a micropuncture arterial line apparatus that includes a smaller diameter wire may be helpful. Chapter 19 presents additional information about vascular access techniques.

KEY POINTS: VASCULAR ACCESS

- A minimum of two large (at least 20 gauge) intravenous catheters should be placed
- Intraosseous access should be placed if intravenous access cannot be established within three attempts or within 90 s of patient arrival
- Intraosseous access can be placed in any long bone and is a safe and effective method of emergency resuscitation

Massive transfusion and fluid resuscitation

Hemorrhage is a leading cause of death in pediatric trauma patients during the first 24–48 h after injury [38]. While damage control resuscitation has become well defined and widely implemented with solid evidence of improved outcomes in the adult population, massive transfusion guidelines have not yet been developed for the pediatric population [39,40]. Finding optimal transfusion strategies within this population poses challenges related to the differences in total blood volume and physiology among children of varying sizes and ages. Attempts to define massive transfusion in pediatric patients have led to a number of suggestions. One definition includes the transfusion of more than 50% total blood volume in 3 h, transfusion greater than 100% total blood volume in 24 h, or transfusion support to replace ongoing blood loss of greater than 10% total blood volume per minute. A commonly used and simpler definition derived from the US Department of Defense Trauma Registry defines massive trauma as 40 mL/kg of all blood products administered at any time within the first 24 h [41].

Since there are differences in adult and pediatric physiology, the strategy of permissive hypotension that has been widely accepted in injured adults without TBI cannot be simply and directly extrapolated to children [42]. As children can maintain their blood pressure in spite of significant blood loss through compensatory mechanisms, waiting for relative hypotension before resuscitation is far too late. Some authors describe the implementation of judicious "permissive tachycardia" while maintaining normal blood pressures, instead, as a mechanism of maintaining perfusion while decreasing the bleeding associated with high blood pressure in actively bleeding patients [43]. However, the goals and efficacy of "permissive tachycardia" have yet to be studied and delineated. Moreover, it is important to keep in mind that the diagnosis of TBI may not be initially revealed if other injuries require emergent surgeries.

When to initiate and how to guide transfusion of packed red blood cells requires the consideration of several factors including estimated fraction of total body blood loss, rate of active bleeding, and the determination of a transfusion threshold. Undertransfusion results in hypoxic and ischemic end-organ damage, while overtransfusion increases the length of intensive care unit (ICU) stay, ventilator dependence, and increased rates of mortality [44]. Similar to the adult Transfusion Requirements in Critical Care trials and other similar studies, transfusion studies in non-trauma critically ill pediatric patients have concluded that hemoglobin thresholds above 7 g/dL do not improve outcomes and may increase morbidity and mortality [45,46]. The support of a more restrictive transfusion threshold, e.g. at a higher hemoglobin, holds true among pediatric patients in septic shock, those with single-ventricle physiology, and those suffering from upper gastrointestinal bleed [47,48]. With the acute fluid shifts and the necessary replacement of active blood loss in trauma patients, decisions surrounding transfusion is more complex.

Advanced Trauma Life Support guidelines suggest initiation of resuscitation using 20-40 mL/kg boluses of isotonic crystalloid. The timing of transfusion needs to consider the rate of bleed, and actively hemorrhaging patients may require earlier transfusion and more crystalloid-restrictive strategies [49]. In the setting of ongoing bleed, and if initial crystalloid boluses are insufficient to cause normalization of vital signs and adequate urine output (1–2 mL/kg), blood should be administered in 30 mL/kg boluses, targeting physiological goals of normal age-appropriate heart rate, blood pressure, and urine output. Point-of-care measures, e.g. arterial blood gas, should be utilized to help guide transfusion and ensure that hemoglobin concentration is maintained within the range of target goals. Packed red blood cell freshness is an important consideration, especially in smaller infants less than 4 months of age. Young children and infants without fully matured kidneys have a decreased ability to handle the potassium load and acidemia associated with a massive transfusion of blood that has been stored for long periods of time. Transfusion with red blood cells that have been stored for over 28 days have been shown to result in longer length of ICU stay, lower discharge GCS scores, and increased mortality rates [50]. For this reason, when possible, "fresher" blood should be prioritized for critically ill younger patients and patients under 4 months should also receive cytomegalovirus negative, irradiated blood.

Once a massive transfusion threshold is triggered (>40 mL/kg), the supplementation of coagulation factors and platelets must be considered. While currently an optimal massive transfusion protocol in the pediatric population has not been established, there is general consensus that fresh frozen plasma and platelets should be administered alongside red blood cells in a 1:1:1 to 3:2:2 ratio [51]. A balanced transfusion approach is supported by overwhelming evidence that early coagulopathy occurs frequently among pediatric trauma patients [52]. Generally, platelet counts increase by 10,000/dL for every 1 mL/kg of platelets administered. Approximately 10–15 mL/kg of fresh frozen plasma will increase factor levels by 15–20%. Cryoprecipitate should be administered for fibrinogen levels less than 1 g/L and is also a source of factor VIII and factor XIII [53].

Coagulopathy in pediatric trauma patients is a result of both trauma-induced and iatrogenic coagulopathy. Iatrogenic coagulopathy describes dyscrasias due to the dilution of coagulation factors, acidosis, and hypothermia. Traumatic-induced coagulopathy describes the activation of the local coagulation system. Studies have demonstrated that children are more susceptible to coagulopathies and bleeding because of lagging coagulant maturity and an increased tendency for hyperfibrinolysis [54]. Studies of pediatric trauma patients in combat hospitals in Afghanistan and Iraq, as well as among civilian populations in the West, have demonstrated that early coagulopathy, defined as an international normalized ratio (INR) greater than 1.5, is an independent predictor for increased in-hospital mortality [55,56]. Results for early coagulopathy in the setting of TBI are more profound and suggest up to a fourfold increase in mortality [57–59]. Hence, resuscitation involving the early correction of coagulopathy using fresh frozen plasma, cryoprecipitate, and platelets is critical to increased survival in pediatric trauma patients, and particularly in those with TBI.

Challenges in optimizing blood component and coagulation factor therapy has led to a discussion of the utility of visoelastic coagulation tests as a rapid diagnostic test to identify early coagulopathy and guide treatment – i.e. thromboelastography, rotational thromboelastometry, and impedance aggregometry [60]. The point-of-care tests, which are utilized perioperatively during pediatric cardiac and liver transplant surgeries, more accurately demonstrate changes in all stages of clot formation and not just the initiation phase of blood coagulation represented by conventional tests [61]. Use of antifibrinolytic therapy, such as tranexamic acid, is also gaining attention. While it is not yet approved for use in children by the US Food and Drug Administration (FDA), trials performed in a combat setting (766 patients) demonstrated that tranexamic acid treatment is independently associated with decreased mortality in pediatric trauma patients as well as improved discharge neurological status and decreased ventilator dependence; there was no evidence of thromboembolic complications or cardiovascular events [62]. Given that tranexamic acid has been shown to reduce perioperative transfusion requirements in pediatric spine and cranial surgery, it may have an important role in pediatric hemorrhage from trauma, pending future studies [63]. Chapter 12 presents additional discussion about transfusion and coagulation monitoring.

KEY POINTS: MASSIVE TRANSFUSION AND FLUID RESUSCITATION

- Massive transfusion is approximately 40 mL/kg or more of all blood products administered within 24 h
- Prioritize fresh packed red blood cells (age <28 days) for small and critically ill infants
- Early treatment of coagulopathy decreases mortality, especially in children with TBI
- Blood transfusion should be guided by physiological goals, i.e. heart rate, blood pressure, urine output, and point-of-care hematocrit levels

Intraoperative management

Conservative management is the most commonly employed strategy for pediatric trauma, and an estimated 15% of pediatric trauma patients require surgery. Emergent surgery for pediatric trauma patients is most commonly for decompressive craniotomy and exploratory laparotomy. Hospitals receiving trauma patients should have the ability to process a patient from door to OR within 30 min, and it is important that there is a designated "crash" OR that is already set-up for trauma (Fig. 39.5). In addition to standard airway equipment such as suction, monitors, and IV access equipment, trauma rooms should have fluid warmers, forced-air warming devices, a readily available transfusion system such as a Belmont® Rapid Infuser System (Belmont Instrument Corp., Billerica, MA, USA), and equipment for ultrasound-guided placement of arterial lines and central lines. In addition, if emergent surgery is imminent, the room should be preheated, and a blood refrigerator with cross-matched products (if available) or uncrossed-matched O negative products for massive transfusion should be available.

The goal is to provide balanced general anesthesia while maintaining systemic and cerebral hemodynamic stability. Medications that decrease blood pressure should be used in reduced doses, especially in hypovolemic and hypotensive patients; efficacy of decreased dosing is generally maintained because of the lower volume of distribution in the setting of hypovolemia. Vasoactive agents should be immediately available for use to prevent induction-related hypotension. Anesthesia is often induced with a combination of medications, and most commonly includes etomidate, judicious doses of propofol, or ketamine. Etomidate causes less hemodynamic instability and should be administered in doses of 0.2–0.4 mg/kg IV. Ketamine causes less hemodynamic derangement than propofol and is administered in doses of 1–3 mg/kg. The shorter onset and duration of action of fentanyl makes it a useful analgesic in trauma, and dose ranges between 25 and 100 μg/kg are typical for the duration of a case. In very unstable patients, small doses of midazolam or scopolamine can be used for amnesia and sedation without causing hemodynamic compromise. Sevoflurane and isoflurane are generally used for maintenance of anesthesia, although doses must again be adjusted based on hemodynamic stability. Nitrous oxide should be avoided in trauma as it causes expansion of enclosed air spaces in the abdomen, thorax, and cranium

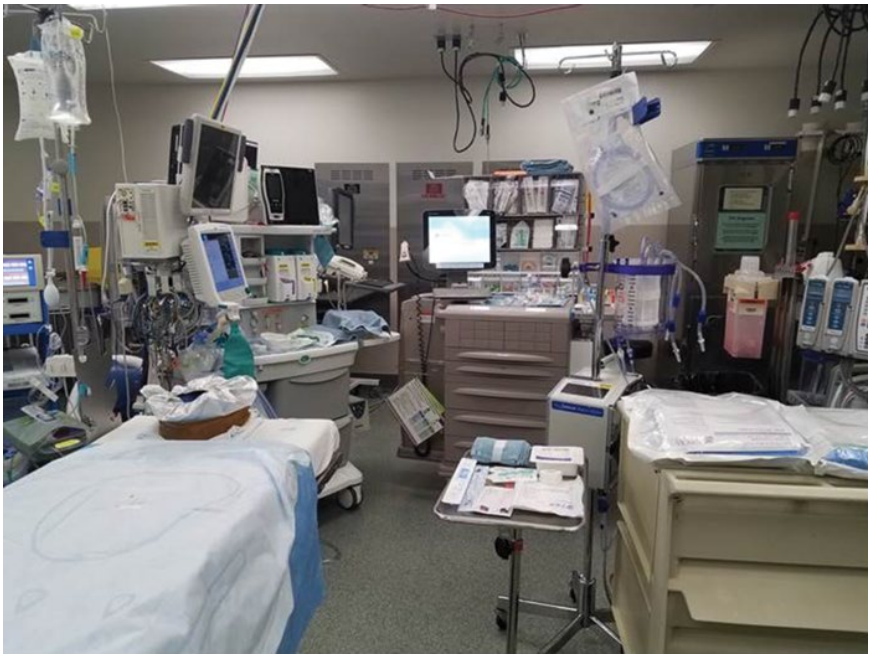

Figure 39.5 Operating room set-up for emergency trauma should include rapid infuser system, line placement equipment, fluid warmer, airway and ventilation equipment, induction and emergency drugs, and patient warming devices.

and reduces the maximum inspired oxygen concentration possible. Succinylcholine should be administered at 2 mg/kg, but should be avoided in patients with hyperkalemia, a family or personal history of malignant hyperthermia, prolonged immobility or in those with burns or denervation injuries that have been untreated for more than 24 h since the time of injury. There are variable opinions regarding pretreatment with atropine when using succinylcholine, but it should be immediately available in doses of 0.01–0.02 mg/kg in the event there is concomitant bradycardia. There exists large institutional variation regarding use of vasopressors. Phenylephrine, norepinephrine, and dopamine remain the most commonly used for blood pressure support. Recently, a study found no statistically significant difference in mean arterial pressure or cerebral perfusion pressure between vasopressor groups, although norepinephrine was associated with clinically relevant higher cerebral perfusion pressures and lower intracranial pressures compared to phenylephrine and dopamine [64].

Laboratory data that should be frequently monitored include arterial blood gases, complete blood counts, coagulation studies, and electrolytes. The stress response of trauma commonly increases glucose, and an insulin drip is often required, which is especially important in the setting of TBI. However, the greater metabolic demand of smaller infants predisposes them to hypoglycemia, particularly when they have been nil per os (NPO) for longer periods of time, so glucose monitoring is crucial and supplementation with dextrose should be administered as needed. Administration of ionized calcium is necessary when transfusing significant quantities of blood, as the citrate in stored blood components chelates calcium. Calcium chloride should be administered preferentially through a central line at boluses of 10–20 mg/kg until the ionized calcium concentration is corrected. Peripherally-administered calcium chloride should be diluted to 10 mg/mL to avoid phlebitis; an alternative is calcium gluconate at 30 mg/kg per dose via a peripheral IV line. If not already in place, a Foley catheter should be inserted to monitor urine output as an indicator of volume status and renal perfusion. It is important to be cognizant that chest tubes be placed on suction to optimize pulmonary function and reduce injury. Temperature management is of utmost important in pediatric trauma patients. Ability to maintain thermal hemostasis is inversely proportional to the patient's size, and children have a higher surface area to volume ratio and decreased ability compensate for hypothermia. Hypothermia (temperature less than 36°C) results in worsened coagulopathy, depressed cardiac output, and slow awakening. Temperature should be optimally maintained above 36°C through the use of forced-air warming, increased ambient room temperature, heat lamps, fluid warmers, and reflective head caps. Conversely, hyperthermia (temperature greater than 38°C) should also be avoided as it increases metabolic demand and undermines neurological outcomes.

KEY POINTS: INTRAOPERATIVE MANAGEMENT

- The choice of induction agent should consider hemodynamic status and goals
- Reduction of induction medication doses are used because of decreased volume of distribution in hypovolemia, and vasoactive agents should be immediately available
- Midazolam and scopolamine can be used for sedation in severely hemodynamically unstable patients
- Hypothermia results in coagulopathy, decreased cardiac output, and delayed awakening

Anesthetic considerations for specific injuries

Traumatic brain injury

Traumatic brain injury is the leading cause of death in children over the age of 1 year. TBI is more common among males (3:2 ratio), and males also have a higher risk of fatal injury [65]. The prevalent mechanism of injury varies depending on age. According to the CDC, falls are the most common mechanism of TBI, particularly in the 1–4-year age group. Bicycle-related accidents and motor vehicle crashes increase in prevalence with age, and motor vehicle collisions are the leading cause of TBI among adolescents. The CDC reports the incidence of TBI-related deaths for each age group to be: 4.3/100,000 (0–4 years), 1.9/100,000 (5–14 years), and an increased rate of 15.6/100,000 (15–24 years) [66]. Other significant mechanisms of injury include sports-related head injury, caused by sudden impact or the accumulation of more minor repetitive injury, in older children, and passenger-side airbag injury in younger children. Providers should take note of the signs and symptoms of of non-accidental TBI, particularly in children under the age of 2 years, as will be discussed later in this chapter.

Providers should have a high index of suspicion for TBI in children with multiple trauma, altered mental status, and other head and neck injuries. Infants with open frontanelles and mobile cranial sutures can accommodate intracranial bleed or swelling with a delayed presentation of symptoms. While infants may present with bulging frontanelles, the absence of a tense frontanelle on examination does not exclude the possibility of TBI. Notably, children are at greater risk for TBI because of their larger head to body ratio, thinner protective skulls, and decreased, more vulnerable myelinated tissue. Subsequently, children are more susceptible to having increased intracranial pressure (ICP). Moreoever, cerebral metabolic rate for oxygen and glucose are higher in children than adults by approximately 50% and 20%, respectively. Primary injury results from the initial impact; secondary injury may involve diffuse cerebral swelling, herniation, ischemia, or infection, as a consequence of primary injury. Primary injury includes both extra-axial injury (epidural hematoma, subdural hematoma, subarachnoid hemorrhage, and intraventricular hemorrhage) and intra-axial injury (diffuse axonal injury, contusion, and intracerebral hemorrhage) [67]. TBI is diagnosed by CT of the brain (Fig. 39.6). Diffuse axonal injury may, however, present with a normal CT scan despite increased ICP and neurological symptoms [68].

In addition to performing primary and secondary surveys, in patients suspected of having TBI, neurological assessment should be conducted using the modified GCS (Table 39.3). A GCS score of <9 necessitates tracheal intubation to ensure adequate respiration, protect the airway from aspiration, and maintain controlled ventilation for ICP management. TBI patients often have concomitant cervical spine injury. Cervical spine immobilization should be pre-emptive and requires that appropriately sized cervical spine collars be placed. In infants aged less than 6 months, a spine board should be used with tape adhered to the forehead and towels around the neck to immobilize the cervical spine. Manual inline stabilization should be performed if the c-collar or tape needs to be removed during direct laryngoscopy.

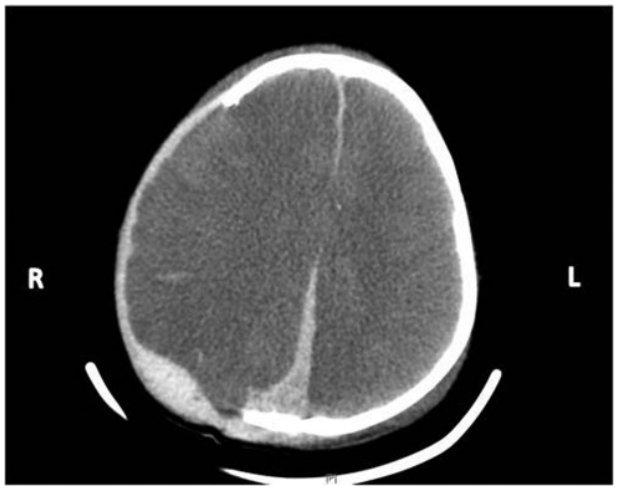

Figure 39.6 CT head without contrast in an 18-month-old victim of a motor vehicle crash showing a right extra-axial hematoma measuring up to 17 mm with subarachnoid and intraparenchymal hemorrhage in the right temporoparietal lobes.

Table 39.3 Modified Glasgow coma scale for young children and infants

Pediatric	Infants	Score
Eyes	Eyes	
Open spontaneously	Open spontaneously	4
React to speech	React to speech	3
React to pain	React to pain	2
No response	No response	1
Verbal	Verbal	
Smiles, appears oriented, interactive	Coos, babbles, interactive	5
Interacts inappropriately for age	Irritable	4
Moans	Cries to pain	3
Irritable, inconsolable	Moans to pain	2
No response	No response	1
Motor	Motor	
Follows commands	Spontaneous movements	6
Localizes pain	Withdraws to touch	5
Withdraws to pain	Withdraws to pain	4
Abnormal flexion	Abnormal flexion	3
Extension posturing	Extensive posturing	2
No response	No response	1

At a minimum, intravenous access adequate for expedient resuscitation and an arterial line are necessary. The addition of ICP monitoring may be used, although it is important to correct any coagulopathy prior to placing the monitor (Fig. 39.7). The degree of cerebral autoregulation impairment is related to the severity of TBI and is associated with poor outcomes; thus, it is critical that cerebral perfusion pressure (CPP) be maintained. In the setting of intracranial hypertension, CPP is measured as the difference between a patient's mean arterial pressure (MAP) and ICP. CPP should be maintained at a minimum of 40 mmHg. However, it may be wise to maintain CPP at 40–50 mmHg depending on the age of the child, with the CPP goals for older children being at the upper ranges. Maintenance of goal CPP often requires that a higher than normal MAP be maintained with the use of vasopressors. Furthermore, TBI can lead to cardiac dysfunction that may additionally require hemodynamic support using

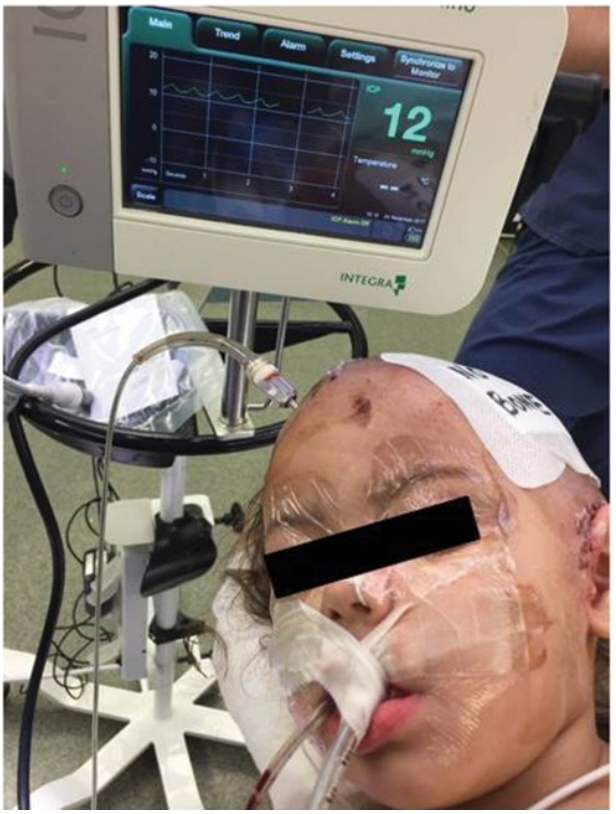

Figure 39.7 Intracranial pressure monitor placed postoperatively in a 2-year-old patient.

vasopressors and positive inotropes [69,70]. Traditional guidelines have advocated against the use of ketamine in TBI because of the notion that it increases ICP. However, recent evidence demonstrates that ketamine may decrease ICP while maintaining CPP [71,72]. Hence, the updated Brain Trauma Foundation guidelines suggest that ketamine is a safe and effective sedative for pediatric patients with TBI [73].

An ICP above 20 mmHg is considered elevated. ICP management involves head elevation, hyperosmolar therapy, placement of an external ventricular drain (plus lumbar drain in refractory cases), high-dose barbituates, and/or decompressive craniotomy. Hyperosmolar therapy is administered in the form of hypertonic (3%) saline or mannitol; 2% hypertonic saline may be considered to avoid phlebitis if it is administered through a smaller peripheral vein. Hypertonic saline may be administered as a bolus dose of 6.5–10 mL/kg followed by a continuous infusion at 0.1–1.0 mL/kg, ensuring that serum osmolarity does not exceed 360 mOsm/L. Mannitol is less studied in the pediatric population but can be administered as a 0.25–1 g/kg bolus over 30 min, to a maximum serum osmolarity of 320 mOsm/L. A Foley catheter should be placed prior to initiation of hyperosmolar therapy, and euvolemia should be maintained by crystalloid replacement. Refractory intracranial hypertension may be treated with barbituates, such as thiopental or etomidate, if the patient has adequate blood pressure to tolerate it. The risk of adrenal suppression must be weighed when using etomidate. Propofol has not been approved by the FDA for long-term use as an infusion in infants and children, and carries the risk of propofol infusion syndrome, which results in acidosis and myocardial dysfunction. Early-onset trauma-related seizures occur with greater frequency among children, and prophylactic phenytoin is often used to reduce the risk of post-traumatic seizures. Interestingly, prevention of early-onset seizures has not been shown to decrease the incidence of late-onset post-traumatic seizures or outcomes [74]. Corticosteroids are not indicated in TBI. Table 39.4 shows the latest guidelines for the management of pediatric TBI.

Table 39.4 Guidelines for acute management of pediatric traumatic brain injury

Physiological parameter	Recommendations
Temperature	Avoid moderate hypothermia (32–33°C) early after severe TBI Hypothermia may be considered for persistent severe TBI after 8 h from injury for up to 48 h If hypothermia is induced, avoid rewarming at a rate of >0.5°C/h
Hyperventilation	Avoid prophylactic severe hyperventilation ($PaCO_2$<30 mmHg) 48 h after injury If hyperventilation is used in the management of severe refractory intracranial hypertension, consider advanced neuromonitoring for evaluation of cerebral ischemia
Cerebral perfusion pressure (CPP)	Maintain a minimum CPP of 40 mmHg Consider a CPP threshold of 40–50 mmHg depending on age, with infants at the lower end and adolescents at the upper end of this range
Hyperosmolar therapy	Consider hypertonic (3%) saline for treatment of severe TBI in boluses of 6.5–10 mL/kg and/or a continuous infusion at 0.1–1.0 mL/kg/h Do not exceed the dose necessary to maintain ICP <20 mmHg Serum osmolarity should be <360 mOsm/L. Mannitol is commonly used 0.25–1 g/kg although no studies meeting inclusion criteria were identified for use of evidence
Antiseizure prophylaxis	May consider prophylactic treatment with phenytoin to reduce early post-traumatic seizures
Sedatives	Consider etomidate or thiopental to control severe intracranial hypertension (consider risk of adrenal suppression with etomidate)
Corticosteroids	Corticosteroid use is not recommended to improve outcome or reduce ICP

ICP, intracranial pressure; TBI, traumatic brain injury.
Source: Reproduced from Bell and Kochaneck et al [77] with permission of Wolters Kluwer.

Decompressive craniotomy is indicated to relieve ICP and prevent herniation. Craniotomy should be performed to evacuate epidural hematomas in comatose patients, particularly if they are larger and likely to be caused by arterial hemorrhage. Subdural hematomas demonstrating a midline shift of >5 mm or that are thicker than 10 mm should also be evacuated. The decision to operate in intraparenchymal injury is supported by worsening of neurological exam, signs, or persistently elevated ICP. Similarly, the 2012 Brain Trauma Foundation guidelines for the mangement of pediatric severe traumatic brain injury recommend that diffuse cerebral edema, which occurs with greater frequency in the pediatric population, should be treated with craniotomy and duraplasty, especially in the setting of worsening signs and symptoms of intracranial hypertension.

Box 39.1: Predictors of poor outcomes after pediatric traumatic brain injury

- Age <4 years
- Cardiopulmonary resuscitation
- Multiple trauma
- Hypoxia (PaO_2 <60 mmHg)
- Hypoventilation ($PaCO_2$ >45 mmHg)
- Hyperventilation ($PaCO_2$ <35 mmHg)
- Hyperglycemia (glucose >250 mg/dL)
- Hyperthermia (temperature >38°C)
- Hypotension (blood pressure < 5th percentile for age)
- Intracranial hypertension (intracranial pressure >20 mmHg)

Source: Reproduced from Kanna et al [67] with permission of Wolters Kluwer.

Factors that independently affect outcomes in patients with TBI include hypoxia, hyperglycemia, fever, hypotension, and hypo- and hypercarbia (Box 39.1). Outcome studies have demonstrated that hypotension early in care results in increased in-hospital mortality (23% versus 8.6%) and decreased Glasgow outcome score upon discharge. Timely treatment of hypotension increases in-hospital survival (adjusted relative risk 0.46). Children who are hypotensive and not resuscitated in a timely manner are at 77% greater risk of in-hospital mortality compared with children who are not hypotensive in the prehospital location or emergency department [75]. Hypoxia, hypocarbia, and hypercarbia are also independently associated with poorer outcomes. Several studies have found that patients with higher PaO_2 (>100 mHg) on admission had an increased rate of survival. Survival benefit was found in patients with an admission $PaCO_2$ of 36-45 mmHg, as compared with those who were either hypo- or hypercapneic [76]. Subsequently, current guidelines recommend that hyperventilation be avoided in pediatric TBI in the initial 48 h postinjury, and should only be considered in refractory cases. If hyperventilation is performed, neuromonitoring should be conducted to prevent cerebral ischemia [77].

Abdominal trauma

Abdominal trauma accounts for the second most common pediatric traumatic injury. Abdominal trauma is present in approximately 25% pediatric trauma patients and is most commonly due to motor vehicle collisions. Children have more compliant chest walls and rib cages, both of which render their internal organs more vulnerable to external forces. Blunt trauma accounts for 85% of abdominal trauma, and 95% of blunt trauma injury is managed non-operatively. Conversely, penetrating trauma is less common in children, but usually requires damage control laparotomy. The spleen is the most commonly injured organ, followed by the liver. Unrecognized abdominal trauma can have fatal consequences. Diagnosis of intra-abdominal injury is most reliably performed through CT scan with contrast. A number of studies have assessed the utility of the focused assessment with sonography for trauma (FAST) exam in the pediatric population, since it is a primary diagnostic modality to measure intra-abdominal free fluid in adult trauma. In children, however, the FAST examination is far less sensitive, as less than half of pediatric patients have free fluid [78]. Many hospitals use a combination of FAST followed by CT, though the results of several recent studies have demonstrated that the addition of a FAST examination does not change management [79].

There are certain injury patterns that should alert the provider to mechanism-specific injury. Injury from seatbelt restraint during a motor vehicle crash is common in children. Presence of abdominal wall bruising or ecchymosis in the seatbelt distribution and abdominal pain is often predictive of underlying intra-abdominal injury [80]. Gastrointestinal mesenteric or bowel injuries represent the most common seatbelt-associated injuries, followed by splenic and hepatic injuries [81,82]. Bicycle handlebar injury represents another common cause of abdominal injury in children and typically presents with an imprint of the handlebar at the edge of the abdomen. Liver laceration is the most common intra-abdominal injury associated with handlebar injury [83,84].

Patients with abdominal trauma should have at least two large-bore intravenous lines in the upper extremity and an active type-and-screen. Non-operative management of abdominal trauma involves initial fluid resuscitation followed by monitoring for signs of hemodynamic instability, unexplained blood loss shown on serial measurements of hematocrit, and in some cases, liver and pancreatic enzymes (aspartate aminotransferase, alanine aminotransferase, and amylase). If the patient presents with penetrating intra-abdominal free air, abdominal free fluid in the presence of solid organ injury, or hemodynamic instability requiring massive transfusion, damage control laparotomy is indicated. If it remains uncertain whether there is intra-abdominal injury, such as in situations where there is intra-abdominal free fluid without solid organ injury, then a diagnostic laparoscopy may be performed [85].

If emergent laparotomy is likely, cross-matched blood products should be prepared. Intraoperative anesthetic management usually involves a rapid-sequence induction since abdominal trauma can cause severe gastric dysmotility, even if the patient is appropriately NPO. Most cases require the placement of an intra-oral or intranasal gastric tube that is connected to suction, as long as there is no concomitant esophageal injury. As in the majority of trauma cases, nitrous oxide should be avoided to prevent insufflation of the bowel or exacerbation of any undiagnosed pneumothorax. The anesthesiologist must account for the large insensible fluid losses associated with even low blood loss during open abdominal surgeries, due to the large incision, exposed bowel, and gastric tube output. Abdominal laparotomies are also associated with severe heat loss, and the anesthesiologist must be extra vigilant to ensure that the ambient room temperature is raised, fluids are warmed, and forced-air warming devices are utilized, which is particularly crucial for very small children.

Spine trauma

The incidence of spine trauma is relatively low in the pediatric population and occurs in less 2% of pediatric trauma patients. Children have more flexible interspinous ligaments and joint capsules, anteriorly wedged vertebral bodies that tend to slide forward with flexion, and flat facet joints; therefore, they tend to be at a lower risk for spinal cord fractures but are more susceptible to having associated ligementous and soft tissue injury. Spine trauma is most commonly caused by motor vehicle collisions (Fig. 39.8), although over 20% of spine trauma is

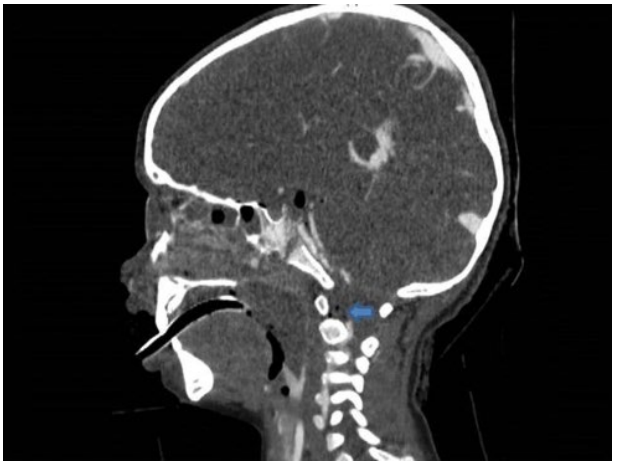

Figure 39.8 Cervical spine ligamentous injury in an 18-month infant following a high-speed motor vehicle crash. Air can be seen within the joint space of the left occipital condyle to C1 joint and C1–2 joint space. This is in association with the intracranial air, thought to represent a ligamentous disruption to the joint capsule.

sports related in older children [86]. Younger patients tend to have higher cervical spine injuries due to the more superior position of the fulcrum at C1–3 in preteens, compared to C5–6 in teenage patients. Evaluation of spine trauma involves a primary physical examination, whereby the patient's spine is immobilized, and the length of the spinal cord is palpated and grossly evaluated for pain or bony abnormalities. If injury is suspected, imaging is performed, consisting of anteroposterior, odontoid images, and lateral views of the cervicothoracic junction. Spinal cord injury without radiological abnormalities (SCIWORA) occurs when there is spinal ligamentous injury without fracture, with symptoms commonly presenting later. A recent study found that SCIWORA represents nearly 20% of spinal injuries in children aged less than 3 years, 9.4 % in children aged 3–12 years, and 5% in patients aged 13–20 years [87]. In cases where SCIWORA is suspected, magnetic resonance imaging is warranted.

Cervical spine immobilization should be pre-emptive during initial evaluation until it can be ruled out, noting that younger children are at higher risk of SCIWORA. For the anesthesiologist, this can mean increased challenges in airway management as intubation is performed with the cervical collar on or using cervical manual inline stabilization. Videolaryngoscopy can improve ease of intubation in such situations where there is limited neck extension and limited mouth opening. Similarly to the management of TBI, special attention should be paid to maintaining blood pressure at the upper ranges of normal, age-appropriate values to facilitate spinal perfusion. Patients with severe spinal injury may suffer from spinal and/or neurogenic shock, and the anesthesiologist must be prepared to support blood pressure with vasopressors and ionotropic support. The use of methylprednisolone is controversial, and studies have demonstrated no improvement in outcome with its use [88,89]. The usual dose is 30 mg/kg IV followed by 5.4 mg/kg/h for 23 h.

Cardiothoracic trauma

Thoracic injury accounts for between 5% and 12% of pediatric trauma. However, according to the 2015 Pediatric Report of the National Trauma Data Bank, thoracic trauma has the highest fatality rate of approximately 7% [90]. Patients with thoracic injury generally have higher injury scores, and the mortality rate of thoracic injury combined with abdominal or head trauma increases the mortality rate to 40% [91]. Blunt injury comprises over 90% of thoracic trauma. As a result of their increased chest wall compliance and increased mobility of mediastinal structures, children are more vulnerable to underlying soft tissue injury, and less at risk for rib fractures compared with adults. The most common pediatric thoracic injuries include pulmonary contusion, rib fractures, and hemothorax and/or pneumothorax [92].

Physical examination may reveal respiratory distress, asymmetrical or paradoxical chest movement with respiration, ecchymosis, and unilateral breath sounds on auscultation. Chest x-ray, a part of the initial ATLS diagnostic screening, can determine the presence of hemothorax, pneumothorax, and widened mediastinum. In the setting of a normal chest x-ray, studies have found that there is little utility for CT scans when looking for thoracic injury in isolation [93]. Pulmonary contusions can present 48–72 h following injury, and treatment is generally supportive. Traumatic pneumothorax requires insertion of a needle through the 5th intercostal space just anterior to the midaxillary line, followed by thoracostomy tube placement. Pneumothoraces seen on CT scan, but not on x-ray, generally do not require placement of thoracostomy tubes [94]. In the setting of persistent air leaks, thoracostomy tubes should be placed on continuous suction. Large air leaks with a persistent pneumothorax on x-ray should be treated with an additional thoracostomy tube. Hemothorax requires evacuation of blood through a thoracostomy tube connected to suction.

Anesthetic management of patients with pulmonary injury involves optimizing gas exchange, and mitigating additional lung injury. When patients with pulmonary injury undergo general anesthesia for operative procedures, nitrous oxide should be avoided to prevent the expansion of diagnosed and undiagnosed pneumothoraces. Chest tubes should be connected to suction in patients who have unresolved hemo- or pneumothoraces during intraoperative mechanical ventilation. If there is significant parenchymal lung injury, lung-protective ventilation strategies (tidal volumes of 6 mL/kg) should be considered to avoid further barotrauma. With severe rib fractures and sternal trauma, careful positioning is important, and additional support or stabilization of the thorax may be necessary, especially in prone cases. If ventilation proves challenging, arterial line placement prior to surgery is prudent to guide oxygenation and ventilation strategies. In these cases, having a size-appropriate fiberoptic bronchoscope readily available is helpful for ruling out challenges due to mucous plugging, inadvertent mainstem intubation, and tracheal tube kinking, from those due to worsening lung pathology.

Blunt cardiac trauma occurs in less than 3% of pediatric trauma patients, over 95% of which are cardiac contusions [95]. Cardiac injury is more likely in patients with anterior rib or sternal fractures, which can be accompanied by unexplained hypotension. Evaluation of patients with a high index of suspicion for having cardiac injury includes performing a 12-lead electrocardiogram (ECG) to look for arrhythmias. Cardiac enzymes can be useful to help monitor the resolution of injury. If hypotension is persistent, an echocardiogram is indicated to evaluate for functional deficits and to rule out cardiac

tamponade. Aside from pericardiocentesis for tamponade, the majority of blunt cardiac trauma is managed by supportive therapy that may include monitoring with telemetry and the use of ionotropes and vasopressors. Great vessel injury, including aortic injury, is very rare in pediatric trauma, and is diagnosed with thoracic CT with contrast.

Orthopedic trauma

Evaluation of orthopedic trauma is performed as a part of the secondary survey, and radiographical tests of the affected area are often added to the initial trauma x-ray scan. Although orthopedic injuries are less commonly life threatening, they frequently incur lifelong morbidity, and should be addressed as early as possible. Orthopedic emergencies include compartment syndrome resulting from bleeding and swelling from a crush injury, associated vascular injuries resulting in ischemic limbs, and unstable pelvic fractures resulting in uncontrolled hemorrhage. Compartment syndrome generally involves high-energy impact, which results in increased interstitial tissue pressure leading to vascular compromise. Abnormally high opioid requirements and pain disproportionate to injury should create a high index of suspicion for compartment syndrome [96]. Pelvic fractures are also a result of high-energy traumas. While the majority of pelvic fractures are stable, unstable pelvic injuries can be associated with damage to visceral structures resulting in hemorrhage and require immediate temporary stabilization while the patient is being resuscitated. Vascular injury presents as pulselessness, pallor, pain, paresthesias, and hypothermia of the affected extremity. Surgical restoration of perfusion is limb saving and should be a priority following the primary resuscitation [97].

Open fractures constitute approximately 10% of fractures in children with multiple injury, and the initial aim is to clean and cover the fracture to prevent infection [98]. Children have actively lengthening bone, and bone growth occurs by the physis near the articular surface. Injury to this area can compromise bone growth and lead to abnormal growth of the limb, with subsequent consequences to function and long-term quality of life of the patient. Hence, closed fractures should optimally be surgically corrected between 48 and 72 h after injury [99]. Intraoperative anesthetic management of patients with orthopedic trauma involves careful positioning of the affected limb, and it is important that communication and collaboration occur between the anesthesiologist and orthopedic surgeon on a plan for best positioning. Femur and pelvic fractures can result in significant blood loss, and a type-and-screen should be attained, with cross-matched blood made readily available. In older children, as with adults, bone fractures increase the risk of both fat and pulmonary emboli, and a high index of suspicion should be maintained in patients presenting with persistent tachycardia, hypoxia, and an unexplained dramatic end-tidal CO_2 to $PaCO_2$ gradient.

Facial trauma

Facial fractures account for between 1% and 14% of fractures in patients younger than 16 years of age. High-energy fractures most commonly involve the midface and mandibular regions. Frontal fractures are the most common in children due to the increased prominence of their foreheads, and time-sensitive surgeries are required in cases of traumatic optic neuropathy and retrobulbar hemorrhage [100]. Mandibular fractures are more common in children than adults and can result in challenging mask ventilation and airway management. The anesthesiologist should be prepared to deal with a difficult airway with the possibility of added challenges due to increased bloody oral secretions. If necessary, spontaneous ventilation should be maintained throughout the intubating process to avoid loss of the airway.

KEY POINTS: ANESTHETIC CONSIDERATIONS FOR SPECIFIC INJURIES

- Infants with open frontanelles and mobile cranial sutures can have intracranial bleed or swelling with delayed presentation of symptoms
- Initial hyperventilation is not recommended in pediatric TBI, and should be reserved for severe, refractory cases; neuromonitoring should be performed if hyperventilation is performed
- Abdominal trauma is most frequently managed non-operatively
- Younger children are at higher risk for spinal cord injury without radiological abnormalities, often not noticeable on CT radiography
- Compartment syndrome should be suspected in children with abnormally high narcotic requirements and pain disproportionate to injury

Child abuse and trauma

Inflicted injury, or traumatic injury resulting from child abuse, comprises approximately 8% of pediatric trauma. In 2012, in the United States alone, 2.2/100,000 children died from child abuse, 44% of whom suffered from physical injury. The 2012 rates of victimization per 1000 children were 14.2 for African-Americans, 12.4 for American Indian/Alaska Natives, 10.3 for multiracial, 8.7 for Pacific Islanders, 8.4 for Hispanics, 8.0 for non-Hispanic whites, and 1.7 for Asians [101]. A review of information from the National Trauma Data Bank found an increased prevalence of non-accidental trauma among males (58.3%). Non-accidental trauma is inversely related to age, and the majority of victims are under the age of 3 years. Children of poorer socioeconomic status are at greater risk, and 64.4% of these patients in this US data base were supported by Medicaid [102]. Non-accidental trauma patients demonstrated overall higher injury severity scores and mortality rates (8.9% versus 1.4%) [103]. Particularly concerning is the fact that up to a third of inflicted trauma cases are not recognized as being a result of abuse, with the miss rate higher at hospitals that do not have ACS verified pediatric trauma centers.

Indicators of inflicted trauma often found on patient history include prolonged interval between time of injury and presentation for medical care, history of multiple emergency room visits, and inconsistent history among parents and guardians. Physical exam indicators that raise suspicion for inflicted

Table 39.5 Association of inflicted trauma with physical exam findings

Highly associated inflicted trauma findings	Odds ratio	Confidence interval
Bruising in pre-mobile child		
Clustering of bruises	4.0	2.5–6.4
Petechiae	9.3	2.9–30.2
Chemical burns	24.6	4.94–13.5
Contact burns	5.2	1.6–22.9
Scald burns	17.4	6.4–7.2
Burns of hands	1.8	1.3–2.6
Burns of feet	6.3	4.6–8.6
Burns of buttocks	3.1	2.2–4.5
Burns of perineum	2.5	1.7–3.7
Subdural hematoma	8.2	6.1–11
Hypoxic ischemic injury	4.2	0.6–2.7
Retinal hemorrhage	14.7	6.4–33.6
Hollow viscous injury especially duodenal Injury <4 h	Unknown	

Source: Reproduced from Escobar et al [105] with permission of Wolters Kluwer.

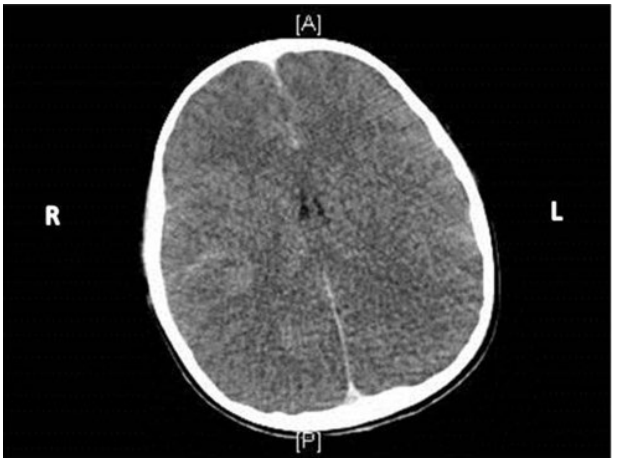

Figure 39.9 CT head without contrast in 1-year-old victim of "shaken baby syndrome" showing diffuse axonal injury with diffuse effacement of the sulci and slit-like ventricles.

trauma include injury disproportionate to history, multiple injuries that appear to be at different stages of healing, and injury mechanisms that are inconsistent with the child's developmental stage [104]. There are a number of very specific findings that are highly associated with inflicted trauma (Table 39.5). Type and pattern of bruising is an important clue, and an increased risk of inflicted trauma is associated with bruising in the pre-mobile child, clustering of bruises, bruises on the cheeks, neck, back, and areas not covering bony prominences, and the presence of petechiae. A large proportion of pediatric burns are due to abuse, most commonly chemical burns, contact burns, scald burns, and burns specific to the hands, feet, buttocks, and perineum. Moreover, inflicted TBI is highly associated with subdural hematomas, hypoxic ischemic injury, and retinal hemorrhage. Hollow viscous injury, in particular duodenal injury in children under the age of 4 years, is indicative of inflicted trauma [105]. Common fractures highly specific for inflicted trauma include rib fractures, metaphyseal corner fractures, scapula fractures, sternal fractures, and spinous process fractures, as well as fractures in children who are not yet walking [106].

More specifically, inflicted TBI is a leading cause of child abuse deaths and accounts for approximately one-third of all child maltreatment deaths [107,108]. Inflicted TBI is associated with skull fractures, subdural hematomas, subarachnoid hematomas, and diffuse axonal injury. Compared with accidental TBI, the incidence of malignant cerebral edema, hypoxic ischemic injury, and retinal hemorrhage is higher in inflicted TBI. While older children who are beaten suffer from more focal lesions, neonates tend to present with diffuse axonal injury due to "shaken baby syndrome" (Fig. 39.9) [67]. A study comparing inflicted to accidental TBI found that victims of inflicted TBI are more likely to be transported from home (60% versus 33.5%, $p < 0.001$), experience apnea (34.3% versus 12.3%, $p = 0.002$), and suffer from seizures (28.6% versus 7.7%, $p < 0.001$). The demographics of inflicted versus accidental TBI is also different. Inflicted TBI victims tends to be younger than accidental TBI victims (1.7 ± 0.32 versus 92.3 ± 0.39 years, $p < 0.001$) and, contrary to accidental TBI victims, inflicted TBI occurs with greater prevalence among females compared with males (54.3% versus 34.8%, $p = 0.032$) [109]. In the United States, healthcare providers are legally required to report cases where child abuse is suspected, which in most hospitals is facilitated through their social work department. Approximately 50% of maltreated children who die are victims of previous episodes of maltreatment that were not reported [24].

KEY POINTS: CHILD ABUSE AND TRAUMA

- Inflicted trauma is most common in pre-verbal children under the age of 3 years
- "Shaken baby syndrome" often presents as diffuse axonal injury
- Approximately 50% of child abuse victims who die are victims of previous episodes of maltreatment that were not reported

Postoperative management and ICU transfer

Pediatric patients who require operative procedures have a higher mortality risk and increased need for pediatric intensive care. Tracheal extubation criteria are similar in the pediatric population to those in adults. Tracheal extubation should be considered only in patients who are hemodynamically stable, do not have significant acid–base derangements, do not have significant oxygenation or ventilation derangements, possess adequate respiratory muscle strength, and demonstrate intact airway reflexes [110]. It is important, however, to note that longer cases and younger age increase the likelihood of early tracheal extubation failure following cardiac surgery [111]. Recent studies have shown that neuromuscular weakness is the most common cause of tracheal extubation failure in critically ill children [112–114].

Postoperative transport to the pediatric ICU (PICU) or other hospital locations (e.g. CT or angiography suites) represents a very vulnerable period in the care of critically ill children, and special caution must be taken to avoid unintended life-threatening mishaps. In many hospitals, the PICU

and radiology suites are significant distances from the operating rooms, which only increases the potential for such events to occur. When feasible, intraoperative CT scanning may reduce the need for transport and transport-related complications. Spine precautions should be carefully adhered to during the transfer of the patient from one bed to another. Careful attention must be paid to avoid inadvertent loss of venous and arterial access. Constant surveillance of the patient's ABCDs should be performed, and monitoring of vital signs using a transport monitor should be continuous. Transport equipment should include an appropriately sized mask, equipment for reintubation, resuscitative medications and muscle relaxants, and an ambu bag with a positive end expiratory pressure valve, even in patients who are transferred on transport ventilators. En route end-tidal CO_2 monitoring should be standard of care. For neurotrauma patients with external ventricular drains, special attention should be paid to ensure that the drain is appropriately leveled if it is kept unclamped during transport. Both clamped and unclamped external ventricular drains should be transduced during transport, so that the ICP can be monitored frequently or continuously. There should be a readily accessible line connected to IV fluids in the event that further fluid resuscitation or medications need to be administered during transport. If the patient is dependent on large doses of vasopressors to maintain hemodynamic stability, it is recommended that a dedicated carrier line is in place to infuse cardiovascular supportive medications, as small interruptions or boluses of these medications can prove catastrophic. Warming is of utmost important as hypothermia is a common problem during ICU transport, and patients should be wrapped in warmed blankets with special attention paid to their heads. It may also help to wrap them in plastic to decrease heat loss.

Hand-off report in the ICU should be performed in the presence of the primary anesthesiology and surgical teams, the responsible PICU physicians, nurses, and respiratory care team to facilitate accuracy of information and promote continuity of care. Hand-off should include the patient's history, summary of trauma burden, and a detailed summary of intraoperative events. If the patient shows signs and symptoms of pulmonary injury, often caused by trauma-related lung injury, transfusion-related lung injury, aspiration, and infection, lung protective ventilator strategies should be employed. Lung protective ventilation involves avoiding baro- and volutrauma by maintaining tidal volumes at 6 mL/kg and using increased positive end expiratory pressure to optimize oxygenation; permissive hypercapneia may be necessary. If pulmonary injury is severe such that these strategies are not effective, extracorporeal membrane oxygenation may be necessary. Once in the PICU, monitoring for ongoing or undiscovered sources of bleeding should be continuously performed. Observation for the presence of additional fractures should also be conducted as distracting fractures or decreased communicability of children can lead to initially undiagnosed fractures. The development and implementation of PICU guidelines for trauma patients is likely to prove important for the adherence to evidence-based guidelines of care and improving outcomes. Implementation of an institutional standard pathway for PICU management of pediatric patients with TBI increases adherence to evidence-based guidelines, which has been associated with improved discharge outcomes [115].

KEY POINTS: POSTOPERATIVE MANAGEMENT AND ICU TRANSFER

- Continuous end-tidal CO_2 monitoring should be performed during the transport of mechanically ventilated patients
- Monitoring for signs and symptoms of undiscovered sources of bleeding is critical once a trauma patient is in the ICU
- Continued observation for the presence of additional, previously undetected fractures and injury is a priority in the ICU; a distracting injury or decreased communication ability of children can increase the likelihood of undiagnosed fractures and injury

Education and outcomes in pediatric trauma

Emphasis in pediatric trauma is increasingly focused on prevention, as data consistently demonstrate that a majority of fatal and non-fatal injuries in the pediatric population is preventable [116]. US government-funded programs include the National Institute of Child Health and Development Pediatric Trauma and Critical Illness Branch, which supports research and training focused on the prevention and treatment of childhood trauma, injury, and critical illness. Moreover, a section of the CDC is focused on child safety and injury prevention and contains nine funded organizations in the United States. The National Action Plan for Child Injury Prevention was created with the goals of raising awareness about child injury and highlighting prevention solutions, including the reduction of fire and burn injuries, drowning, fall-related injuries, motor vehicle-related injury, sports- and recreation-related injuries, suffocation injuries, and poisoning injuries. The center is also focused on mobilizing action on national and local levels towards the reduction of child injury [117]. While campaigns for increased awareness and safety measures regarding proper use of protective equipment such as helmets, proper seatbelt usage, and concussion awareness have been effective, resources for these campaigns are limited and are not equally distributed across all socioeconomic groups. The limitations in funding for injury prevention occur mostly in the lower income group, where disparities in pediatric trauma is very prevalent [118].

The continued development and improvement of a system-wide data collection system (i.e. registry) that aims to identify and monitor pediatric trauma care quality metrics is integral to improving quality of care and evaluating specific in-hospital care processes associated with changes in clinical outcomes [21,119]. Furthermore, TBI has been shown to have longstanding effects on behavioral, cognitive, and psychosocial outcomes of children [120,121]. Children who have experienced trauma are predisposed to suffering from post-traumatic stress disorders [122,123]. Concomitant research focusing on factors that affect post-trauma long-term outcomes, such as issues of mobility, behavior, cognition, and psychiatric well-being, is imperative to improving pediatric trauma care.

CASE STUDY

Our patient is a 1.5-year-old, previously healthy male who reportedly suffered from a ground level fall one day prior. Per reports, he was in his usual state of health until the following day when when he was found down and unresponsive. His caregiver called emergency medical services and started performing cardiopulmonary resuscitation. Upon arrival, paramedics found the patient to be posturing with a GCS score of 5, a blood pressure of 49/20, and a heart rate of 155. He was intubated in the field with a 4.0 mm cuffed tracheal tube, and a 22 gauge IV was placed into his right arm. He was placed on a backboard, and his cervical spine was stabilized with a cervical collar. During transport, he was given 120 mL of IV fluid and ephinephrine. Per his father, he had no pertinent past medical history, normal growth and development, and no known allergies.

Initial assessment in the emergency room revealed a blood pressure of 110/56, heart rate of 146, and oxygen saturation of 95% on 100% oxygen. He was estimated to be approximately 12–14 kg according to estimation using a Broselow tape. A neurological examination revealed a GCS score of 5. Physical examination revealed left flank hematoma but no other abnormalities. An additional 22 gauge IV was placed into his left arm and laboratory values including a complete blood count, emergency hemorrhagic panel, basic metabolic panel, and type-and-screen were undertaken. The on-call neurosurgery resident was called, and because of concern for intracranical hypertension, the patient was sent to the CT scanner for a head, abdomen, and pelvis scan.

A preliminary read of the CT scan reported a right occipital skull fracture and an epidural hematoma. CT also revealed fluid surrounding his left kidney and a previous non-displaced femur fracture. Imaging of his chest revealed bibasilar pleural effusions versus consolidations, possibly due to aspiration. There was no evidence of cervical, thoracic, or lumbar spine injury. Laboratory results were significant for a lactate of 3.9, increased aspartate aminotransferase and alanine aminotransferase, hematocrit of 31, and INR of 1.5. A 10 Fr Foley catheter was placed revealing non-bloody urine, and the patient was given a 65 mL bolus of mannitol before being sent to the PICU for further monitoring.

On arrival at the PICU, the patient's ICP was 18 mmHg, but over the course of the hour began to increase to the high 20s. A repeat CT scan revealed an interval increase of right subdural fluid collection measuring 11.8 cm, now associated with a 6 mm leftward midline shift with subfalcine herniation of the right frontal lobe and diffusedly effaced cortical sulci. The CT report noted concern for older blood present in addition to the acute bleed, raising concern for more than one head injury. The neurosurgery attending consulted the pediatric anesthesiology attending, and the patient was sent immediately to the OR for emergent craniotomy.

The patient arrived at the OR with a blood pressure of 79/53, heart rate of 138, and oxygen saturation of 78–95%. Of note, he had begun to have periods of rapid oxygen desaturation with decreased pulmonary compliance. In the OR, the anesthesiologists attached the patient to monitors, administered 20 mg of IV rocuronium, and connected the patient's endotracheal tube to the ventilator. His end-tidal CO_2 was 30 mmHg. He was given 20 μg of IV fentanyl and 0.5 mg of IV midazolam and 400 mg of IV cefazolin. A 20 gauge angiocath was placed into his left saphenous vein. IV fluids connected to a fluid warmer were connected to the saphenous IV line. A 22 gauge left radial arterial line was placed using ultrasound guidance. The blood bank was called, and 3 units of cross-matched packed red blood cells, 3 units of fresh frozen plasma, and 1 unit of platelets were brought to the OR. An arterial blood gas revealed a $PaCO_2$ of 45 mmHg, PaO_2 of 70 mmHg, and a hematocrit of 29%. The anesthesiologist increased the minute ventilation, and attempted gentle recruitment of the lungs, which sounded rhonchorous bilaterally. The patient was given a 100 mL bolus of plasmalyte through the fluid warmer and boluses of phenylephrine were administered to maintain mean arterial blood pressures above 70 mmHg. A third intravenous line – an 18 gauge angiocatheter – was placed in his right antecubital vein using ultrasound guidance.

Once the sterile drapes were secured, an under body and lower body air-warming blanket was turned on. The patient maintained his blood pressure with intermittent 1–2 μg/kg phenylephrine boluses during initial incision. An infusion of 1 unit of packed red blood cells and 1 unit of fresh frozen plasms was initiated. However, upon opening of the dura, his blood pressure fell precipitously to the 50s/30s. The anesthesiologist communicated with the surgeon who responded that they were noting brisk bleed. Pressure bags were used to administer fresh frozen plasma and packed red blood cells that were wide open. An epiphephrine drip was started at 0.05 μg/kg/min. The blood bank was asked to bring additional products as well as platelets to the OR. The neurosurgeon noted that the patient appeared to have a massive laceration of his transverse sinus and pulsating arterial subdural bleed. Massive transfusion of packed red blood cells, fresh frozen plasma, and platelets continued to be administered at a 1:1:1 ratio as well as boluses of epinephrine and calcium. The patient received a total of 1 L of packed red blood cells, 1 L of fresh frozen plasma, and 300 mL of platelets. Tranexamic acid was not considered because of the prolonged time since initial injury. In spite of several attempts to achieve hemostasis, the intracranial bleed could not be controlled. The decision was made to close the skull, after which the patient's blood pressure increased to 126/85 and his heartrate decreased to the 60s, consistent with Cushing's reflex. An intraoperative head CT revealed continued increasing subdural hematoma. An ICP monitor was placed revealing intracranial pressures in the 50s.

The patient was brought up the PICU using a transport ventilator, and transport monitoring including monitoring of his heart rate, blood pressure by arterial line transducer, ECG, pulse oximeter, end-tidal CO_2, and ICP. Warmed blankets were wrapped around his entire body as well as his

head. ICU hand-off included the attending and resident anesthesiologists, neurosurgery team, PICU attending and resident, PICU nurse, and respiratory therapy. In the PICU, muscle relaxation was reversed so that a neuro exam could be performed. The patient had fixed, dilated, pupils, no corneal or gag reflexes, and no notable extremity response to noxious stimuli. Medical management of his ICP was continued using hyperosmolar therapy with 3% sodium chloride. A femoral central line was placed under ultrasound guidance, and an epinephrine drip was titrated to maintain goal MAPs above 90 mmHg. EEG monitoring revealed profound generalized slowing and voltage attenuation that worsened over the course of the course of the next 2 days. Because of his refractory intracranial hypertension, cooling to 35°C was initiated. Hourly neurological examinations revealed no improvement, and on postop day 3, transcranial Doppler was performed, revealing low velocities.

The social worker, who had been consulted on admission by the emergency department team for suspicion of child abuse, discovered that the child had been dropped, and in spite of subsequent daytime sleepiness, had not been brought immediately to the hospital until he became unresponsive 1 day after the injury. A review of the patient's x-rays concluded that the non-displaced femur fracture occurred prior to this injury and was highly suspicious for prior occurrence of child abuse. The patient's half-sibling was removed from the home and placed in foster care as the investigation continued. The patient was declared brain dead and medical management was discontinued on hospital day 3.

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 40
Anesthesia for Burns

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Introduction

Burn injuries are an important cause of morbidity and mortality in the pediatric patient and have many important implications for anesthetic care. The pediatric age group comprises 30% of all burns in the United States [1] and generates medical costs exceeding 2 billion dollars per year [2]. The most common cause is fire or flame injuries in all children, except for children under 5 years, where scald injuries are the most common cause [1]. Other types of burn include electrical burns, which usually cause tissue destruction by direct thermal damage and associated injuries, and chemical burns, whose severity depends on the chemical, its concentration, and the duration of exposure [3].

The severity of burn injury is characterized by the depth and location of the burn, the total body surface area (TBSA) involved, and the presence or absence of inhalational injury. The definitions of a major burn injury are summarized in Box 40.1. It is important to note that severe burns in infants and neonates occur with a smaller TBSA due to the immaturity of their organ systems and the subsequent difficulty maintaining homeostasis [4].

Estimation of the TBSA affected is a crucial aspect of the care of the burned child, as inaccurate estimates can lead to inappropriate resuscitation [5,6]. Because a child's head size is disproportionately larger than the body in comparison with adults, the traditional rule of nines does not accurately approximate TBSA in children. A tool for approximation of TBSA in children of various ages is shown in Figure 40.1.

Pediatric burn patients present many anesthetic challenges, such as difficult airways and vascular access, fluid and electrolyte imbalances, altered drug pharmacokinetics and requirements, and impaired thermoregulation, among others. The anesthesiologist may participate in the care of these critically ill children during initial resuscitation, operative procedures, and in the intensive care unit. The relevant pathophysiological and pharmacological changes that result from burn injuries as well as guidelines for intraoperative management and pain control are discussed in this chapter.

Pathophysiology

The skin serves as a barrier to protect the host from infection as well as heat and fluid losses, and, predictably, the destruction of this barrier by burn injury leads to infection and altered heat and fluid regulation. These changes are especially marked in children, given their high surface area to mass ratios.

A major burn injury also leads to the release of local and systemic mediators of inflammation. Local mediators, which include prostaglandins, leukotrienes, bradykinin, nitric oxide, histamine, and oxygen free radicals produce both localized and systemic capillary leak with resultant edema [7]. Systemic mediators, which include interleukin (IL)-1, IL-6, IL-8, IL-10, and tumor necrosis factor α (TNF-α), cause a systemic inflammatory response almost immediately after a burn injury [8]. This milieu of proinflammatory cytokines leads to the release of stress hormones that eventually create a hypermetabolic state, which begins 3–5 days postinjury [9] and correlates in magnitude with burn size[10].

Ultimately, a severe burn injury causes a pattern of pathological changes in all organ systems, which can be divided into the acute phase, which resolves within 24–48 h, and the hypermetabolic or late phase, which persists for much longer. These changes are discussed below and summarized in Table 40.1.

Cardiovascular

During the acute phase of burn injury, patients have a transiently decreased cardiac output due to hypovolemia and decreased venous return, depressed myocardial function, increased blood viscosity, and increased systemic vascular resistance from the release of vasoactive substances [8]. Patients with severe burns develop shock primarily due to

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

hypovolemia from the loss of intravascular volume and extravascular edema [10,11] as well as direct myocardial depression from the inflammatory response; they may also develop overt ventricular failure [12].

During the hypermetabolic phase, cardiac output increases dramatically and systemic vascular resistance decreases, and patients may develop persistent tachycardia and systemic

Box 40.1: Definitions of major burn injury

- Greater than 10% TBSA of third-degree burns
- Greater than 20–25% TBSA of second-degree burns
- Greater than 15–20% TBSA of second-degree burns in infants and neonates
- Burn injuries involving the face, hands, feet, or perineum
- Inhalational burn injuries
- Chemical or electrical burns
- Burns with associated trauma
- Circumferential burns, particularly chest
- Burns in children with significant co-morbid disease

TBSA, total body surface area.

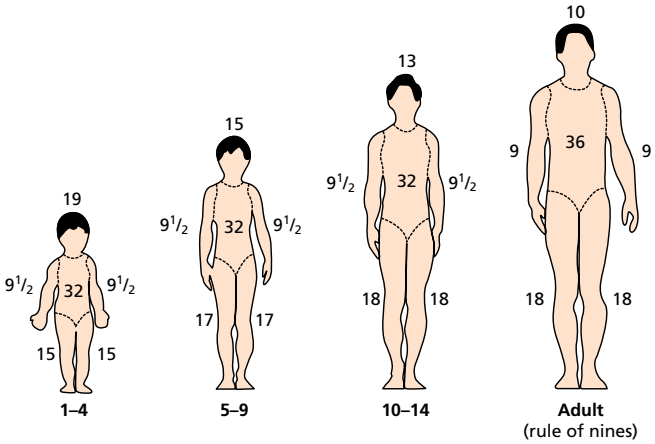


Figure 40.1 Approximation of total body surface area in children of various ages and in adults. The numbers beneath the figures denote age in years; the numbers adjacent to body areas indicate percent body surface areas. *Source*: Reproduced from Carvahal [200] with permission of Elsevier.

Table 40.1 Pathophysiological changes due to burn injury

	Early change	Late change
Cardiovascular	Hypovolemia	↑ Cardiac output
	↓ Cardiac output	Tachycardia
	↑ Systemic vascular resistance	Systemic hypertension
Pulmonary	Airway obstruction and edema	Chest wall restriction
	Pulmonary edema	Tracheal stenosis
	Carbon monoxide poisoning	Pneumonia
	Cyanide toxicity	Acute respiratory distress syndrome (ARDS)
Renal	↓ Glomerular filtration rate	↑ Glomerular filtration rate
	Myoglobinuria	↑ Tubular dysfunction
Endocrine and metabolic		↑ Metabolic rate
		↑ Core body temperature
		↑ Muscle catabolism
		↑ Lipolysis
		↑ Glycolysis
		↑ Futile substrate cycling
		↑ Insulin resistance
		Hyperglycemia
		↓ Thyroid hormones
		↓Vitamin D
		↓ Parathyroid hormone
Hepatic	Hypoperfusion	Hypoperfusion
	Cell apoptosis with ↑ AST, ALT, bilirubin	↑ Metabolism
	↑ Intrahepatic fat and edema	
	Impaired protein synthesis	
Gastrointestinal	↓ Perfusion with mucosal damage	Stress ulcers
	Increased gut permeability	Adynamic ileus
	Endotoxinemia	Acalculous cholecystitis
		Abdominal compartment syndrome
Hematological	Hemoconcentration	Anemia
	Hemolysis	Possible hypercoagulable state
	Thrombocytopenia	
Neurological	Cerebral edema	Hallucinations
	↑ Intracranial pressure	Personality change
		Delirium
		Seizures
		Coma

(*Continued*)

Table 40.1 (Continued)

	Early change	Late change
Infectious/immunological	Endotoxemia	Chronic immune dysfunction Burn wound infection Respiratory infection Bloodstream infection Urinary tract infection Endotoxemia Antibiotic-associated enterocolitis Infection with antibiotic-resistant organisms

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

hypertension [13]. There is some global evidence that prolonged stress responses can eventually lead to cardiomyopathy [8], although this has not been clearly demonstrated in burned children. However, there are data to suggest that children hospitalized for a burn may have an increased rate of cardiovascular disease for years after recovery and discharge, including an increased incidence of ischemic heart disease [14]. Medications such as propranolol have been studied and shown to reduce cardiac index and cardiac work in burned children during and after this hypermetabolic phase [8,13,15], which may allow for better preservation of muscle mass and strength [8]. Studies have not yet addressed whether such intervention reduces the long-term risk of cardiac events in these children.

Pulmonary

Recognizing inhalation injury in burned children is extremely important as it predicts increased resuscitation requirements as well as increased morbidity and mortality [16–18]. Pulmonary physiology is affected directly by this inhalational injury and indirectly by systemic effects of the burn, as well as independently by carbon monoxide poisoning and cyanide toxicity [19].

Direct Inhalation Injury

Pulmonary dysfunction from inhalation injury results from a variety of factors, including direct mucosal edema and sloughing, impaired mucociliary clearance, formation of endobronchial casts, inactivation of surfactant, and interstitial edema [20–22]. In general, only the upper airways (carina and above) are affected by direct thermal injury because the respiratory tract is an efficient heat exchanger; the exception to this is steam inhalation, which can cause damage more distally [23,24].

Inhalation injury should be suspected in patients with facial burns, singed nasal hairs, soot in the airway, stridor, hoarseness, dyspnea, or wheezing [25,26]. Clinically, these patients may develop stridor, laryngospasm or bronchospasm, pneumonia, tracheobronchitis, ventilation-perfusion mismatch, and increased pulmonary compliance. The diagnosis of inhalation injury is best confirmed by bronchoscopy (Fig. 40.2), with findings of mucosal erythema, edema, ulceration, and necrosis with or without carbon particles seen in the airway [27–29]. Chest radiography is often normal immediately following injury and is therefore less useful [25,26,30], but a computed tomography (CT) scan may show ground glass opacities, atelectasis, and consolidation suggestive of inhalation injury [31,32].

If inhalation injury is suspected or there are large burns to the face and neck, the most important element of treatment is early intubation, as massive edema of the tongue, uvula, epiglottis, and subglottic regions may make intubation more difficult or

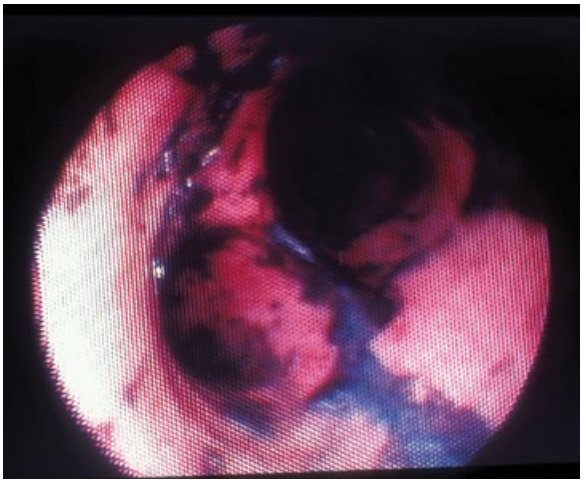
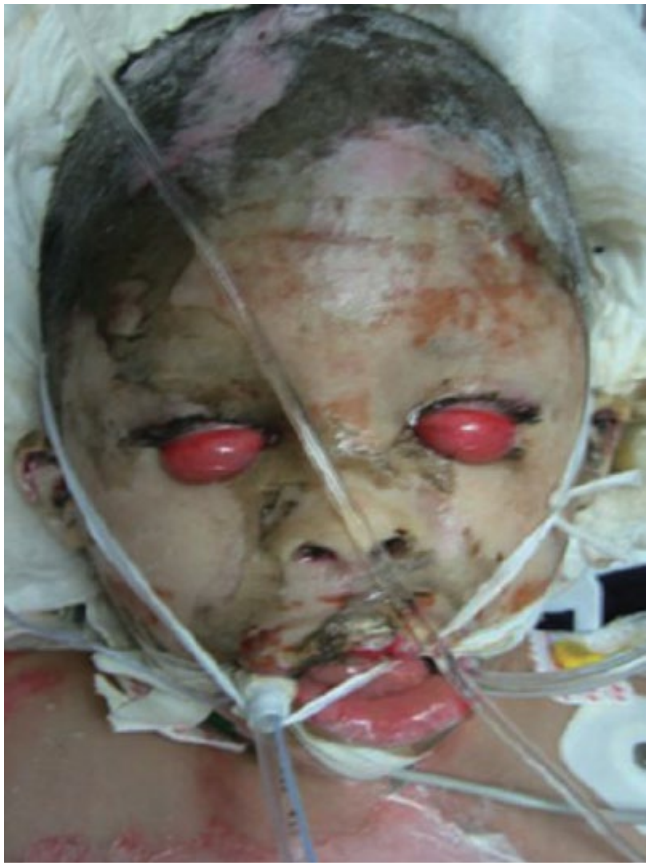


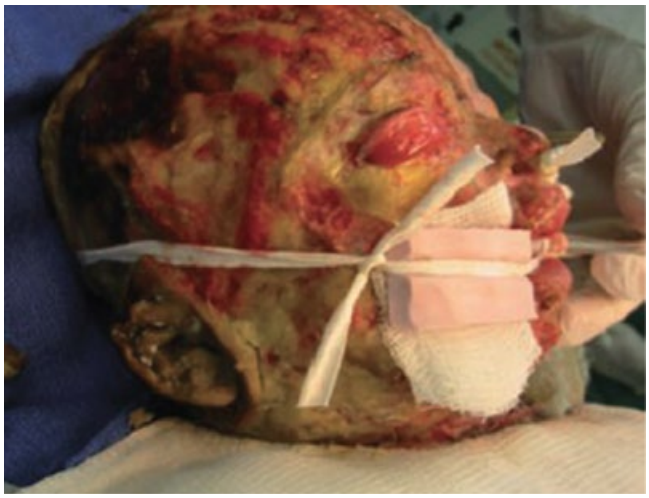
Figure 40.2 Bronchoscopy image showing a burned bronchus from inhalational injury.

even impossible if delayed (Fig. 40.3) [26]. The use of a cuffed endotracheal tube is preferred as the higher pressures required to ventilate the less compliant lungs of a burn patient may lead to circuit leaks. The subsequent need to exchange the endotracheal tube in an edematous and critically ill patient can prove quite dangerous, and is ideally avoided [33].

The initial 2–5 days after inhalation injury may allow for normal ventilation prior to the development of endobronchial slough and shunting. The literature generally suggests that ventilation of the child with inhalation injury should be approached with a lung-protective strategy that aims to minimize barotrauma with low tidal volumes and peak pressures [34,35], and potentially some degree of permissive hypercapnia [36]. However, it is worth noting that these recommendations are extrapolated from acute respiratory distress syndrome (ARDS) studies in adults, and the benefits of low tidal volume strategies have not truly been demonstrated in children [34]. There may even be some data to suggest that higher tidal volume ventilation may reduce the incidence of ARDS and total ventilator days in pediatric burn patients [37]. One alternative ventilation strategy is high-frequency percussive ventilation (HFPV), which delivers high frequency (450–600/min), subtidal bursts of gas over a conventional respiratory cycle, allowing for stepwise inflation of the lung [38]. HFPV is thought to facilitate evacuation of airway debris in patients with inhalation injury [37]. HFPV has been shown to decrease peak inspiratory pressures and work of breathing while improving oxygenation in children with inhalation injury [37–39], but has not been shown to improve major outcomes



(A)



(B)

Figure 40.3 Facial edema. (A) Marked facial edema in a burn patient. (B) The same patient after initial debridement. *Source*: Reproduced from Fidkowski et al [19] with permission of John Wiley and Sons.

such as pneumonia, time to extubation, or mortality [38]. In addition to intubation and mechanical ventilation when needed, supportive care for the patient with inhalation injury includes aggressive pulmonary toilet, including chest physical therapy, forced coughing, therapeutic bronchoscopy when appropriate, and, if possible, early ambulation [35,40].

Pharmacological therapy for pediatric patients with inhalation injury may include aerosolized albuterol, epinephrine, nitric oxide, and a heparin–N-acetylcysteine combination. Corticosteroids do not appear to improve pulmonary function in patients with inhalation injury [41]. As patients develop bronchitis and reactive airways, nebulized albuterol is an intuitive treatment. In an animal model, it has been shown to be effective in improving compliance and decreasing peak pressures, decreasing shunt fraction, and improving the arterial–alveolar oxygen gradient [42]. While there are no prospective human data in this context, it is a reasonable intervention. Aerosolized racemic epinephrine falls into a similar category; it can help by reducing mucosal edema via a localized vasoconstrictive effect, in addition to its bronchodilatory benefits [35], though data are largely based on animal studies [43,44]. Nitric oxide has also been shown to decrease ventilation/perfusion mismatch and improve oxygenation in children with inhalation injury [45]. However, survival benefit has not been demonstrated with nitric oxide, possibly due to the key limitation of small sample sizes. A combination of nebulized N-acetylcysteine with heparin, attempting to prevent airway cast formation by antagonizing fibrin production, has been shown to reduce reintubation rates and mortality in children with inhalation injury [46]. A recent meta-analysis also found that such inhaled anticoagulant regimens improved survival and decreased morbidity without causing systemic anticoagulation [47].

Overall, evidence supporting the use of these pharmacological adjuncts generally comes from small studies or animal data, and they are therefore difficult to recommend empirically. However, they do appear to have some effectiveness with little harm, and at the very least provide useful rescue strategies for more complex children with inhalation injury. Box 40.2 shows a sample protocol used at the Shriner's Hospital in Galveston, Texas to treat inhalational injury.

Carbon monoxide poisoning

Carbon monoxide (CO) poisoning should be suspected in any child with inhalational injury or burns from open fires. Carbon monoxide impairs tissue oxygenation by displacing oxygen from hemoglobin, shifting the oxygen dissociation curve to the left and decreasing oxygen delivery, and binding to cytochromes to disrupt cellular metabolism [48,49]. Carbon monoxide poisoning is suspected clinically and confirmed by elevated carboxyhemoglobin levels on co-oximetry. The oxygen saturation will be inaccurate and typically reads 100% due to the conventional pulse oximeter interpreting carboxyhemoglobin as

Box 40.2: Inhalation injury treatment protocol

- Titrate humidified oxygen to maintain saturation >90%
- Cough and deep breath exercises every 2 h
- Turn patient side to side every 2 h
- Chest physical therapy every 4 h
- Aerosolize 3 mL of 20% N-acetylcysteine every 4 h with a bronchodilator
- Alternate aerosolizing 5000 units of heparin with 3 mL normal saline every 4 h
- Nasotracheal suctioning as needed
- Early ambulation on postoperative day 5
- Sputum cultures for intubated patients every Monday, Wednesday, and Friday
- Pulmonary function studies prior to discharge and at outpatient visits
- Patient/family education regarding inhalation injury

The protocol is continued for 7 days.

Source: Reproduced from Mlcak et al [35] with permission of Elsevier.

oxyhemoglobin [49–51]. However, new pulse oximeters are available that can detect carboxyhemoglobin, and these may be useful for diagnosis and monitoring treatment [52–54]. Presenting symptoms depend on the carboxyhemoglobin level: from nausea and headaches with mild CO poisoning (<20% carboxyhemoglobin) to seizures, coma, and cardiac arrest with severe poisoning (60–70% carboxyhemoglobin) [49].

The most important treatment for CO poisoning beyond supportive care is 100% oxygen, which should be initiated immediately if there is any suspicion of CO poisoning. This reduces the half-life of carboxyhemoglobin from 240–320 min at room air to 40–80 min when breathing 100% oxygen [49]. Treatment with hyperbaric oxygen is controversial and not well studied in burn patients, but hyperbaric treatment is known to further reduce the half-life of CO and may have some immunomodulatory benefits [55]. As such, after thorough consideration of the patient's other injuries and treatment needs, hyperbaric oxygen can be considered in hemodynamically stable patients with severe CO poisoning symptoms such as loss of consciousness, neurological symptoms, or ongoing acidosis.

Cyanide toxicity

Cyanide toxicity should be also be suspected in any child with inhalational injury, as cyanide can be released from the burning of plastics and glues in a fire [23,56,57]. Cyanide impairs tissue oxygenation by disrupting cellular metabolism [58–60], and will frequently present as an elevated venous oxygen level and refractory lactic acidosis. Definitive diagnosis is with a serum cyanide level, but this will likely not be determined quickly and if there is clinical suspicion, treatment decisions should not await the result. However, empirical treatment for possible cyanide exposure for burn patients without evidence of toxicity is not generally recommended in children [59].

Cyanide toxicity can be treated with sodium thiosulfate, the vitamin B12 precursor hydroxocobalamin, or nitrites such as amyl or sodium nitrite. Thiosulfate serves as a sulfate donor, which augments the intrinsic detoxification of cyanide to thiocyanate [58,59], while hydroxocobalamin binds intracellular cyanide to form the non-toxic cyanocobalamin (vitamin B12) [59,61]. Nitrites work by increasing the concentration of methemoglobin available for binding cyanide [58,61–63], but this may be dangerous in inhalation injury patients given coexisting carboxyhemoglobinemia. Moreover, young children are especially sensitive to methemoglobinemia as fetal hemoglobin converts more readily to methemoglobin and they have lower levels of methemoglobin reductase activity compared with adults [58]. As such, treatment with hydroxocobalamin may be preferred in children with smoke exposure given the absence of increased methemoglobin production and the rapid onset of action [59].

Renal

During the acute phase of burn injury, the glomerular filtration rate is decreased due to hypovolemia, decreased cardiac output, and the compensatory increased vascular tone from circulating catecholamines, vasopressin, and upregulation of the renin–angiotensin–aldosterone system [64]. As the hypermetabolic phase develops and cardiac output increases, the glomerular filtration rate also increases, but tubular dysfunction may occur in some patients and the degree of renal injury is variable from patient to patient. It is also important to note that patients with electrical or crush injuries are at increased risk of renal failure due to rhabdomyolysis and myoglobinuria [65].

Endocrine and metabolic

The hypermetabolic state that arises 24–48 h after a burn injury is the result of several mediators, including catecholamines, vasopressin, renin, angiotensin, aldosterone, glucagon, and cortisol. The magnitude of the hypermetabolic response is proportional to burn size [10,66] and is characterized by increased energy expenditure, core body temperature, muscle catabolism, lipolysis, glycolysis, futile substrate cycling, and insulin resistance [67–69]. While it was initially thought that this hypermetabolic state resolved with wound closure, there is evidence that it persists beyond this period and gradually returns to baseline during the subsequent 9–12 months postinjury [70].

One of the most important consequences of the hypermetabolic state is hyperglycemia resulting from the corticosteroid surge, reduced glucose extraction from the blood by muscle tissue, and insulin resistance [71]. Hyperglycemia in pediatric burn patients is associated with an increased rate of infections, greater catabolism, skin graft loss, and mortality [71]. Intensive insulin therapy has been shown to improve lean body mass and reduce rates of infection and multiple organ failure in burned children, but vigilance is needed to prevent hypoglycemic episodes [72,73]. Because hypoglycemia carries its own risks of morbidity and mortality [74], a blood sugar in the range of 130–150 mg/d has been suggested as a range that balances the risks of hyper- and hypoglycemia [72].

One alternative to intensive insulin therapy that is beginning to be studied is exenatide, an incretin-based drug. Because exenatide requires a hyperglycemic state in order to be effective, the risk of hypoglycemia is low, and there may be other benefits such as some protection against ischemia–reperfusion injury [75]. Studies thus far have only shown a reduction in total insulin administered when exenatide and insulin were combined, but data are not yet sufficient to determine if any outcomes are improved [75].

Other endocrine derangements include decreased levels of thyroid hormones (T3 and T4) and vitamin D [76–78], secondary to acquired hypoparathyroidism [79]. The resultant hypocalcemia and hypomagnesemia can lead to adverse cardiovascular effects and should therefore be aggressively treated in these children.

Attenuating the global hypermetabolic response is an ongoing topic of research; potential benefits of doing so include reduced cardiac work and stress, greater preservation of lean body mass and bone density, improved insulin sensitivity, and better overall growth [8]. Non-pharmacological approaches to inhibiting the hypermetabolic response include early excision and wound closure, aggressive treatment of sepsis, high protein and carbohydrate enteral feeds, environmental temperature elevation, and a resistive exercise program [9]. The best-studied pharmacological agents that may reduce hypermetabolism include insulin [80], the anabolic steroid oxandrolone [81–84], and propranolol [8,13,15,85].

Hepatic

During the acute phase of burn injury, hepatic injury and cell apoptosis result from hypoperfusion, ischemia–reperfusion

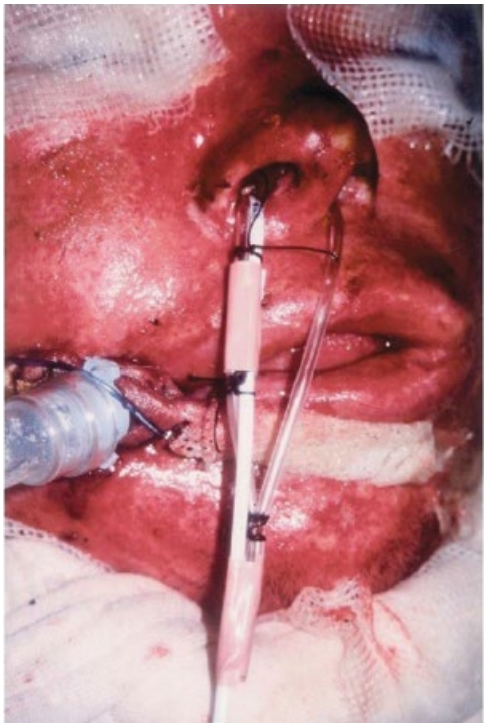


Figure 40.4 Nasojejunal tube secured with a nasal sling in a patient with facial burns. *Source*: Reproduced from Sefton et al [137] with permission of Elsevier.

injury, and circulating inflammatory cytokines [86]. Clinically, the liver enlarges and protein synthesis is impaired. This injury is reflected in elevated transaminases and bilirubin, which are typically elevated immediately postburn and return to normal over the subsequent 2–6 weeks [86]. Other pathophysiological changes include hepatic enlargement due to intrahepatic fat and edema, a decrease in the hepatic proteins albumin and transferrin, and an increase in acute phase reactants, haptoglobin, C-reactive protein, and complement. These latter changes can persist for up to 6–12 months postinjury.

Gastrointestinal

Hypoperfusion, ischemia–reperfusion injury, and circulating inflammatory mediators also damage the gut, weakening its mucosal barrier and allowing for entry of bacteria and endotoxins [87]. Additionally, patients are at high risk for ileus due to the edema from resuscitation, and for additional constipation due to opioids and sedatives [88]. However, this is not a contraindication to enteral feeding in the acute period (Fig. 40.4). On the contrary, in addition to reducing the risk of malnutrition, early enteral nutrition has been shown to reduce mucosal damage and ileus development, and to decrease endotoxinemia and TNF-α levels, thereby reducing the inflammatory and hypermetabolic responses [88]. Early enteral nutrition has also been shown to significantly reduce hospital length of stay and mortality [89]. While definitions of "early" for nutrition vary in the literature, within 6–12 h of injury is considered very early and ideal [88]. Inadequate feeding can lead to delayed wound healing and other causes of morbidity, including immunosuppression, sepsis, and loss of lean body mass [90].

Burn patients are at risk for developing gastric and duodenal stress ulcers, which may lead to gastrointestinal bleeding. Prophylactic treatment with H_2-antagonists or proton pump inhibitors may be beneficial, in addition to early feeding [88,91]. Patients can also develop acute enterocolitis, acalculous cholecystitis, or adynamic ileus requiring gastric decompression [92].

Abdominal compartment syndrome (ACS) is also an important consideration in burned children, and is routinely fatal if untreated [93]. ACS consists of elevated intra-abdominal pressures, typically a bladder pressure above 25 mmHg, with associated organ dysfunction, including reduced pulmonary compliance, oliguria, or hemodynamic instability [93,94]. The increased pressures result from decreased abdominal compliance, ascites, and bowel edema from capillary leak and ischemia–reperfusion injury. Large fluid resuscitation volumes are associated with ACS, likely by contributing to ascites and bowel edema [95,96]; in particular, resuscitation greater than 237 mL/kg over 12 h was identified as a threshold value for development of ACS [96], although this is certainly not absolute. Treatment for ACS is usually open decompression of the abdomen, which markedly reduces mortality associated with ACS [93].

Hematological

Acutely, systemic edema and intravascular volume depletion lead to hemoconcentration, which increases the hematocrit and blood viscosity. However, after initial resuscitation, anemia develops as a result of blood loss at wound sites, dilution from resuscitation, and hemolysis from heat-damaged erythrocytes [97]. In the absence of other illness, patients can likely tolerate a relatively low hematocrit in the 20–25% range, but it may be desirable to target a higher level in severely burned children to mitigate further drops from ongoing blood loss.

Thrombocytopenia can also occur due to platelet aggregation at wound sites, as well as sepsis, dilution, and medication effects[98]. Greater thrombocytopenia is associated with increased mortality in burn children [98]. A compensatory increase in clotting factor production may then occur, leading to a hypercoagulable state and possibly even disseminated intravascular coagulation [97,98].

Neurological

A number of different neurological sequelae can develop in the burned child. Elevated intracranial pressure can occur due to cerebral edema [99]. Seizures may occur, most commonly due to fever or hyponatremia [100], but other risk factors include a history of epilepsy, hypoxia, and sepsis [100,101]. Hypertensive encephalopathy can also develop, and is one of the rarer causes of seizures [102]. Electrical burn patients may additionally manifest direct spinal cord damage [103,104] or brain injury [105], depending on the entry and exit sites of the electric current.

Additionally, severely burned children can develop burn encephalopathy, a syndrome that includes personality change, delirium, hallucinations, seizures, and coma. Its incidence may be as high as one in seven severely burned children [105,106]. The most common causes of encephalopathy are hypoxia, followed by sepsis, hyponatremia, hypovolemia, and cortical vein thrombosis [106]. Although our understanding of neurological outcomes is far from complete, the majority of children who manifested burn encephalopathy made good neurological recoveries [106,107]. However, if there is a hypoxic insult associated with the burn injury, more recent data suggest that there may be up to a 33% chance of long-term cognitive deficits and emotional difficulties after recovery [107].

Immunological

Burn patients are especially vulnerable to infections for multiple reasons, including the loss of the skin barrier, the presence of multiple invasive lines for prolonged periods, hyperglycemia [108], prolonged ventilation [91], dysfunction of immune cells [92], and critical illness. Indeed, infections are the leading cause of morbidity and mortality in burn patients [109,110], and it is thought that 75% of all deaths following burn injuries are related to infection [111]. Important pathogens include gram-positive and -negative bacteria and fungi [109]. Multidrug-resistant bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* are particularly important agents in burned children, and may require special consideration in selection of antibiotics [91,109,112]. In addition, *Clostridium difficile* infection should be considered in patients with excessive diarrhea, and is associated with increased mortality in pediatric burn patients [113]. However, the use of prophylactic antibiotics is not currently recommended for pediatric burn patients [111,114]. Evidence also suggests that perioperative antibiotics do not seem to reduce the incidence of graft or donor site infection, though they remain common practice [92,111].

KEY POINTS: PATHOPHYSIOLOGY OF BURN INJURY

- Burns result in inflammation that affects every organ system, beginning with an acute 24–48 h phase that develops into a much longer lasting hypermetabolic phase
- Burn patients may initially present in severe hypovolemic and distributive shock, requiring aggressive resuscitation and/or vasopressor support
- With inhalation injury, edema may make it difficult to secure the airway; carbon monoxide poisoning or cyanide toxicity may also occur
- Early enteral feeding decreases morbidity and mortality, and should be practiced whenever possible
- Burn patients are at risk for infections from loss of the skin barrier and dysfunction of the immune system. Infection is the leading cause of mortality in burn patients

Fluid resuscitation in the acutely burned patient

Acute burn injury is accompanied by a tremendous inflammatory response that can cause significant fluid shifts [96]. Beyond this, children have even more significant evaporative and insensible loss of fluid than adults, due to their higher body surface area to mass ratios [115]. Profound hypovolemic and distributive shock can result, making appropriate resuscitation of the burned child crucial to acute management. However, there are a number of different formulae and approaches to resuscitation, with significant controversy as to which formula best approximates fluid needs and which fluid should be used, from the type of crystalloid to whether albumin or plasma should be included.

The Parkland formula remains the most widely used tool to approach the initial resuscitation of burned children [94,96,116–118], preferred by 69% of respondents surveyed at the American Burn Association meeting in 2009 [119]. The Parkland formula estimates resuscitation requirements at 4 mL/kg/%TBSA burned per 24 h; half of this is given in the first 8 h, and the remaining half in the subsequent 16 h. The fluid used is typically lactated Ringer's and, in children, is often added to the hourly maintenance requirement to account for the additional fluid losses observed in smaller patients. The modified Brooke formula is also sometimes used, albeit less frequently [119]; this predicts 2 mL/kg/%TBSA fluid volumes for resuscitation [120] given over a similar timeframe as the Parkland formula volume. Other approaches are also being developed and tried, such as nurse-driven protocols or computer-based algorithms that aim to adjust resuscitation rates based on urine output and/or hemodynamic parameters [96], but these are not in widespread use.

The choice of fluid used for resuscitation is an important one. In earlier work, colloid (particularly plasma) was considered an essential part of resuscitation using the Parkland formula. However, colloid was omitted from some recent iterations of the Parkland formula, perhaps in light of studies suggesting that it provided no outcome benefit over crystalloid, and even one review (in critically ill patients, including a small number of burn patients) that suggested that it may increase mortality [96,118]. The relative underuse of colloid is one proposed reason for the recent observation that many patients were requiring resuscitation volumes far in excess of what the Parkland formula predicted, an observation termed "fluid creep" [96,117,121–124]. This observation has led to a renewed interest in colloids and an increase in the use of albumin in resuscitation [118].

The use of colloid in burn resuscitation remains an area of controversy, including whether its use confers any benefit at all, and if so, when it is appropriate to initiate colloid therapy. Animal studies have shown that the use of colloids does not reduce the formation of burn wound edema, but does reduce edema formation in the non-burned soft tissue and reduces resuscitation fluid requirements without an increase in fluid accumulation in the lung [118]. Human data have also shown that the use of colloid reduces the overall volume of fluid needed to resuscitate burn patients [96,123]. Several studies have hinted at other benefits, including reduced edema formation, reduced mortality, reduced risk of extremity compartment syndrome, and reduced risk of renal failure [96,118,123]. However, the quality of evidence in these studies is relatively low, as many are retrospective cohort studies. Separately, several studies have documented an association between increased resuscitation volumes and complications such as ACS, extremity compartment syndrome, prolonged ventilator times, pneumonia, and sepsis [17,96,116,125–127], suggesting that there may be some benefit to reducing the overall volume of resuscitation. Overall, it is likely that there is some benefit to resuscitation with albumin, either as a rescue in case of escalating crystalloid requirements, or as a routine part of resuscitation, but studies thus far have been underpowered to find any significant benefits. Further research on this important topic is needed.

The traditional endpoint of resuscitation has been urine output of 0.5–1 mL/kg/h, up to 1.5 mL/kg/h in younger children [117]. However, in addition to standard hemodynamic variables, such as arterial blood pressure and waveform variation and central venous pressure, additional endpoints are

being used, such as cardiac output calculated by transpulmonary thermodilution (TPTD) [128]. One retrospective study of 76 children found that the cohort that had their fluid resuscitation adjusted based on cardiac output determined by TPTD was able to be resuscitated as well as the conventionally monitored group, with less overall fluid administered [126]. The benefit of TPTD is that it requires only a central line and not a pulmonary artery catheter; as these cardiac output monitors become more widely available, they will likely figure more prominently in resuscitation algorithms.

Other adjuncts to resuscitation have also been studied, such as high-dose ascorbic acid (vitamin C). As an antioxidant, it is thought that its benefit may stem from reducing the initial vascular permeability in the setting of inflammation. Despite concerns of potential renal toxicity [129], some recent data have shown vitamin C to reduce fluid requirements without significant side-effects [130]. This is not a widespread practice, though, so larger scale data are needed before vitamin C can be recommended routinely, particularly in children.

KEY POINTS: FLUID RESUSCITATION

- Aggressive fluid resuscitation remains the cornerstone of initial burn management, but there is controversy as to the best approach
- The most commonly used tool for initial fluid resuscitation is the Parkland formula: 4 mL/kg/%TBSA burned per 24 h; half of this is given in the first 8 h, and the remaining half in the subsequent 16 h
- The use of colloid is controversial, but is again gaining popularity in light of data on fluid creep and the dangers of over-resuscitation
- While urine output is commonly used as an endpoint for resuscitation, other means such as cardiac output monitoring and echocardiography are increasingly being used

Anesthetic management for acute burn procedures

Management of the pediatric burn patient presents many challenges for the anesthesiologist. Burned children may be critically ill with multiorgan dysfunction, and many aspects of their management, such as fluid resuscitation and temperature regulation, warrant even greater consideration than in the average child. However, despite how ill some of these patients may be, wound excision should not be delayed, as early excision has been shown to decrease blood loss, improve mortality, and decrease length of hospital stay [131–133]. This section discusses general considerations for the anesthetic management of pediatric burn patients in the acute perioperative setting.

Preoperative assessment and management

The preoperative assessment of the burned patient begins with an evaluation of the type of burn as well as the extent and depth, and any associated injuries. Patients with major burns or or burns of greater than 30% TBSA generally require formal fluid resuscitation and will develop some of the physiological derangements discussed earlier, while those with minor burns or or burns of less than 10% TBSA typically do not. However, in the presence of significant underlying medical illness, even patients with minor burns may require more aggressive treatment and resuscitation. As such, it is important to have a global understanding of the patient's overall physiological state, which can be understood by assessing parameters such as the patient's current hemodynamics and/or pressor requirements, pulmonary compliance and ventilator settings, volume status, and urine output.

The physical exam should include a thorough airway evaluation in order to identify patients with distorted airway anatomy who might be difficult to ventilate or intubate. Even if the patient is already intubated, the airway should still be evaluated as reintubation may occasionally be required due to a leak around the endotracheal tube or an unintended extubation. It is also important to note the locations of existing intravenous access and invasive monitors, and to identify potential sites for additional lines if needed.

Review of the burn patient's laboratory studies for electrolytes, complete blood count, coagulation studies, and metabolic and acid–base status is crucial. The patient should also have an active blood type and screen. In patients with inhalation injury, a chest x-ray may also be helpful. If there is suspicion of carbon monoxide poisoning or other inhalation-associated pathology, co-oximetry results should be evaluated.

Fasting guidelines and nil per os (NPO) guidelines warrant special consideration in burn patients, given their high metabolic needs. In general, enteral nutrition should be continued for as long as possible preoperatively. There are some data to suggest that a fasting period of 2 h for nasogastric tube feeds is adequate [134], but the data are limited [135] and there is some evidence that burn patients can develop gastric stasis [136,137]. As such, transpyloric feeds are preferred, as continuing them throughout the perioperative period does not appear to increase aspiration risk [136]. As a general rule, nasogastric feeding tubes should be placed to suction preoperatively, and then left to drain to gravity intraoperatively. Enteral nutrition is strongly preferred over parenteral nutrition because the latter is associated with altered gut physiology and increased permeability, a greater risk of sepsis, and increased mortality [138,139].

Transport to the operating room should be carried out with precautions appropriate to critically ill patients, including (as needed) a transport monitor and ventilator or bag–mask, and easy access to resuscitation medications and airway equipment. The decision to premedicate a child will depend on their mental status and degree of anxiety, as well as their hemodynamic and respiratory status.

Monitoring

The general principles of perioperative monitoring are no different for pediatric burn patients than for other pediatric patients, including standard American Society of Anesthesiologists (ASA) monitors and further invasive monitors as indicated by the patient's status. However, the logistics and details are frequently more complicated in burn patients.

Large areas of burn injury may make standard monitor placement difficult, and may necessitate creative electrocardiogram (ECG) lead placement or use of alternatives such as esophageal ECG monitoring [140]. Pulse oximetry on a finger or toe may be less reliable with extensive burn injury, hypothermia, or high-dose vasopressor use; alternative sites include the ear, buccal mucosa, tongue, and esophagus [141–143]. Temperature monitoring is especially important, as burn patients can lose heat quickly. An arterial line may be of benefit if large fluid shifts or blood loss are expected, or if extremity injuries preclude use of a blood pressure cuff. Central venous pressure and urine output may be used along with blood pressure to assess the patient's volume status and resuscitation needs, but may be less useful if there is intra-abdominal hypertension or ACS [93].

Intravenous access

The large fluid shifts and potential blood loss that accompany excision and grafting surgeries necessitate good intravenous access for fluid resuscitation. However, obtaining intravenous access in burn patients can be difficult if there is insufficient surface area left for the placement of lines. Central venous catheters are commonly used, but the catheter length and resistance limit the speed of fluid replacement when compared to shorter, larger bore peripheral catheters. In cases where intravenous access cannot be obtained but access is urgently needed, temporary intraosseous lines can be placed fairly rapidly and are an acceptable back-up [144].

Pharmacokinetics of induction and maintenance drugs

Burn injury results in altered pharmacokinetics of many anesthetic drugs due to changes in the volume of distribution, protein binding, and metabolism [145]. The volume of distribution increases because of the large extracellular volume resulting from capillary leak and fluid resuscitation. Protein binding is also altered as there may be increased α_1-acid glycoprotein and decreased albumin concentrations [9]. Drug metabolism is initially reduced due to renal and hepatic hypoperfusion, but during the hypermetabolic phase drug clearance is often greater than baseline.

In general, most conventionally used induction and maintenance agents are safe to use in pediatric burn patients, including propofol, thiopental, ketamine, potent inhalational agents, nitrous oxide, and opioids. Induction can be inhalational or intravenous, and if the patient's airway and clinical status are favorable this can even be done prior to moving the child to the operating table in order to reduce painful movement. If patients are too hemodynamically unstable to tolerate a potent inhalational anesthetic, a nitrous/narcotic technique with or without ketamine supplementation is often better tolerated.

The pharmacology of neuromuscular blocking agents is markedly altered in burn patients. Burn injury causes a significant upregulation of extrajunctional nicotinic acetylcholine receptors, which leads to a greater efflux of potassium when the depolarizing muscle relaxant succinylcholine is administered. Additionally, these extrajunctional receptors are more immature and therefore stay open longer, which leads to even greater potassium efflux and the potential for lethal hyperkalemia [146,147]. This receptor upregulation generally occurs at the 48–72 h mark [147]; as such, succinylcholine is generally considered safe to use up to 24 h after burn injury, with the 24–48 h range being a slightly more gray area. In general, succinylcholine should also be avoided for 1–2 years after major burn injury, as the pharmacodynamics may not return to normal until the patient's wounds are healed and functional mobility is regained [147].

Non-depolarizing muscle relaxants do not carry the same risk as depolarizing muscle relaxants. However, the same upregulation of acetylcholine receptors also leads to slower onset times and larger total dose requirements for non-depolarizing agents [146]. Data from one study demonstrating the difference in rocuronium onset and recovery between burn patients and controls are shown in Table 40.2. When muscle relaxation is necessary, the patient's train of four should be monitored carefully and muscle relaxants titrated to effect.

Table 40.2 Rocuronium onset, twitch recovery, and quality of intubating conditions in burn patients and controls

	Controls	Burns	Controls	Burns
Dose of rocuronium (mg/kg)	0.9	0.9	1.2	1.2
Onset to 95% paralysis, mean ± SD (s)	68 ± 16	115 ± 58*	57 ± 11*	86 ±20
Recovery to TOF ≥0.8, mean ± SD (min)	132 ± 23	103 ± 25*	162 ± 28*	126 ± 14*
Excellent intubating conditions (%)	65	38*	79	67*

* $p < 0.05$ compared with controls with same dose.
TOF, train of four.
Source: Reproduced from Martyn et al [146] with permission of Wolters Kluwer.

Airway management

Airway management in the pediatric burn patient can be extremely challenging (Fig. 40.5). Facial and airway edema can significantly distort normal airway anatomy, and limited neck mobility and mouth opening may compound this. As such, any child with face, neck, or upper chest burns should be approached as a potentially difficult airway. The airway should be assessed carefully and a clear management plan developed, including the availability of a surgeon capable of performing a surgical airway should it become necessary.

Perhaps the most important element of the plan to secure the difficult airway is deciding whether the patient should be awake, sedated, or under general anesthesia, and if the latter, whether the patient should be paralyzed or breathing spontaneously. While awake intubation may be favored in the presence of craniofacial abnormalities or facial burns that suggest difficult mask ventilation, doing so may only be practical in older, cooperative patients. Spontaneous ventilation can still be maintained in younger children; although they may not be awake and cooperative, deep sedation or general anesthesia can be induced using a combination of agents that do not significantly reduce respiratory drive, including ketamine, dexmedetomidine, and volatile agents. This provides an

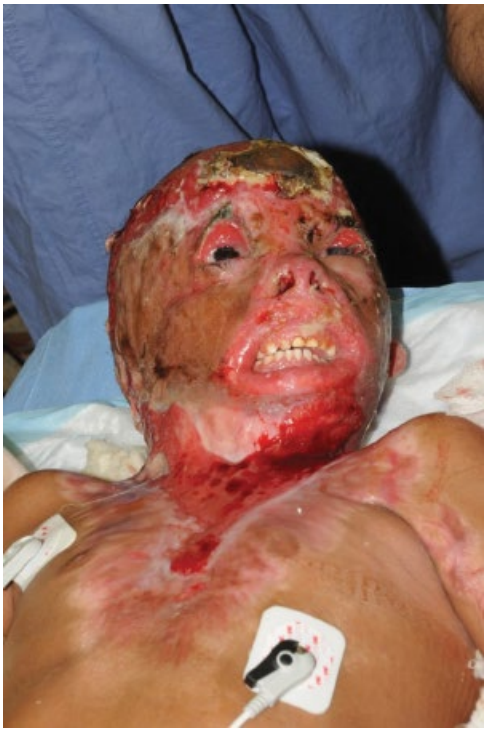
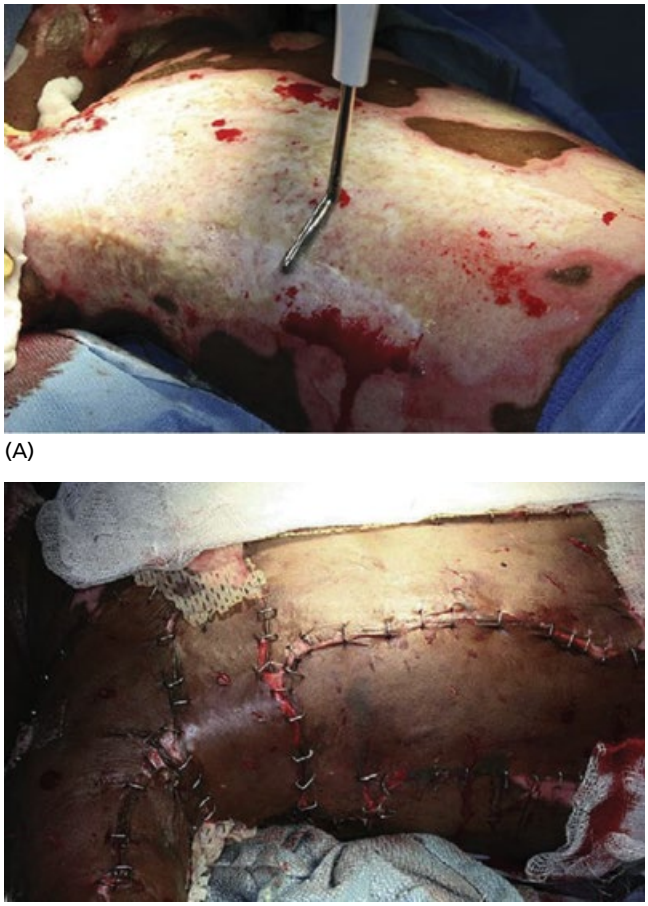


Figure 40.5 A burn patient with an anticipated difficult airway. Note the neck contractures and hence inability to extend the neck, contractures and tightness of perioral tissue that limit mouth opening, and singed nares with minimal opening.



(A)

(B)

Figure 40.6 (A) Debridement and excision of a full-thickness burn injury with hydrosurgery. (B) Coverage of the same full-thickness burn with a split-thickness skin graft. *Source*: Reproduced from Fabia and Groner [90] with permission of Elsevier.

additional margin of safety in the burned child who may prove difficult to intubate or ventilate. If a paralytic is to be used, the time since burn injury must be considered when selecting a paralytic and dosage (discussed elsewhere in this chapter).

Endotracheal tubes can be placed orally or nasally, and in some patients there may be only one option. When possible, oral intubation is generally preferred given the potential for sinus infection with prolonged nasal intubation. Practice has generally moved away from uncuffed endotracheal tubes to low-pressure, high-volume cuffed endotracheal tubes, as leaks may develop around uncuffed tubes at the higher ventilatory pressures that may be required to ventilate the noncompliant lungs in the patient with inhalational injury [33].

Fluid management

Excision and grafting procedures in the operating room (Fig. 40.6) can cause significant blood loss, but the exact amount can be difficult to quantify. Estimates in the literature vary widely; an average across several estimates was 5.48% of total blood volume lost per 1% TBSA excised [148], although the same authors found their own estimate with the use of the aforementioned blood conservation techniques to be 0.84% of total blood volume lost per 1% TBSA excised. Blood loss in the head and face may be higher still [149]. Formulae are useful in general but limited in their ability to accurately estimate blood loss for a specific patient; as such, measurement of laboratory values remains crucial in the setting of ongoing bleeding. Intraoperative blood loss can be replaced with crystalloid, colloid, or blood products, as determined by the patient's lab values and estimated blood loss. There is some evidence to suggest that when transfusing blood products in the setting of pediatric burn excision, a ratio of 1:1 PRBC:FFP results in less immediate postoperative coagulopathy and acidosis when compared to a 4:1 ratio, as well as an overall reduction in amount of blood product transfused [149].

A number of techniques can be employed to reduce the amount of intraoperative blood loss, including the use of electrocautery, topical or infiltrated epinephrine, compressive dressings, and extremity tourniquets [131,132]. Earlier excision also significantly reduces blood loss, as the wound becomes progressively more hyperemic with time [131,132]. Staged high-dose epinephrine clysis, or subcutaneous injection, with an average dose of 24.6 μg/kg of epinephrine has been shown to be safe and effective in reducing blood loss in children [150], and a meta-analysis recently showed reduced blood transfusion with the use of clysis [151]. As with any use of tumescent solution, the patient's volume status should be carefully monitored, as excessive fluid uptake and associated complications have been reported [152,153].

Temperature regulation

The loss of an intact skin layer significantly increases the burn patient's intraoperative heat loss, and children are especially

vulnerable given their larger surface area to volume ratios. In addition to the usual dangers of hypothermia, the metabolic energy that is used to increase heat production is diverted from other areas, such as wound healing [154]. Strategies that may be useful for minimizing heat loss in burn patients include warming the operating room, using heat lamps or reflective barriers (e.g. a plastic sheet) over the patient, using forced-air warming blankets, administering warmed IV fluids and blood products, and humidifying anesthetic gases.

KEY POINTS: ANESTHETIC MANAGEMENT

- Preoperative airway examination, a global sense of fluid balance, NPO status, and continuation of nutrition when possible are important considerations
- Most anesthetic agents are safe to use in burn patients, including propofol, thiopental, ketamine, potent inhalational agents, nitrous oxide, and opioids
- Succinylcholine is contraindicated after 24 h due to the risk for lethal hyperkalemia from upregulated, extrajunctional acetylcholine receptors
- Non-depolarizing muscle relaxants are safe, and dose requirements for these drugs will generally be significantly increased
- A difficult airway in burn patients can be from edema, limited neck mobility and mouth opening, and scarring
- Intraoperative blood loss during excision and grafting procedures can be significant and requires vigilance on the part of the anesthesiologist

Pain control

Unlike acute postsurgical patients, children with second- and third-degree burns experience chronic pain with superimposed acute pain during a prolonged course of treatment. Burn pain is frequently undertreated [155,156] and burned children continue to report extremes of pain, especially with dressing changes and wound care [157]. Additionally, it has become clear that undertreatment of childhood burns has long-standing negative consequences on children's physical and psychological well-being. Physical consequences include a neurohormonal stress response that is associated with slower wound healing [158], as well as long-term alterations in somatosensory and pain processing [159] that may prime children for more intense future pain responses [160]. From a psychological standpoint, in-hospital pain in burn patients has been directly correlated to post-traumatic stress disorder symptoms in children of all ages [161], and better pain control may in fact reduce many of these symptoms [162,163]. As such, improving pain control in pediatric burn patients is imperative. One approach to optimizing pain management for burned children is to consider the different sources of pain in their hospitalization – including background pain, procedural pain (e.g. dressing changes), and perioperative pain – and develop a plan for each. Figure 40.7 summarizes recommended interventions as well as those needing further investigation for each of these phases of care.

Background pain and sedation

One of the most commonly used medication regimens for background pain and sedation in burned children is acetaminophen along with a combination of an opioid such as morphine and a benzodiazepine such as midazolam [164–167]. However, there are few data evaluating this regimen in comparison to others, and no data to suggest that one opioid or benzodiazepine is superior to another in this context. The addition of dexmedetomidine to a morphine/midazolam combination has been shown to improve sedation in burned children [166], but it should be started as an infusion (without a bolus) or doses of other agents should be reduced to avoid hypotension with dexmedetomidine initiation [164]. The use of non-steroidal anti-inflammatory drugs as co-analgesics is not well studied in pediatric burn patients due to concerns for potential side-effects, especially bleeding risk, gastrointestinal complications, and renal toxicity [167,168].

Gabapentin, an anticonvulsant that has increasingly been used for chronic and neuropathic pain, has been studied as an adjuvant background pain medication in adult burn patients, but not in children. The adult studies have had mixed results; two smaller studies reported reduction in pain [169] and opioid consumption [170] with scheduled gabapentin use after admission, but a larger controlled trial did not find any benefit [171]. As such, it is unclear if patients benefit from the routine addition of gabapentin.

Procedural pain

Approaches to analgesia and sedation for burned children undergoing dressing changes have generally focused on varying combinations of propofol, ketamine, dexmedetomidine, and remifentanil to provide deep sedation. Because several different combinations of drugs were compared to each other in a number of small studies, it is difficult to evaluate each regimen on its own merits or find one to be unequivocally superior to the others based on current data.

Doses that have been suggested in the literature for sedation in this context include propofol 1–2 mg/kg, ketamine 1–2 mg/kg, and dexmedetomidine 0.5–1 μg/kg, with infusions of these agents as indicated by the duration of the procedure, and remifentanil 0.1 μg/kg bolus followed by 0.05 μg/kg/min infusion [172–175]. Ketamine and dexmedetomidine have the benefit of being agents that do not cause significant respiratory depression.

Non-pharmacological approaches to procedural pain are also valuable adjuncts. Child life therapy, for example, can significantly reduce pain and anxiety scores during dressing changes [176]. New technologies such as virtual reality are also rapidly advancing and growing in their medical applications. By replacing the sensory experience of the hospital and immersing patients in a computer-generated world, virtual reality can distract patients from pain and significantly improve their experience [177]. A number of small studies have shown significant reductions in pain scores during dressing changes for both adults and children when using virtual reality compared with control distraction techniques [178–181]. As such, as these technologies become more widely available, they may become more regularly used elements of treatment in burn patients.

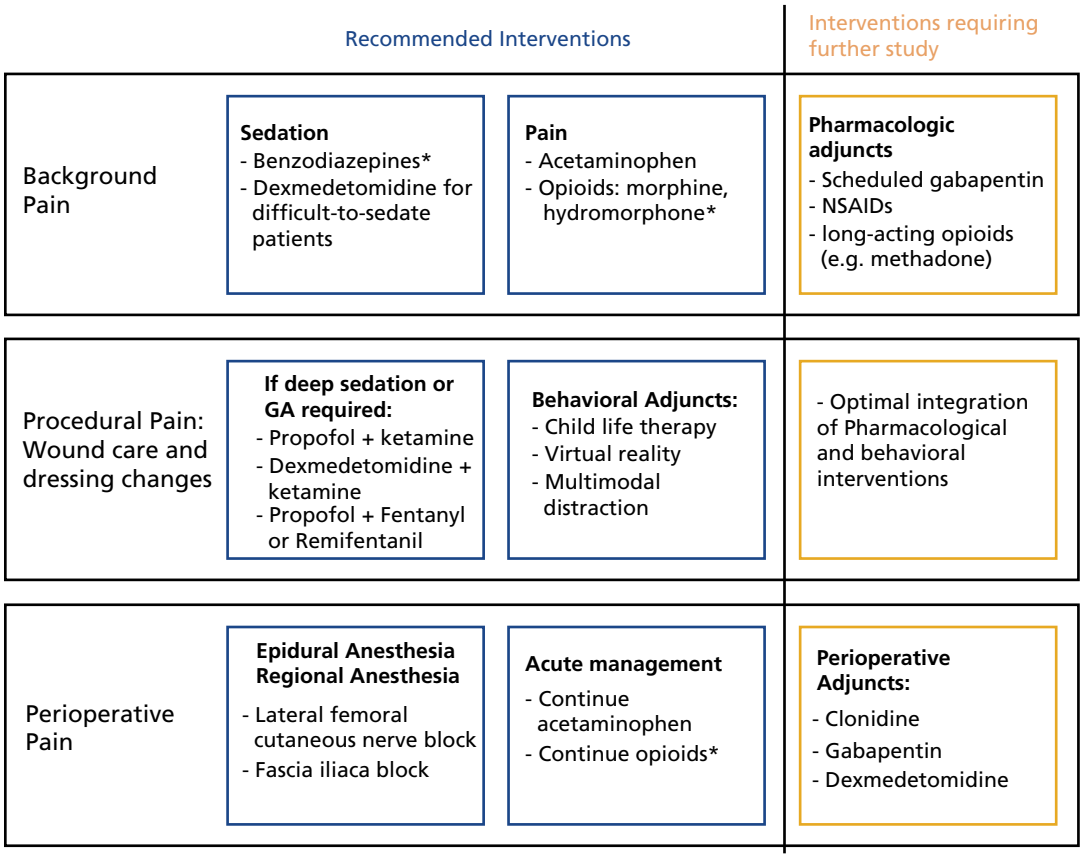


Figure 40.7 Approaches to pediatric burn pain management in different phases of care. This figure provides a summary of evidence-supported interventions for pediatric burn pain, as well as areas requiring further study before recommendations can be made. Given the overall paucity of data, some of the recommended interventions are based on incomplete data and still need to be evaluated further, but have a promising literature base. Medications noted with an asterisk (*) are considered by authors in the literature to represent widespread current practice, and their inclusion as recommended interventions is based on this status quo and opinion rather than clear data. *Source*: Reproduced from Pardesi and Fuzaylov [191] with permission of Wolters Kluwer.

Perioperative pain

There is considerable overlap between the management of background pain and perioperative pain in burn patients. Background medications such as acetaminophen and opioids are generally continued in the perioperative period and make up the mainstay of acute postoperative pain management. However, while studies on perioperative adjuncts are growing in the general pediatrics literature, such research is almost non-existent in burned children. This may be due to the fact that the optimal timing and use of a perioperative adjunct is unclear for a burn patient already in baseline pain. Agents that have been studied as general perioperative adjuncts include clonidine, gabapentin, dexmedetomidine, and ketamine.

Preoperative oral clonidine 4 μg/kg has been shown to significantly reduce postoperative analgesic requirements and pain scores in children [182], but its utility for burn patients is unknown. Gabapentin (15 mg/kg) has some encouraging data on its use as a premedication when studied in pediatric scoliosis patients [183], but these data are far from conclusive and burn patients have not been studied. Similarly, dexmedetomidine premedication (1 μg/kg) [184–187] has been shown to reduce postoperative pain [187,188], but the only study in burn patients was equivocal, likely due to its small sample size [189]. The intraoperative use of ketamine has also been evaluated in the general pediatrics literature, where it was found to decrease postoperative pain for only the first 6 h, without an opioid-sparing effect [190]. As such, while there are some data to support the preoperative administration of clonidine, gabapentin, and dexmedetomidine for reduction of postoperative pain in pediatric surgical patients, these agents have not been evaluated in burn patients as to ideal frequency and timing.

Therapeutics studied in the perioperative management of pediatric burn patients are summarized in Table 40.3 [191].

Regional anesthesia

Regional anesthesia has been evaluated primarily in the context of control of pain at donor sites for graft harvesting – which are frequently noted to be more painful than recipient sites – but has also been studied for dressing changes. The nerve blocks studied include primarily the lateral femoral cutaneous nerve (LFCN) and fascia iliaca blocks. The LFCN innervates the lateral thigh, covering one of the most common sites for donor harvest [192,193], while the fascia iliaca block covers the LFCN as well as the femoral nerve, which allows the block to cover the anterior thigh for larger graft harvests [192].

A handful of studies have evaluated the use of regional anesthesia in burn patients. In the only prospective trial to date of nerve blocks for pediatric skin graft harvests, 19

Table 40.3 Therapeutics studied in perioperative pain management of pediatric burn patients

Phase of care	Medication/procedure	Notes
Preoperative (premedications)	Clonidine: 4 μg/kg	Strong evidence to suggest reduced postoperative pain in non-burn literature
	Gabapentin: 15 mg/kg	Moderate evidence to suggest reduced postoperative pain in non-burn literature
	Dexmedetomidine: 1 μg/kg	Strong evidence to suggest reduced postoperative pain in non-burn literature; one negative trial in burn patients
Intraoperative	Ketamine	No evidence to support use for postoperative pain improvement
	Dexmedetomidine: 1 μg/kg	Strong evidence to suggest reduced postoperative pain in non-burn literature; unstudied in burn population
Postoperative	Acetaminophen	Effective; continue as background medication
	Opioids: morphine and hydromorphone	Mainstay of acute postoperative management; no evidence to favor one opioid over another
	Peripheral nerve blocks: LFCN and fascia iliaca	Likely performed pre- or intraoperatively
		Good evidence for improved postoperative pain control (pediatric and adult data)

LFCN, lateral femoral cutaneous nerve.
Source: Reproduced from Pardesi et al [191] with permission of Wolters Kluwer.

children were randomized to surgical infiltration of local anesthetic (control group), an ultrasound-guided single-shot LFCN block, or a fascia iliaca block with catheter. Children who received either nerve block had less postoperative pain than those who received the surgical infiltration of local anesthetic. LFCN block patients were more comfortable in the immediate postoperative period, while patients with a fascia iliaca catheter were more comfortable in the subsequent 48 h [192]. Studies in adult burn patients have also shown reduced postoperative pain, opioid consumption, and nausea and vomiting in burn patients receiving nerve blocks [194]. Additionally, dressing changes can also be comfortably performed in patients with nerve blocks, as has been shown in some adult patients [195]. There were no significant complications associated with regional anesthesia in any of these studies.

Taken together, these data suggest that there is a significant role for regional anesthesia in pain control for burn patients, both for graft harvests as well as for dressing changes, and regional techniques should be employed whenever possible and appropriate.

KEY POINTS: PAIN CONTROL

- Pain is often undertreated in burn patients; this can have physiological and psychological consequences, from potentially delayed wound healing to post-traumatic stress disorder
- Background pain is commonly treated with benzodiazepines and opioids, but dexmedetomidine has been shown to be a good adjunct
- Sedation for dressing changes often includes combinations of propofol, ketamine, dexmedetomidine, and/or remifentanil. Non-pharmacological treatments are useful, including child life support and distraction technologies such as virtual reality
- Regional anesthesia, such as lateral femoral cutaneous nerve or fascia iliaca blocks, should be considered for treatment of graft donor sites

Anesthetic management for reconstructive procedures

After the primary burn wound is healed, burn patients often return to the operating room multiple times for reconstructive procedures, such as scar revisions, re-excisions, and grafting. At this stage, remote from the initial burn, patients will generally no longer display extreme physiological disturbances, and pharmacokinetics gradually return to normal.

Anesthesia for reconstructive surgery is generally similar to that of other plastic surgical operations. Previous anesthetic records are generally an important source of information regarding airway management and pain medication requirements. Because reconstructive procedures do not typically result in large amounts of blood loss or extensive fluid shifts, a single peripheral intravenous line and standard monitors are often sufficient, although each case should be assessed individually. It is important to bear in mind that these children will often be returning for repeat procedures, so careful attention should be paid to anxiolysis and tailoring the type of induction to the child's comfort and preferences so as to minimize potential fear, anxiety, and unpleasantness. With appropriate attention to these aspects of the patient's experience, adverse psychological outcomes can be avoided in patients undergoing frequent general anesthetics [196].

One area that warrants special consideration in the recovered burn patient is airway management. Patients with head and neck burns can develop severe contractures that can distort the airway, limit mouth opening and neck flexion, and obstruct the nares [197], all of which can lead to a difficult airway. Mask ventilation can be difficult in these patients because the jaw thrust and chin lift maneuvers may be precluded by scarring and contractures, and insertion of oral or nasal airways may be precluded by microstomia or scarring of the nares [197]. As such, if difficulty with mask ventilation is anticipated, it is advisable to maintain spontaneous ventilation either throughout the induction and intubation, or at least until confirmation of the ability to mask ventilate. The airway can then be approached using difficult airway adjuncts, including the laryngeal mask airway (LMA), videolaryngoscopy, or a fiberoptic scope. In severe cases, the patient may require surgical release of contractures in order to

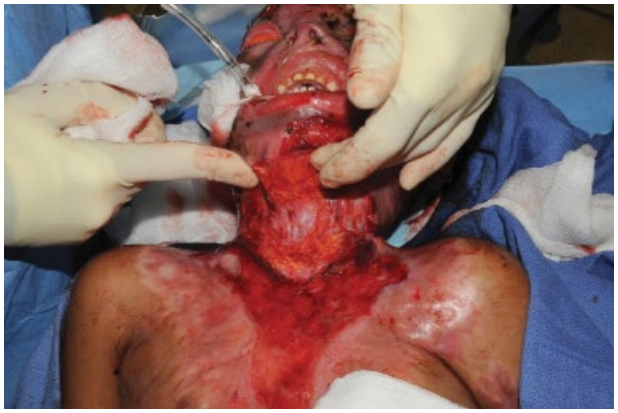


Figure 40.8 A difficult airway in a burned child, requiring neck dissection with local anesthetic and deep sedation with spontaneous ventilation in order to facilitate endotracheal intubation.

facilitate intubation (Fig. 40.8); this can be done with the patient anesthetized and spontaneously breathing volatile agents via a facemask or LMA, supplemented with local anesthesia [198,199]. If a difficult airway is anticipated in the recovered pediatric burn patient, it is also critically important to have available a surgeon who could perform a potentially challenging tracheostomy as a rescue option.

KEY POINTS: ANESTHETIC MANAGEMENT FOR RECONSTRUCTIVE PROCEDURES

- Burn patients may return to the operating room many times for reconstructive procedures, often long after the initial burn, and will generally no longer display extreme physiological disturbances
- Airway evaluation is crucial, as poorly treated burns can develop scars and contractures that may profoundly limit head and neck mobility or mouth opening
- With a difficult airway, securing the airway, spontaneous ventilation, and using medications such as ketamine and potent inhalational agents may allow a more controlled situation for airway management

CASE STUDY

An 18-month-old girl was transferred to a burn hospital from a rural village. She had suffered severe head and chest burns from hot oil at 1 year of age, but had been otherwise healthy prior to this injury. On initial presentation, she had required a tracheostomy for airway control due to widespread burns to the mouth and face that precluded safe oral intubation. When the neck swelling had decreased and the burn wounds completely healed, the tracheostomy was decannulated prior to discharge from hospital. The patient now presented for treatment of her profound neck and mouth contractures and facial deformity, as shown in Figure 40.9A.

Although the burn wounds had healed, the progressive severe contractures of the face, anterior neck, and shoulders led to increasing respiratory compromise, including obstructive sleep apnea with bradycardia and desaturation to 70–80%. The airway was more prone to obstruction in the supine position. Hence, the child most often slept prone on her mother's shoulder and chest. Because of the contracture-related microstomia, she was only able to swallow liquid food. The chin and the sides of the face were pulled down and tethered to her upper sternum and upper chest wall. The anterior neck structures (larynx, trachea, carotids) were not palpable. Her nares were completely occluded such that no nasal discharge was noted even during her crying spells. The skin of her face and facial contour were markedly irregular. Neither flexion nor extension of her head was possible.

Direct visual examination of the oral cavity and pharynx was impossible due to the extreme microstomia and lack of cooperation of the patient. Attempts by the ear, nose, and throat (ENT) surgeon to examine the air passages by fiberoptic endoscopy were futile in view of the closed nares. CT scan of the head and neck confirmed the obstruction of the external nares, and showed relatively normal oropharyngeal, glottic, and laryngeal structures.

After extensive discussions between pediatric, burn, cardiothoracic, and ENT surgeons and anesthesiologists, a plan was formalized. The first step was the establishment of a safe method for gas exchange as a precautionary measure. This was achieved by extracorporeal membrane oxygenation (ECMO) via cannulation of the femoral vein during ketamine sedation and analgesia. The second step was induction of general anesthesia while the child was on ECMO. The third step was the release of the neck contractures to provide anterior access to the trachea for an emergency tracheostomy, if necessary, and to facilitate endotracheal intubation. Oral commissurotomy was deliberately avoided as the child was heparinized for the ECMO. Any bleeding from the commissurotomy into the oral cavity had the potential to impair visibility during intubation and lead to aspiration and/or laryngospasm. The final step was direct laryngoscopy and intubation.

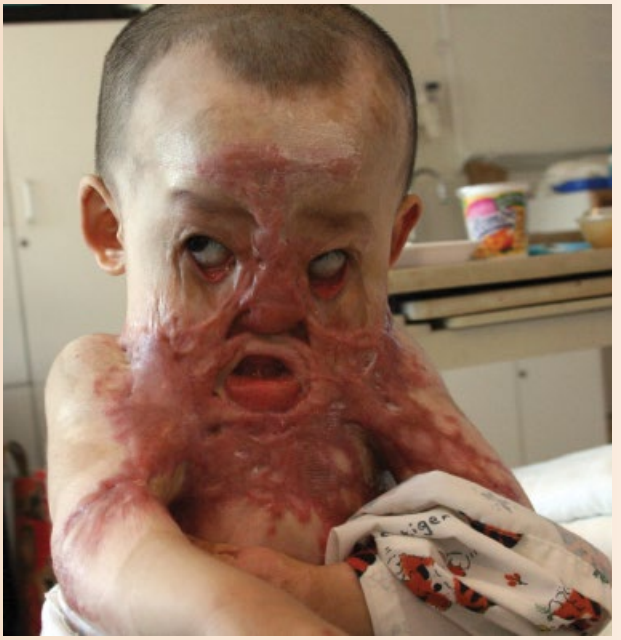
The day before surgery, a peripheral intravenous line was placed. Antacid prophylaxis was initiated with pantoprazole and ranitidine 2 h before surgery. The child was reassessed in the induction room with her mother. Scopolamine (0.1 mg) and atropine (0.2 mg) IV were administered for sedation and to reduce oral secretions that may occur with the subsequent planned use of ketamine. After placement of a pulse oximeter, incremental doses of ketamine (0.25 mg/kg per dose up to 3.5 mg/kg) were titrated over 30 min to sedate the child and separate her from her mother. The patient was positioned supine on the operating room table, and other standard monitors were attached. Surprisingly, the patient did not manifest any serious airway obstruction in the supine position when asleep with ketamine.

Additional doses of ketamine (total dose 5.5 mg/kg) were administered to provide analgesia and sedation. Local anesthetic was administered in the groin by the surgeons. Intravenous heparin was administered for anticoagulation. Femoral vein cut-down and ECMO cannulation were expeditiously completed. At this point, general anesthesia was slowly induced with sevoflurane through an anesthesia facemask. With general anesthesia maintained via facemask and successful assisted mask ventilation, the surgeons performed a limited neck release, which now provided a potential access to the trachea anteriorly if necessary. Having confirmed the ability to ventilate, muscle relaxant was administered (rocuronium 1 mg/kg) and the patient was successfully intubated with a styletted 3.5 mm cuffed endotracheal tube with extreme anterior pressure on the larynx. Anesthesia was maintained with sevoflurane and nitrous oxide, with additional muscle relaxation and opioids. Tracheostomy was considered as an option to secure the airway, but was decided against because of the potential for intratracheal bleeding due to the anticoagulation.

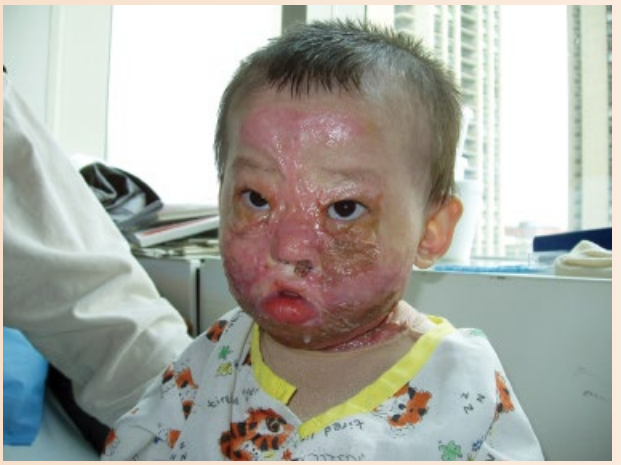
With the endotracheal tube in place, further neck release and dissection were performed. The ECMO circuit was then gradually weaned, and vital signs indicated that ventilation and gas exchange were adequate, allowing discontinuation of ECMO. Over the course of the operation, she received 500 mL lactated Ringer's solution. About 100 mL of blood was transfused from the ECMO reservoir. After grafting of the neck was completed, she was transferred to the pediatric intensive care unit, intubated and in a stable condition. She was extubated uneventfully in the ICU 2 days later.

The patient subsequently underwent multiple additional surgeries for revisions. For these procedures, endotracheal intubation was achieved by direct laryngoscopy, after induction of anesthesia with ketamine, sevoflurane, and muscle relaxant. Figure 40.9B shows the improvement in the patient's scarring partway through her process of reconstructive surgery.

This case study demonstrates just how difficult the airway of the recovered pediatric burn patient can be. In this case, many factors suggested a difficult airway: severe contractures, difficulty identifying anatomical structures, inability to move the head and neck, microstomia, and obstructed nares. An additional factor worth noting is the presence of obstructive sleep apnea, suggesting the need for additional caution when inducing the patient. One of the most instructive elements of this case is the importance of multidisciplinary collaboration in care of the complex patient, and using that expertise in order to develop a clear plan for management of the patient. With appropriate preparation and careful planning, even extremely challenging airways can be managed when approached systematically.



(A)



(B)

Figure 40.9 (A) An extremely difficult airway presented by a pediatric burn patient who developed severe contractures of the face, neck, and chest. (B) Improvement in the patient's scarring and contractures after the first of several reconstructive procedures.

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A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 41

Anesthesia and Sedation Outside the Operating Room

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Introduction

Improved anesthetic techniques and advanced technology in the last two decades [1] have led to an increase in invasive and non-invasive pediatric procedures performed outside the operating room in most institutions. In the past years, as operating room cases increased by 250% at Boston Children's Hospital, anesthesia services outside the operating room increased by almost 350% (Table 41.1). In 2016, 10,200 out of 32,476 (31%) anesthetics were administered to patients outside the operating at Cincinnati Children's Hospital Medical Center. Although the majority of procedures are accomplished in the radiology suite, they are now complemented by anesthesiology support in gastroenterology, pulmonology, radiotherapy, and the dental and oncology clinics (Table 41.2). Anesthesiologists have been leaders in establishing guidelines and recommendations for sedation and anesthesia services provided by both anesthesiologists and non-anesthesiologists [2–7]. In this chapter we will explore the special considerations for providing anesthesia and sedation services in various clinical areas outside the operating room and will review common organizational, equipment, and personnel considerations and strategies. We conclude with the roles of quality improvement and simulation in non-operating room anesthesia (NORA) locations and speculation about the future of pediatric sedation outside the operating room.

Specific NORA sites

Diagnostic radiology

Computed tomography scans

Computed tomography (CT) was introduced into clinical practice in the late 1970s. CT differentiates between high-density (calcium, iron, bone, contrast-enhanced vascular and cerebrospinal fluid (CSF) spaces) and low-density (oxygen, nitrogen, carbon in air, fat, CSF, muscle, white matter, gray matter, and water-containing lesions) structures. Because the scan time is quick, CT may be preferable for patients who are medically unstable and in need of rapid diagnosis. Understanding the goal of each imaging study allows the sedation/anesthesia provider to choose the safest and most effective regimen to allow a meaningful study. As an example, in order to obtain the high-quality "high-resolution" CT required to evaluate lung parenchymal detail, motion-free images at inspiration and expiration are required. Significant atelectasis may lead to difficulty with interpretation and diagnosis. A consistent anesthetic approach will often optimize interpretive results among radiologists [8]. Atelectasis in the dependent regions of the lung appears within 5 min of anesthesia induction [9], regardless of anesthetic choice or respiratory management [10]. In "healthy" lungs, collapsed areas are re-expanded, and a normal functional residual capacity restored if airway pressures are raised beyond the alveolar opening

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

Table 41.1 Anesthetic cases outside the operating room (OR), Boston Children's Hospital

Year	1992	2008	2016
Total anesthetic cases	13,679	34,311	41,669
Radiology: sedation + general anesthesia	346	4,129	5,563
Cardiac catheter lab	900	1,908	2,355
Gastrointestinal endoscopy	0	918	2,529
Oncology clinic	0	528	806
Radiotherapy	1,065	248	299
Total outside OR	2,311	7,731	11,552

Table 41.2 Multidisciplinary programs involving the department of anesthesiology: Boston Children's Hospital

Program	Departments
Advanced Fetal Care Center	Anesthesia, cardiology, general surgery, genetics, medicine, neurology, neurosurgery, newborn medicine, ORL, plastic surgery, radiology, urology
Brain Injury Program	Anesthesia, general surgery, neurology, neurosurgery, orthopedics, psychiatry/psychology, sports medicine
Center for AeroDigestive Disorders (CADD)	Anesthesia, GI, ORL, pulmonary program
Cleft Lip and Palate Program	Anesthesia, audiology, dentistry, general surgery, genetics, nursing, oral and maxillofacial surgery, ORL, pathology, plastic surgery, psychiatry/psychology, social work
Craniofacial Anomalies Program	Anesthesia, audiology, dentistry, genetics, neurosurery, nursing, oral and maxillofacial surgery, ORL, pathology, plastic surgery, psychiatry/psychology, social work
Heart Transplant Program	Anesthesia, cardiac surgery, cardiology, cardiovascular program, general surgery, nutrition, physical therapy, pathology, radiology
Intestine and Multivisceral Transplant Program	Anesthesia, general surgery, GI, nutrition
Liver Transplantation	General surgery, gastroenterology, nutrition center, psychiatry
Lung Transplant Program	Anesthesia, cardiac surgery, cardiology, general surgery, psychiatry/psychology, respiratory diseases
Pain Treatment Service	Anesthesia, physical and occupational therapy, psychiatry, rheumatology
Trauma Program	Anesthesia, critical care medicine, emergency medicine, general surgery, neurosurgery, orthopedics, psychiatry/psychology, radiology
Vascular Anomalies Center	Anesthesia, cardiology, cardiovascular program, dermatology, endocrinology, general surgery, hematology, medicine, neurology, neurosurgery, nursing, oncology, oral and maxillofacial surgery, ORL, orthopedics, pathology

GI, gastrointestinal; ORL, otorhinolaryngology.

pressure. The recruitment maneuver has been shown to improve arterial oxygenation and lung compliance. It is important to note that while using high inflating pressures is benign in most cases, high-pressure ventilatory strategies can lead to hemodynamic compromise and possibly cause lung injury from overdistension of non-collapsed lung areas [11,12].

CT scans for visualizing the sinuses, ears, inner auditory canal, and temporomandibular bones (e.g. for choanal atresia or craniofacial abnormalities) may require direct coronal imaging with extreme head extension or absolute immobility for 3D reconstruction. The more common studies involving 3D reconstruction are cardiac, craniofacial, and pulmonary (larynx, trachea, bronchi, and pulmonary parenchyma) imaging [13]. The cardiac studies are often done in collaboration with cardiologists and radiologists who are able to make structural and functional assessments of the heart. These scans can also be challenging because adenosine is often requested in order to briefly pause heart function so that image quality is optimized [14].

Any patient who is at risk for cervical instability should be properly screened prior to neck extension, such as children with Down syndrome, whose incidence of instability varies from 12% to 32% [15]. Many children with Down syndrome require cervical spine radiographs prior to participating in advance sports events. Usually, the parents are well aware of the radiological findings. The cervical spine films, however, do not predict at the risk of dislocation [16]. Rather, neurological signs or symptoms such as abnormal gait, increased clumsiness, fatigue with ambulation, or a new preference for sitting games are predictors of risk. The asymptomatic Down syndrome child with radiological evidence of instability may be approved for procedural sedation, however unnecessary neck movement should be avoided. Any child who displays neurological signs or symptoms should not be sedated by either a nurse or an anesthesiologist until neurosurgical or orthopedic consultation is obtained.

Radiologists employ gastrografin (diatrizoate meglumine and diatrizoate sodium) when evaluating abdominal masses. Gastrografin diluted to 1.5% is usually considered a clear liquid, however the volume administered orally is not insignificant. Newborns less than 1 month of age receive 60–90 mL, infants between 1 month and 1 year of age may receive up to 240 mL, and children between the ages of 1 and 5 years receive between 240 and 360 mL. In order to opacify the bowel optimally for abdominal examination with CT the contrast is best administered 1 h prior to imaging [17]. Waiting several hours after the administration of contrast will often result in inadequate opacification of the small bowel [17]. Because sedation or anesthesia should usually be accomplished within a window of 1–2 h after ingestion of the contrast, most "elective" nil per os (NPO) guidelines would be violated, yet the scan must be completed while the gastrografin is still in the gastrointestinal tract. There are no published data to guide optimal induction or sedation techniques as they relate to aspiration risk in these circumstances. Some providers may choose to perform rapid-sequence induction of general anesthesia with tracheal intubation while others may choose deep sedation without airway protection [18,19]. Full-strength (3%) gastrografin is hyperosmolar and hypertonic. All gastrografin should be diluted to an isosmolar and isotonic 1.5% concentration of neutral pH. There is one case report of 1.5% gastrografin aspiration in a child with no adverse sequelae [20]; therefore, the risk of using a 1.5% concentration of gastrografin seems low [21].

The radiation dose for children undergoing CT scanning has long been a concern, and the recent Image Gently campaign has been effective in dramatically reducing the

radiation exposure for CT scans in children by standardizing approaches to the technical aspects of scanning, as well as indications for the scan itself [22,23]. In addition, modern multislice CT scanners can obtain detailed images quickly and with significant reduction in radiation exposure, often with minimal or no sedation. With the great increase in magnetic resonance imaging (MRI), CT scan imaging decreased, but in the modern era with the concern over prolonged sedation and anesthesia in young children [24] (see Chapter 46), CT scanning once again has become the modality of choice in some indications, including some congenital heart disease studies [25].

Magnetic resonance imaging

The first commercial MRI scanner was introduced in 1990. Over the past three decades MRI has evolved beyond a diagnostic tool to encompass a broader role in diagnosing and evaluating obstructive sleep apnea, developmental delay, behavioral disorders, seizures, failure to thrive, apnea/cyanosis, hypotonia, and mitochondrial/metabolic disorders. Magnetic resonance angiography and venography evaluate vascular flow and can sometimes replace invasive catheterization studies for follow-up or initial evaluations of vascular malformations, interventional treatment, or radiotherapy [26].

Functional MRI (fMRI) is an evolving technology which measures the hemodynamic or metabolic response related to neural activity in the brain or spinal cord. The hemodynamic response (increase in cerebral blood flow, cerebral blood volume, and cerebral capillary and venous oxygen saturation) is the basis of image contrast in fMRI. fMRI is often able to localize sites of brain activation and is now dominating brain mapping techniques due to its low invasiveness and lack of radiation exposure [27–29]. Some fMRI studies require cognitive facility and are typically interactive with a conscious and responsive patient. The current use of fMRI in children is primarily focused on presurgical evaluation of language and memory function for intractable epilepsy, and preoperative assessment of eloquent cortex in patients with brain lesions (tumors, cavernous malformations). Currently it is an established tool for pain research and recently has been applied to the understanding of anesthetic mechanisms, brain injury, and respiratory control [29]. fMRI that requires patient responsiveness is generally performed in unsedated children with the aid of distraction techniques and most recently with the use of video goggles (Resonance Technology, Northridge, California, USA) (Fig. 41.1). These goggles are designed specifically for fMRI and are approved for the 1.5 and 3T environment. They are able to deliver audio and visual stimulation, measure patient response through the use of patient input devices, and are able to track eye movement. In addition, they can be used for children as young as 4–5 years of age to avoid sedation for MRI studies. fMRI studies on sedated children is a relatively new field and those who provide sedation describe propofol and dexmedetomidine infusions as agents that can maintain spontaneous ventilation and immobility while also enabling the child to respond to verbal, tactile, or auditory stimulation. fMRI studies on children who require sedation to maintain immobility will be a challenge facing anesthesiologists as we move through the next decade.

Anesthesiologists need to adapt to these evolving technologies. Magnetic resonance enterography, for example, is a method of examining the bowel without the use of ionizing radiation and has recently emerged as highly effective method of assessing inflammatory bowel disease in children. This technique requires the administration of oral contrast. Appropriate timing of imaging after oral contrast agent administration is crucial in order to opacify the bowel and optimize the images. These authors administer enteric contrast through an oral gastric tube after placement of an endotracheal tube and extubate these patients awake after suctioning the stomach at the conclusion of the study [30].

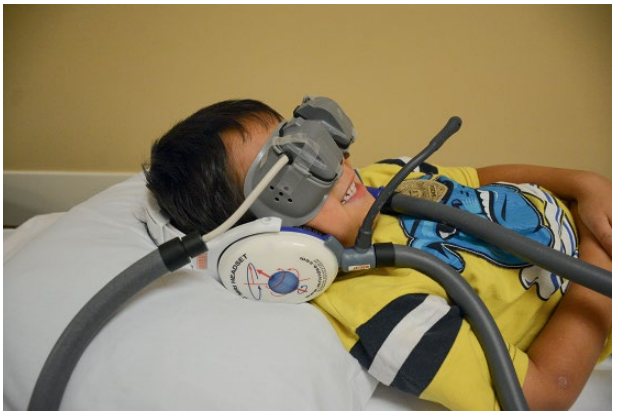

Figure 41.1 Virtual reality system for functional MRI, and avoidance of sedation in young children. See text for details. *Source:* Courtesy of Cincinnati Children's Medical Center.

Three-dimensional studies utilizing MRI have evolved in concert with CT studies. Airway studies, in particular, provide a means of diagnosing areas of airway compromise and collapse that were not identified on bronchoscopy and fluoroscopy. These studies have specific anesthetic management implications as they require that the trachea remains unintubated and the patient breathes spontaneously in order to be able to visualize areas of collapse. The use of intravenous dexmedetomidine, among other techniques, will allow immobility, simulation of natural sleep, and maintenance of spontaneous ventilation. As these children present with obstructive sleep apnea, however, the anesthesiologist must anticipate that airway obstruction can occur under sedation as it does during natural sleep [31–34].

MRI-guided surgical procedures, commonly referred to as magnetic resonance therapy, have evolved over the past decades, enabling surgeons to benefit from MRI in real or near-real time intraoperatively. The logistical challenges in creating a surgical suite that is equipped with an MRI scanner are considerable. In addition to the routine precautions that must be taken in a typical diagnostic MRI suite, all surgical supplies and equipment must be magnetic resonance safe or conditional. In general, access to this surgical suite is restricted to personnel fluent in MRI safety procedures and guidelines. Magnetic resonance therapy is currently being used for neurosurgery to guide the resection of tumors, seizure foci, and vascular malformations [35]. Additional applications have extended its use to otolaryngological, general surgery, and orthopedic procedures [36].

The MRI environment is unique because of its strong static magnetic field, high-frequency electromagnetic (radiofrequency or RF) waves, and a pulsed magnetic field. Magnetic field strengths are measured in units of Gauss (G) and Tesla

(T): 1 T is equal to 10,000 G. The main magnetic field of a 1.5 T magnet is about 30,000 times the strength of the earth's magnetic field. The main magnetic field of a 3 T system is 60,000 times the earth's magnet field. To put this into context, the strength of electromagnets used to pick up cars in salvage yards is equivalent to the field strength of a 1.5–2.0 T magnet. This field strength is able to transform static oxygen cylinders into flying projectiles which can travel at speeds approaching 40 miles per hour. The American College of Radiology established guidelines to minimize the risk of MRI-related mishaps [37], but did not directly address anesthesiologists' unique needs. In 2008 the American Society of Anesthesiologists (ASA) assembled a task force composed of anesthesiologists, a radiologist with MRI expertise, and two methodologists; a practice advisory on anesthetic care for magnetic resonance imaging followed [38]. This document establishes important recommendations for safe practice as well as consistency of anesthesia care in the MRI environment. In 2008, the Joint Commission on Accreditation of Healthcare Organizations, USA (the Joint Commission) recognized the existing and potential hazards of the MRI environment when they published a sentinel event alert [39] specifically identifying eight types of possible injury.

As technology has advanced, 1.5 T magnets have been supplanted by 3 T magnets. The field strength and magnetic force generated by a 3 T MRI scanner is unforgiving to the careless or accidental introduction of a ferrous object into the environment. Placing a magnet outside the MRI scanner is a crude and sometimes inaccurate way to test objects. If the object is not attracted to the magnet, this is not an absolute indication that there is no ferrous material present; a positive attraction, however, will provide critical information to the anesthesiologist. Some unusual objects that have found their way into the MRI suite in order to become projectiles include a metal fan, pulse oximeter, shrapnel, wheelchair, cigarette lighter, stethoscope, pager, hearing aid, vacuum cleaner, calculator, hair pin, oxygen tank, prosthetic limb, pencil, insulin infusion pump, keys, watches, and steel-tipped/heeled shoes [40]. Small objects can usually be easily removed from the magnet; large objects may have so much attractive force with the MRI scanner that they are impossible to remove by manual force. In these circumstances, quenching the magnet may be the only way to release the object. This process is not without substantial risk: as helium gas is vented, condensation and considerable noise fills the suite. All personnel are required to vacate the suite during a quench as there is a risk of hypoxic conditions should helium accidentally enter the room.

It is important to remember that the magnet is always on, and the dangers of the electromagnetic field are always present. The American College of Radiologist recommends that the MRI suite be divided into four zones with increasing safety and access requirements as patients, staff, and equipment move closer to the scanner. The establishment of safety zones in the MRI environment addresses restrictions to access of the MRI environment (Table 41.3) [37]. This safety approach was acknowledged by the MRI Task Force of the ASA in its updated practice advisory in 2015 [41]. Because the 1.5 and 3 T scanners have different magnetic field strengths, an object which is MRI safe in a 1.5 T magnet is not necessarily safe in a 3 T magnet. MRI safety labeling is specific for magnetic field strength.

As advances have been made in the technology of MRI as well as in clinical experience, there has been a parallel evolution in labeling practices from the initial standards established by the US Food and Drug Administration (FDA) in 1997 to the current standard for labeling equipment established by the American Society for Testing and Materials International in 2005 (Table 41.4) [42]. For example, the magnetic resonance (MR) compatible terminology has been deleted because it became apparent that the terms "MR safe"

Table 41.3 MRI safety zones

Zone	Definition	Access
Zone I	This region includes all areas that are freely accessible to the general public. This area is typically outside the MR environment itself and is the area through which patients, healthcare personnel, and other employees of the MR site access the MR environment	General public
Zone II	This area is the interface between the publicly accessible uncontrolled zone I and the strictly controlled zone III. Typically, the patients are greeted in zone II and are not free to move throughout zone II at will, but rather are under the supervision of MR personnel. It is in zone II that patient histories, answers to medical insurance questions, and answers to MRI screening questions are typically obtained	Unscreened MRI patients
Zone III	This area is the region in which free access by unscreened non-MR personnel or ferromagnetic objects or equipment can result in serious injury or death as a result of interactions between the individuals or equipment and the MR scanner's particular environment. These interactions include, but are not limited to, those with the MR scanner's static and time-varying magnetic fields. All access to zone III is strictly restricted, with access to regions within it (including zone IV) controlled by, and entirely under the supervision of, MR personnel	Screened MRI patients and personnel
Zone IV	This area is the MR scanner magnet room. Zone IV, by definition, will always be located within zone III because it is the MR magnet and its associated magnetic field that generates the existence of zone III.	Screened MRI patients under constant direct supervision of trained MR personnel

MR, magnetic resonance; MRI, magnetic resonance imaging.
Source: Reproduced from Kanal et al [37].

Table 41.4 Current terminology used to label implants and devices [42]

Definition	US Food and Drug Administration	American Society for Testing and Materials (ASTM) International	Icon label
MR safe	The device, when used in the MRI environment, has been demonstrated to present no additional risk to the patient or other individual, but may affect the quality of the diagnostic information. The MRI conditions in which the device was tested should be specified in conjunction with the term MR safe since a device which is safe under one set of conditions may not be found to be so under more extreme MRI conditions	An item that poses no known hazards in all MRI environments. Using the new terminology, MR safe items include non-conducting, non-metallic, non-magnetic items such as a plastic Petri dish. An item may be determined to be MR safe by providing a scientifically based rationale rather than test data	"MR" in green in a white square with a green border, or the letters "MR" in white within a green square
MR conditional		An item that has been demonstrated to pose no known hazards in a specified MRI environment with specified conditions of use. Field conditions that define the MRI environment include static magnetic field strength, spatial gradient, dB/dt (time-varying magnetic fields), radio frequency (RF) fields, and specific absorption rate (SAR). Additional conditions, including specific configurations of the item (e.g. the routing of leads used for a neurostimulation system), may be required. In particular, testing for items that may be placed in the MRI environment should address magnetically induced displacement force and torque, and RF heating. Other possible safety issues include, but are not limited to, thermal injury, induced currents/voltages, electromagnetic compatibility, neurostimulation, acoustic noise, interaction among devices, and the safe functioning of the item and the safe operation of the MR system	"MR" in black inside a yellow triangle with a black border. Item labeling must include results of testing sufficient to characterize the behavior of the item in the MRI environment
MR unsafe		An item that is known to pose hazards in all MRI environments. MR unsafe items include magnetic items such as a pair of ferromagnetic scissors	"MR" in black on a white field inside a red circle with a diagonal red band

MR, magnetic resonance; MRI, magnetic resonance imaging.

and "MR compatible" were confusing and were often used interchangeably or incorrectly [43]. Portable equipment to be brought into the magnet room (zone IV) should be identified with a green square "MRI safe" label. A yellow triangle "MRI safe" label should be affixed to equipment that requires strict precautions to be observed when used inside the magnet room. For example, the anesthesia machine is an MRI conditional device, and needs to be placed a minimum distance from the magnet to remain safe and functional. Portable equipment that is required for use in the controlled zones but has ferrous components will have a red circle "MRI unsafe" label and must not be brought into zone IV. The safety of any unlabeled devices to be brought in the controlled area should be discussed with MRI staff and an MRI safety officer.

Personal risks in the MRI environment apply to anesthesiologists and patients. Anesthesiologists must be aware of many personal items taken for granted – clipboards, pens, watches, scissors, clamps, credit cards, eyeglasses, paper clips, etc. [44–46]. MRI safety issues include implanted objects (e.g. cardiac pacemakers), ferromagnetic attraction creating "missiles," noise, biological effects of the magnetic field, thermal effects, equipment issues, and claustrophobia. Some stainless steel may contain ferritic, austenitic, and martensitic components [47–49]. Martensitic alloys contain fractions of a crystal phase known as martensite, which has a body-centered cubic structure, is prone to stress corrosion failure, and is ferromagnetic. Austenite is formed in the hardening process of low carbon and alloyed steels, and has ferromagnetic properties. Iron, nickel, and cobalt are also ferromagnetic. For this reason, the components of *any* implanted device should be carefully researched prior to entering the magnet. Stainless steel or surgical stainless objects interacting with an external magnetic field may produce translational (attractive) and rotational (torque) forces. Intracranial aneurysm clips, cochlear and stapedial implants, shrapnel, intraorbital metallic bodies, and prosthetic limbs may move and potentially dislodge. Special precautions should be taken with cochlear implants in the 3 T environment as those non-removable magnets may suffer demagnetization in the scanner [50]. Some eye make-up and tattoos may contain metallic dyes and therefore cause ocular, periorbital, and skin irritation [51,52]. Some tissue expanders employed in reconstructive surgery have a magnetic port to help identify the location for intermittent injections of saline [53]. Bivona® tracheostomy tubes (Smiths Medical, Kent, UK) usually contain ferrous material (although not specified in the package insert) and should be replaced with a Shiley®

tracheostomy tube (Covidien-Nellcor, Boulder Colorado, USA) prior to entering the MRI environment. Recognizing the unique hazard posed by the MRI environment, in 2008 the Joint Commission issued a sentinel event alert [39].

Cardiac pacemakers present a special hazard in and around the MRI scanner, especially in patients who are pacemaker dependent. Most pacemakers have a reed relay switch that can be activated when exposed to a magnet of sufficient strength [54]. This activation could convert the pacemaker to the asynchronous mode. There are at least two known cases of patients with pacemakers who died from cardiac arrest while in an MRI scanner. The autopsy of one patient determined that the death was the result of an interruption of the pacemaker in the magnetic environment [55]. In addition to the risk of pacemaker malfunction, there is also the chance that torque on the pacer or pacing leads may create a disconnect or microshock [56]. Recent studies demonstrate that with careful preparation, selected patients with permanent pacemakers and implantable cardioverter defibrillators may safely undergo imaging in the 1.5 T environment without any inhibition or activation of their device [57]. Patients with implanted cardiac pacemakers or cardioverter defibrillators should only be scanned in locations staffed with radiologists and cardiologists of appropriate expertise [37]. In general, MRI should not be performed on patients with implanted electronic devices. When MRI is considered essential by the referring physician and consulting radiologist, a plan for managing these patients during the scan should be developed in collaboration with the ordering/referring physician, medical director, or on-site radiologist and other appropriate consultants (e.g. the patient's pacemaker specialist or cardiologist, or device manufacturer). For implanted pacemakers and implantable cardioverter defibrillators, it is anticipated that the cardiologist will be physically available during the scan should the device malfunction [38]. Following the MRI, a cardiologist should confirm function of the device and recheck it within 1–6 weeks. MRI-compatible pacemakers have been available since 2011 [58]. These devices are specifically designed to retain normal function during and after the MRI process and are now available from several manufacturers. Despite the availability of these devices, the same precautions noted above, including cardiologist availability, should be followed.

The biological effect of MRI should be considered when offering parent-present induction if the parent is pregnant. To date, there is no evidence to support the risk of MRI-caused chromosomal aberrations in humans. Studies in amphibians demonstrate that exposure to a 4 T magnetic field does not cause any defects in embryological development [52]. Most institutions do not routinely allow pregnant family members to accompany their children into the MRI scanner. MRI scans during pregnancy are discouraged by the American College of Radiology during the first and second trimester, unless fetal imaging is required or the MRI is necessary for emergent medical care [14].

Some patients experience claustrophobia and have difficulty cooperating during the study. Anxiety reactions [59] are estimated to occur in 4–30% of patients [60]. Patients with extreme skeletal abnormalities such as advanced scoliosis or flexion contractures, although motivated, may be unable to lie motionless or supine on the solid, uncushioned MRI table for the extended duration of a spine MRI. These patients may require general anesthesia for positioning and comfort or may need adjunctive pain medication.

Current advances in physiological monitors and anesthesia machines for the MRI environment have optimized the ability of the anesthesia care provider to provide safe care in the MRI suite. Remote monitor displays make it unnecessary for the anesthesiologist to remain in the scan room during most of the procedure; only during breath-holding procedures or contrast injection is it necessary for the anesthesiologist to enter the scanner room during the imaging procedure. The Dräger Fabius® MRI (Dräger Medical AG, Lubeck, Germany) was designed for MRI and approved by the FDA in 2008 for use within both a 1.5 and 3 T magnetic field up to field strength of 400 G (Fig. 41.2). The Fabius, equipped with two vaporizers, has an electronically controlled ventilator capable of

(A)

(B)

Figure 41.2 (A) Modern MRI-compatible anesthesia machine, with two vaporizers and a ventilator capable of multiple ventilation modes. This system is certified for function in 1.5 and 3 T MRI systems. The machine must be situated outside the 400 G magnetic field radius for proper functioning. (B) Close-up view of the magnetic field detection alarms; these are set off when in a magnetic field of 400 G or more. *Source:* Courtesy of Drager Medical Inc., Telford, PA, USA.

delivering multiple modes of ventilation in the MRI suite. Advances in physiological monitoring now offer the ability to monitor electrocardiogram (ECG) and pulse oximetry in a 1.5 and 3T MRI scanner via wireless, fiberoptic communication (Invivo Precess®, Invivo, Orlando, FL, USA and Medrad Veris® Monitor, Bayer, Indianola, PA, USA) (Fig. 41.3). Conventional ECG monitoring is not possible because as the lead wires traverse the magnetic fields, image degradation occurs and, most importantly, the ECG leads will heat and cause patient burns. Fiberoptic ECG monitoring is necessary to minimize the risk of patient burn. Even with fiberoptic cables, it is important to recognize that the connections between the ECG pads and the telemetry box are still hardwired, and careful attention must be paid to prevent frays, overlap, exposed wires, and knots in the cables [61]. It is advisable to provide an interface between the patient's skin and the ECG leads (e.g. a facecloth). There have been reports of burns from the ECG leads as a result of a current generated between the leads and the patient's sweat. Pulse oximeters are also fiberoptic. Failure to remove the conventional pulse oximeter probe/adhesive has resulted in second- and third-degree burns [61,62]. Respiratory and anesthetic gas monitoring has advanced to the point that complete monitoring, as would occur in the operating room, is now routine with MRI-compatible equipment. For patients with a natural airway, a divided nasal cannula both to administer

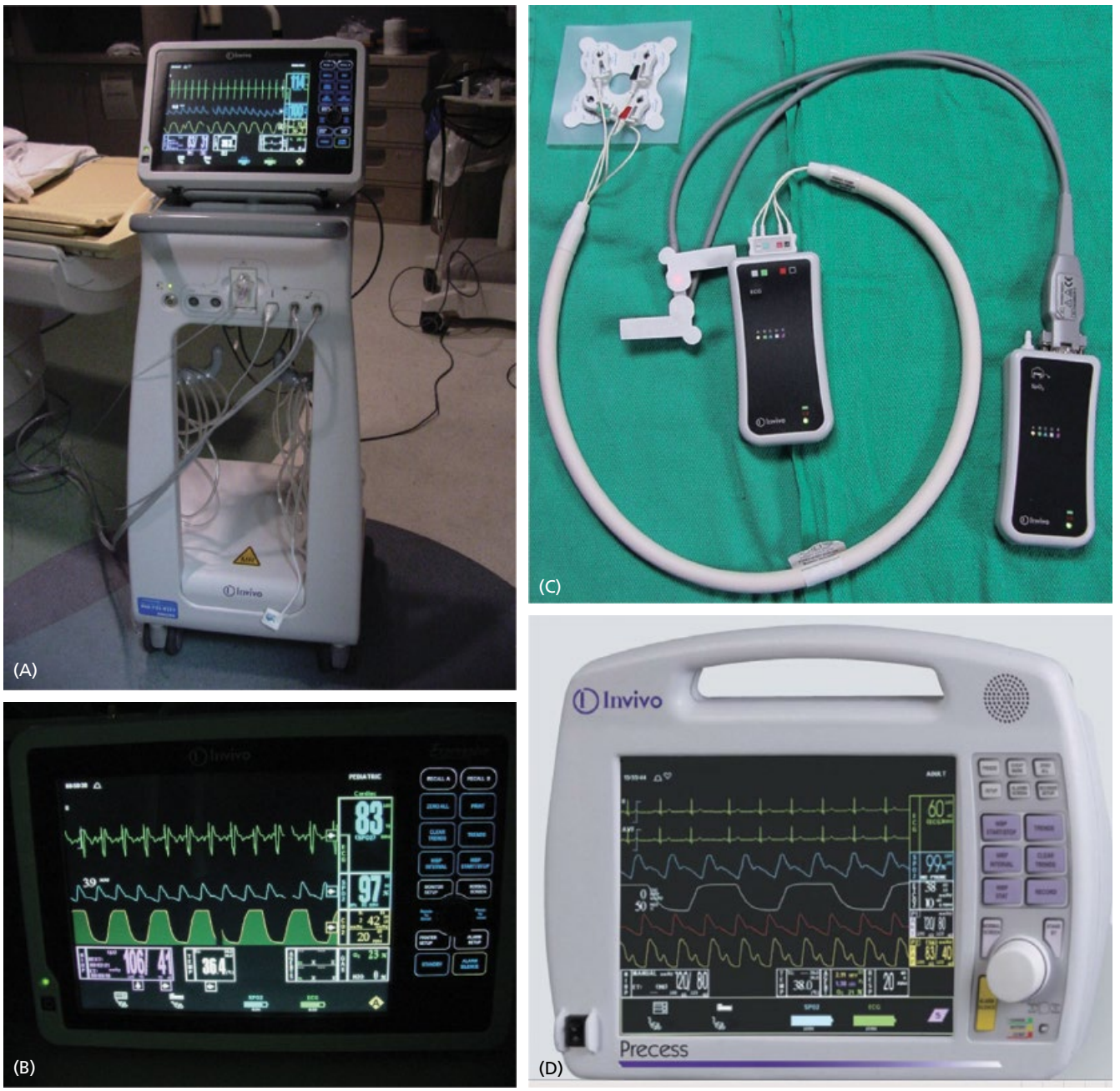

Figure 41.3 (A) Modern MRI-compatible monitor situated in a MRI scanner room. These monitors are capable of monitoring ECG, SpO_2, oscillometric blood pressure, end-tidal CO_2 via a nasal cannula, endotracheal tube, or laryngeal mask airway, anesthetic gases, temperature, and two invasive blood pressures. (B) Remote display in the control room. (C) Wireless technology for ECG and SpO_2 which minimizes artifacts and allows accurate signal transmission. (D) Close-up of monitor screen with all parameters displayed. *Source:* Courtesy of Invivo Corp., Orlando, FL, USA.

supplemental oxygen and to monitor end-tidal CO_2 to detect airway obstruction and to ensure optimal ventilation, is important.

Despite the advancing technology in physiological monitors and anesthesia equipment, the MRI environment continues to pose some limitations for anesthesia care. Surface (skin) temperature monitoring cables are available, but axillary temperature may not be an adequate substitute for rectal or esophageal temperatures. Core temperature monitoring can be accomplished with a FDA-approved physiological device and disposable temperature probes that are MRI conditional and manufactured by Invivo (Orlando, FL, USA) and Philips Healthcare (Andover, MA, USA).

The advent of special MRI-compatible infusion pumps for agents such as propofol allow the pump to be deployed in the scan room itself, with short tubing lengths to allow accurate delivery of the intended drug or fluid dose. These pumps include the MRIdium® (iRadimed Corp., Winter Park, FL, USA) and Medrad Continuum Infusion System® (Warrendale, PA, USA) (Fig. 41.4). These pumps have remote consoles so that the infusion rates can be changed from the MRI control room via wireless communication algorithms. Although some conventional infusion pumps (e.g. Medfusion® 3500 syringe pump, Smiths Medical, Kent, UK) claim safety in an MRI environment beyond specified distances from the magnet, depending on magnet strength, it is not recommended that these devices be used in the scanner room. Besides the MRI safety aspect, the magnetic and radiofrequency fields can cause pump malfunction in standard systems. An alternative is to utilize standard infusion pumps just outside the door of the scanner room, with multiple lengths of infusion tubing threaded under the door, reaching inside the bore of the scanner to the patient. This is commonly used for patients receiving vasoactive infusions requiring very accurate microinfusion pumps. Problems with this approach include increased resistance through the long tubing causing pump malfunction.

The magnetic field may also affect the ECG. The changes in the T wave are not due to biological effects of the magnetic field but rather to superimposed induced voltages. This effect of the magnetic field on the T wave is not related to cardiac depolarization, since no changes to the P, Q, R, or S wave have ever been observed in patients exposed to fields up to 2 T. There are no reports of MRI affecting heart rate [63], ECG recording [64], cardiac contractility [65], or blood pressure [66]. One study, however, found that humans exposed to a 2 T magnet for 10 min developed a 17% increase in cardiac cycle length (CCL, the duration of the R-R interval). The CCL reverted to pre-exposure length within 10 min of removing the patient from the magnetic field [67]. The implications of this finding are unclear. While this change in patients with normal hearts may be of no consequence, the implications of this finding in patients with fragile dysrhythmias or sick sinus syndrome have yet to be determined.

Average noise levels of 95 decibels (dB) have been measured in a 1.5 T MRI scanner, comparable to noise levels of very heavy traffic (92 dB) or light road work (90–110 dB). Exposure to this level of noise has not been considered hazardous if limited to less than 2 h per day [68]. There are case reports, however, of both temporary [69] and permanent [70] hearing loss after an MRI scan. Magnets of 3 T offer the advantage of less image degradation and improved neuro- and musculoskeletal imaging. However, as the field strength increases, so does the noise [71]. In fact, the peak sound pressure level of a 3 T magnet exceeds 99 dB, the level approved by the International Electrotechnical Commission. Ear protection is required of all

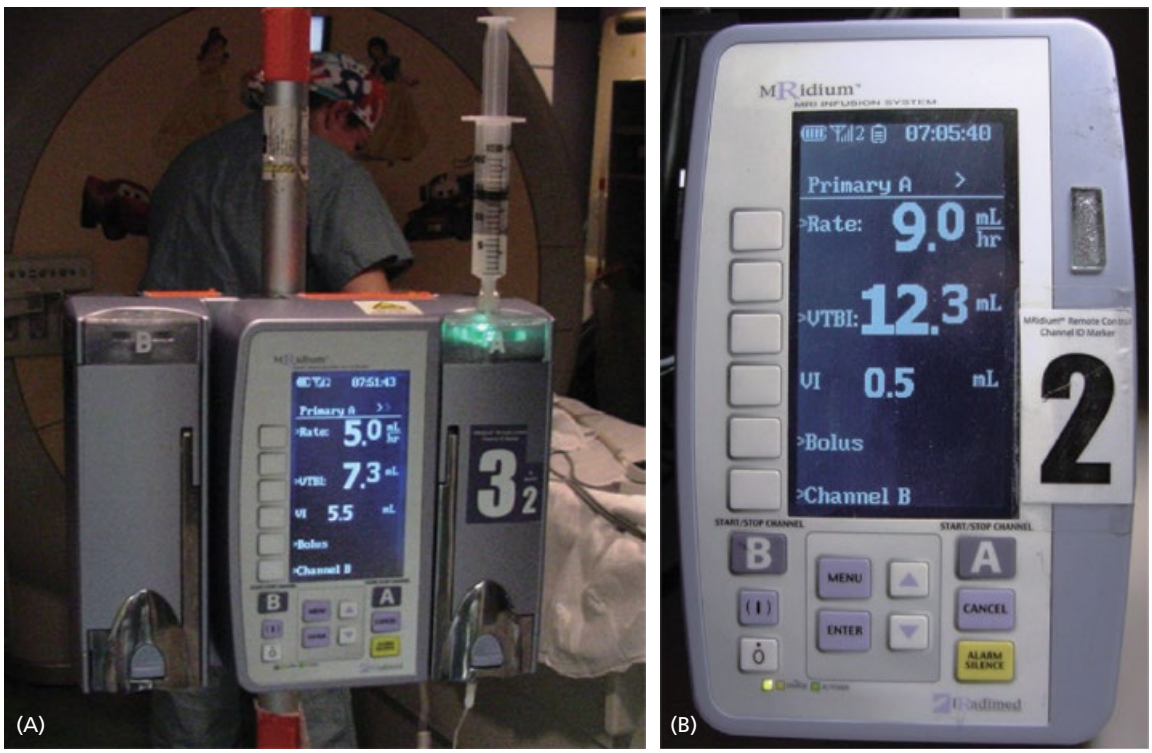

Figure 41.4 (A) MRI-compatible infusion pump in the scan room, with propofol infusing in a 7 kg infant. (B) Remote wireless display and controller.

patients undergoing MRI studies for research purposes [37]. Earplugs or MRI-compatible headphones are strongly encouraged for all patients and personnel (family members included) who remain in the 3 T magnet during imaging. fMRI provides additional challenges in the 3 T environment: the noise of the 3 T magnet can interfere with the acoustic stimulation generated for purposes of obtaining the fMRI [72,73].

Although studies in mice [74] and dogs [75] suggest that exposure to magnetic fields may increase body temperature, it is unlikely that static magnetic fields up to 1.5 T have any effect on core body temperature in adult humans [76]. This may be of greater concern in infants and small children, for example in cardiac MRI studies, which require a long time for the procedure [77]. The specific absorption rate (SAR) is measured in watts per kilogram and is used to follow the effects of RF heating. The FDA allows a SAR of 0.4 W/kg averaged over the whole body [78]. *Ex vivo* exposure of large metal prostheses to fields over six times that experienced in MRI have not revealed any appreciable heating [79]. So far, there has been no conclusive evidence that RF is a significant clinical issue in magnets up to 3 T. Conversely, the need for a cool room to ensure functioning of the MRI scanner, and the lack of MRI-compatible forced-air warming systems, combined with the frequent need for small infants to undergo MRI scanning, often results in hypothermia. Usually, the best prevention is to swaddle the infant in warmed blankets before the procedure to minimize heat loss, and utilize a condenser humidifier if an endotracheal tube or laryngeal mask airway (LMA_ is used to manage the airway.

Intravenous gadopentetate dimeglumine (gadolinium (e.g. Magnevist®)) is used to enhance MRI images. With an elimination half-life of 1.3–1.6 h, gadolinium is excreted via the kidneys after forming a complex with chelating agents [80]. Adults and children have similar elimination half-lives, with 95% excreted within 72 h [81]. Because gadolinium does not contain iodine, it does not produce an osmotic load [82]. Important warnings from the FDA suggest that patients with advanced kidney failure are at risk of developing nephrogenic systemic fibrosis or nephrogenic fibrosing dermopathy after gadolinium-based MR contrast agents. The FDA first notified healthcare professionals and the public about this risk in June 2006. The ASA MRI Advisory Panel concluded that anesthesiologists should not administer gadolinium to patients with acute or severe renal insufficiency because of the elevated risk of nephrogenic systemic fibrosis. Rather, the need for and actual administration of gadolinium contrast in this patient group should be the responsibility of the radiologist, nephrologist, and other appropriate consultants [37]. Newer forms of gadolinium-based contrast agents (gadoteridol (e.g. ProHance®), gadobutrol (e.g. Gadavist®), gadoterate meglumine (e.g. Dotarem®)), have chemical structures (macrocylic versus open chain) that minimize the likelihood of dissociation of the gadolinium from its chelate to become toxic-free gadolinium, the cause of the nephrogenic systemic fibrosis [83].

KEY POINTS: DIAGNOSTIC RADIOLOGY

- It is important to remember that the magnet is always on and the dangers of the electromagnetic field are always present
- Portable equipment to be brought into the magnet room (zone IV) should be identified with a green square "MRI safe" or yellow triangle "MRI conditional" label
- The American College of Radiology recommends that the MRI suite be divided into four zones with increasing safety and access requirements as patients, staff, and equipment move closer to the scanner
- Core temperature monitoring can be accomplished with a FDA-approved physiological device and disposable temperature probes that are MRI conditional
- Cardiac pacemakers present a special hazard in and around the MRI scanner, especially in patients who are pacemaker dependent

Interventional radiology and angiography

Interventional techniques include non-vascular and vascular intervention [78]. Embolization and sclerotherapy are utilized for treating vascular malformations, aneurysms, fistulas, and hemorrhage as well as accomplishing renal ablation and presurgical embolization of hypervascular masses. Percutaneous transluminal angioplasty and fibrinolytic therapy are emerging techniques in pediatric institutions. Even in the smallest babies, great success is being reported, and the important contribution that adequate sedation and analgesia can make to ultimate outcome has been recognized [84,85]

Vascular malformations are congenital aberrant connections between blood vessels and may be composed of lymphatic, arterial, and venous connections. These lesions, present at birth, are often discrete and not clearly visible, although they may expand rapidly, growing with the child (Fig. 41.5). This rapid proliferative phase may occur in response to hormonal changes (pregnancy, puberty), trauma, or other stimuli [86]. Moreover, they may be high-flow or low-flow lesions, depending on which vessels are involved. High-flow lesions include arteriovenous fistulas, some large hemangiomas, and arteriovenous malformations. High-output cardiac failure and congestive heart failure with possible pulmonary edema should be anticipated especially with high-flow lesions. Low-flow lesions consist of venous, intramuscular venous, and lymphatic malformations. Careful planning is essential in the management of these patients as well as for unanticipated emergencies. Vein of Galen aneurysmal malformations (VGAMs) constitute 1% of all intracranial vascular malformations [87]. This lesion is actually a cerebral arteriovenous fistula of the median prosencephalic vein that fails to regress during fetal life. It usually has multiple arterial feeder vessels, and drains via the straight sinus or persistant falcine sinus (Fig. 41.6) [88,89]. Anesthetic management of this challenging congenital anomaly requires familiarity with the nature and technical demands of the interventional radiology procedure, along with the underlying anatomical and physiological challenges and associated risks. Cardiac failure occurs in these patients as the large flow volume of the VGAM shunt is returned to the right atrium and pulmonary circulation with pulmonary vasoconstriction and pulmonary hypertension resulting in right ventricle failure. Early identification and staged embolization of the feeding arteries and draining veins may reduce blood flow and lead to a greater survival

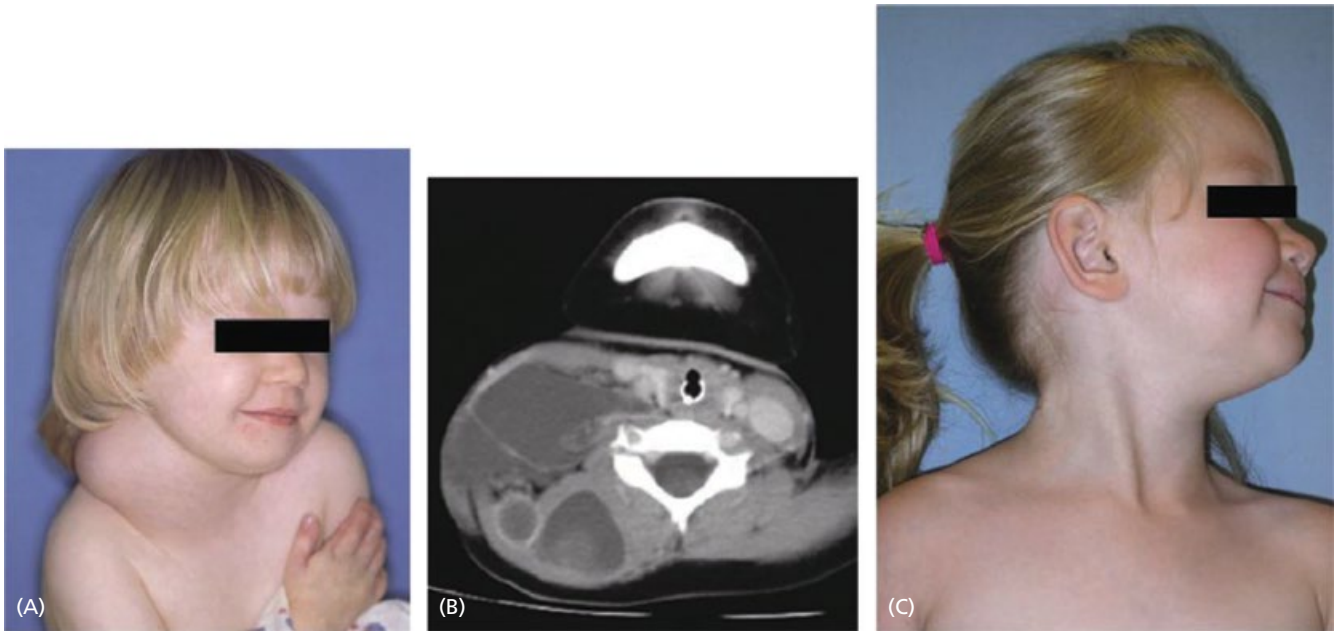

Figure 41.5 Macrocystic lymphatic malformation of the neck and right upper extremity, treated with direct injection of ethanol and then four sessions of OK-432 injection. The ethanol injections were ineffective, but the OK-432 injections resulted in complete regression of the mass. (A) Clinical photograph before OK-432 sclerotherapy showing a large focal right neck mass. (B) Axial CT scan after intravenous contrast medium injection showing macrocysts in the right neck. The thick-walled cyst was previously injected with ethanol. (C) Clinical photograph taken 1 year after four injections of OK-432 showing complete regression of the right neck mass. *Source:* Reproduced from Burrows and Mason [309] with permission of Elsevier.

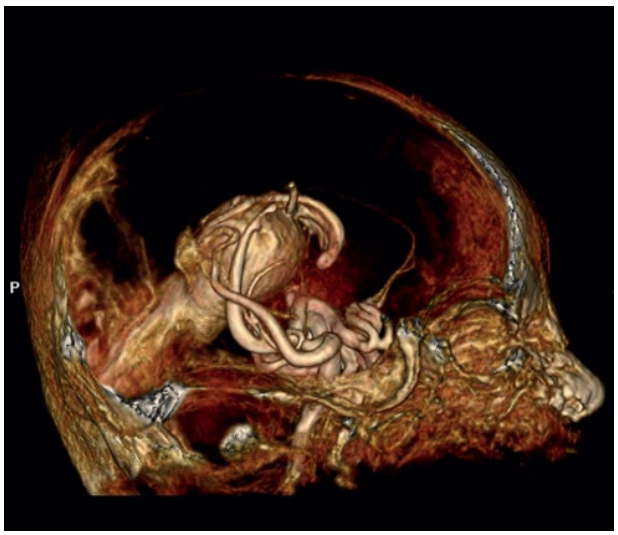

Figure 41.6 MRI angiography 3D reconstruction of a very large Vein of Galen aneurysmal malformation located in the pineal region with aneurysmal dilation. It receives blood predominantly from the vertebral arteries although some anterior supply is also suspected. Drainage is via the straight sinus to the torcula and bilaterally to the internal jugular veins. *Source:* Courtesy of A. Prof Frank Gaillard, Radiopaedia.org, rID: 22778.

rate in these patients [90]. Anesthetic management must address this complex pathophysiology and be tailored to the severity of heart failure and pulmonary hypertension [91]. The most critically ill of these patients are neonates receiving substantial ventilatory support, in addition to inotropic support and inhaled nitric oxide. Right-to-left shunting via a patent ductus arteriosus and patent foramen ovale is common, patients are often cyanotic, and injection of embolic material may traverse the malformation and reach the right ventricle, worsening the pathophysiology. Often several staged embolization procedures are needed to reduce the level of shunting and stabilize the patient. A recent systematic review and meta-analysis of VGAM endovascular embolization documented 34 published studies involving 667 patients [92]. Forty-four percent of the patients were neonates, and 41% were infants 1 month to 2 years of age. Complete occlusion was obtained in 57%, partial occlusion in 43%, and mortality rate was 12%; causes included intractable heart failure, neurological complications, and technical problems. The overall complication rate for cerebral hemorrhage and venous thrombosis was lowest with three or more staged embolizations (42% versus 59% with a single embolization). This review underscores the complex nature of the VGAM treatment paradigm and the need for thorough multidisciplinary planning in the approach to these challenging patients.

Because vascular malformations enlarge over time, even asymptomatic lesions may require intervention. Symptomatic patients may suffer from pain, tissue ulceration, disfigurement, airway or cardiovascular compromise, impairment of limb function, coagulopathy, claudication, hemorrhage, and progressive nerve degeneration or palsy. Because large vascular lesions require multiple embolizations, parents and patients are often comforted by seeing familiar faces, another benefit of having a team of anesthesiologists staffing the radiology suites. Sequential vascular embolization can be used as a bridge to surgical resection.

Large hemangiomas may be associated with the coagulopathy of the Kasabach–Merritt syndrome. In this condition, the hemangioma traps and destroys platelets and other coagulation factors, resulting in thrombocytopenia and an increased risk of bleeding. As the hemangioma involutes, the coagulation status improves [93]. A condition described as systemic intravascular coagulation can occur after the embolization of extensive vascular malformations. This condition is marked

by an elevated prothrombin time with a decrease in coagulation factors and platelets.

When embolizing vascular malformations, radiologists often aim to cut off not only the feeding vessels but also the central confluence (nidus) where much of the arterial shunting occurs. Embolic agents include stainless steel mini-coils, absorbable gelatin pledgets and powder, detachable silicone balloons, polyvinyl alcohol foam, cyanoacrylate glue, and ethanol. The choice of agent depends on the clinical situation and the size of the blood vessel. When permanent occlusion is the goal, polyvinyl alcohol foam and ethanol are often employed. Both occlude at the level of the arterioles and capillaries. Medium to small-sized arteries may be occluded with coils, which are the equivalent of surgical ligation. Particularly in trauma situations, when only temporary (days) occlusion is the goal, absorbable gelatin pledgets or powder are used [94].

Absolute ethanol is injected in vascular malformations to promote sclerosis. Sclerotherapy or embolization with absolute (99.9%) ethanol increases the risk of developing a post-procedure coagulopathy [95] marked by positive d-dimers, elevated prothrombin time, and decreased platelets. Ethanol causes thrombosis because it injures the vascular endothelium [96]; it also denatures blood proteins. Extensive ethanol injections can cause hematuria and urinary catheters should be inserted to monitor urine output, diuresis, and hematuria. Liberal intravenous fluid replacement will ensure that the hematuria clears prior to discharge. Ethanol can cause neuropathy and tissue necrosis if not injected selectively. Finally, ethanol can also produce significant serum alcohol levels (Fig. 41.7). Up to 1 mL/kg of ethanol can be administered; blood ethanol levels have been greater than the intoxication level of 0.008 mg/dL [97]. Patients with high serum ethanol levels are either sedated or extremely agitated, depending on their individual response to intoxication.

Embolization or balloon occlusion of arteriovenous malformations (AVMs), vascular tumors, intracranial aneurysms, and fistulas carries considerable risk of catastrophic results. Such risks include a sudden intracranial hemorrhage, acute cerebral ischemia, or catheter or balloon migration. If sedated, the patient may require urgent airway management. Very long cases require a urinary catheter, especially if contrast material is utilized. AVMs involving the head and neck frequently require cannulation of the external carotid artery branches and the thyrocervical trunk. All patients scheduled for embolization should be typed and cross-matched for blood. Those patients who undergo embolization of AVMs of the head and neck are at risk for stroke, cranial nerve palsies, skin necrosis, blindness, infection, and pulmonary embolism [98]. It is important to assess and document the full return of baseline neurological status after the patient is extubated.

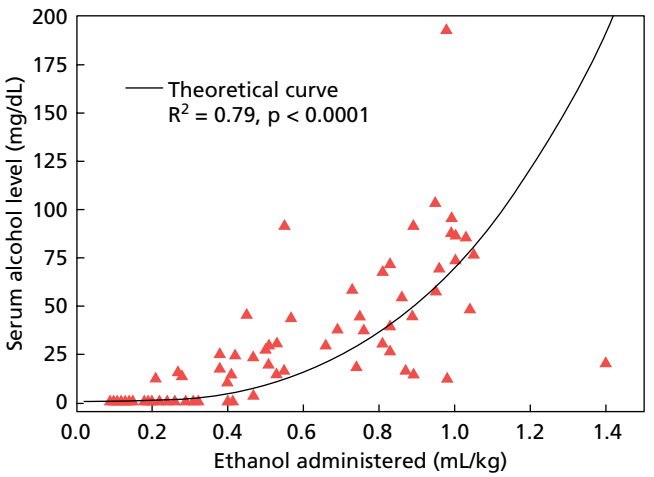

Figure 41.7 Graph showing the positive relationship between serum ethanol level and amount of ethanol administered. Solid line indicates the theoretical curve, where *x* is the amount of ethanol administered, and *y* is the predicted serum ethanol level. Triangles represent empirical values. *Source:* Reproduced from Mason et al [97] with permission of RSNA.

Recent advances have involved the use of provocative testing during cerebral imaging in order to identify and protect targeted areas of the brain prior to embolization. Provocative or superselective Wada testing (intracarotid sodium amobarbital procedure) has become an important part of endovascular management of numerous extracranial and intracranial vascular conditions. It can be used with neurophysiological monitoring in cases in which patient cooperation and steadiness are important [99]. Nevertheless, the value of awake neurological assessment (wake-up test) cannot be underestimated when neurophysiological monitoring responses are equivocal. Barbiturates, etomidate, propofol, and, most recently, dexmedetomidine have been described as agents able to maintain sedation while still preserving the patient's ability to respond [100–105].

Anesthesiologists need to have in-depth understanding of the physiology of the cerebral lesions to be treated, the requirements for successful treatment, and the potential effects of the proposed treatment. Cerebral angiography requires motionlessness as well as exquisite control of ventilation. Anesthetic technique, in choice of agent as well as in control of arterial CO_2 tension, may affect cerebral blood flow and volume and hence the quality of the scan. Cerebral angiography in children may be performed for the diagnosis or follow-up of Moya Moya disease and the anesthetic technique should minimize the risk of transient ischemic attacks and stroke during the procedure [106]. An arterial line for this short procedure is generally not required. Normocapnia is desirable in the vast majority of cases, and any proposed acute hypocapnia should be discussed with the proceduralist. The risk of significant bleeding is rare but adequate intravenous access is prudent. Other considerations include controlled ventilation to facilitate access to and visualization of the vasculature for the radiologist. In the event of vasospasm or difficult access, the radiologist's direct administration of nitroglycerin in small doses (25–50 μg) may facilitate visualization and access. Occlusion of the venous portion of the AVM without complete occlusion of the arterial inflow vessels could result in acute swelling and bleeding. Vascularity reduction through occlusion of major feeder vessels is the goal of embolizing large AVMs prior to planned surgical excision. This may be accomplished as a staged procedure over several days, involving repeat anesthetics.

Angiographic imaging may be enhanced through the use of glucagon. Glucagon is effective for digital subtraction angiography, visceral angiography, and selective arterial injection in the viscera. When needed, glucagon is administered in divided doses of 0.25 mg to a maximum of 1.0 mg intravenously. Risks include glucagon-induced hyperglycemia, vomiting (particularly when given rapidly), gastric hypotonia,

and provocation signs of pheochromocytoma [107–109]. Children who receive glucagon should routinely receive prophylactic antiemetics.

Ultrasound-directed procedures

Needle biopsies and drainage procedures (kidney, liver, lung, muscle, unknown mass, unknown fluid) are directed with ultrasound guidance. Ultrasound is useful for placement of difficult central catheters and peripherally inserted central catheters. The requirement for general anesthesia versus sedation for ultrasound-guided procedures depends in part on the duration of the procedure, the location involved, the risks associated with the procedure, and any procedural requirements. The need for controlled ventilation with breath holding may require an endotracheal tube and general anesthesia. Associated secondary effects of the end-organ disease must be kept in mind in the overall anesthetic care plan.

Biopsies of anterior mediastinal masses pose serious challenges because of the risk of cardiopulmonary catastrophes [110]. Maintenance of spontaneous breathing is generally recommended because positive pressure ventilation can compromise blood flow in the pulmonary vessels which are already narrowed by the tumor mass. The supine position can exacerbate the changes in hemodynamic and respiratory physiology. Turning the patient prone or lateral may alleviate the obstructive symptoms or cardiac compromise. An otolaryngologist with a rigid bronchoscope or, in some cases, the ability to initiate cardiopulmonary bypass, should confirm ability to maintain spontaneous breathing before the procedure. Many anesthetic strategies can facilitate this goal, including inhalation techniques with potent volatile agents or intravenous anesthetic techniques such as use of ketamine/dexmedetomidine [111]. Regardless of the choice, an inadequate anesthetic with subsequent patient movement risks accidental puncture of the internal mammary vessels that can result in a life-threatening hemorrhage [112,113]. See Chapter 26 for further discussion about anterior mediastinal masses.

KEY POINTS: INTERVENTIONAL RADIOLOGY AND ANGIOGRAPHY

- Anesthetic management of challenging vascular malformations requires familiarity with the nature and technical demands of the interventional radiology procedure, along with the challenges and associated unique risks of the underlying disorder
- VGAM may result in severe heart failure and pulmonary hypertension in the neonate, and requires significant resources and multidisciplinary planning for staged procedures that can optimize outcomes
- Large hemangiomas may be associated with the coagulopathy of the Kasabach–Merritt syndrome
- Anesthesia for ultrasound-guided biopsies of anterior mediastinal masses is usually designed to preserve spontaneous breathing and may be accomplished with volatile or intravenous anesthetics including combining the analgesic effect of ketamine with the sedative effect of dexmedetomidine

Nuclear medicine

Nuclear medicine is one of the oldest functional imaging disciplines. These scans are useful for identification of epileptic foci in refractory epilepsy, evaluation of cerebrovascular (Moya Moya) disease, and the evaluation of cognitive and behavior disorders [114]. Anesthesiologists become involved when the child's medical history suggests that procedural sedation would not be appropriate. In order to complete these scans, the child must remain motionless for at least 1 h.

The two most common nuclear medicine studies that require the administration of an anesthetic are single photon emission computed tomography (SPECT) scans and positron emission tomography (PET) scans. SPECT scans use single-photon γ-emitting radioisotopes and rotating gamma cameras to produce 3D brain images. SPECT scans involve the use of radiolabeled technetium-99 (half-life 6 h), which has a high rate of first-pass extraction as well as intracellular trapping in proportion to regional cerebral blood flow [115]. This scan is ideal when seeking seizure foci, and often precedes surgical resection of the identified focus. The technetium radionuclide is ideal because it remains intracellular and can be visualized on the scan hours after a seizure has occurred. Ideally, the child should be scanned within 1–6 h of the seizure. The radionuclides are physiologically harmless and non-allergenic. Caretakers should, however, wear gloves to minimize contact with radiation-containing secretions.

PET scans use PET and radionuclide tracers of metabolic activity such as oxygen or glucose metabolism [116,117]. Unlike SPECT scans, PET scans should be performed during the seizure itself. Because of the short half-life of the glucose tracer (110 min), the scan is best completed during the seizure or within 1 h thereafter.

In addition to using PET scans for diagnostic purposes, nuclear imaging is also being used as an intraoperative adjunct to identify neoplasms, in much the same way that MRI has been incorporated into the surgical suite. Surgical suites are currently being built that are equipped with PET scanners [118]. The anesthetic implications of the nuclear medicine environment involve largely the safety precautions that must be implemented with respect to the radioactive nucleide. All bodily fluids (includes saliva, sweat, and urine) must be handled with radiation safety precautions.

Metaiodobenzyl guanidine (MIBG) is a compound that can be combined with radioactive iodine (^{131}I) to deliver targeted radiotherapy to treat high-risk neuroblastoma. MIBG is a compound that is absorbed by neuroblastoma cells; when combined with ^{131}I it provides targeted radiation to neuroblastoma cells with much less risk to normal, adjacent tissue.

Magnetoencephalography

Magnetoencephalography (MEG) is a neuroimaging modality that uses extremely sensitive magnetometers to record and localize electrical activity of the brain [119,120]. The signals are produced by superconducting quantum interference devices and amplified, and are used most often in children to localize seizure foci in preparation for epilepsy surgery. MEG is a functional modality utilized in the awake patient whenever possible, but some younger children will require sedation to hold still and tolerate positioning in the head coil for the procedure. There is a paucity of published reports about sedation techniques for MEG in children; but a regimen that

has been effective at Texas Children's Hospital is dexmedetomidine 1 μg/kg load over 10 min, and infusion of 0.5–2 μg/kg/h for the scan, which preserves the MEG signals and allows successful completion of a diagnostic-quality study in young children in most all cases. Opioid supplementation with fentanyl or remifentanil is frequently utilized; propofol is to be avoided. The scans require 1.5–2 h, and the patients are prone to seizures; if seizures are brief they may occur without airway compromise, but can be treated with midazolam if necessary.

Radiation oncology

Radiation oncologists use ionizing photons to destroy lymphomas, acute leukemias, Wilms tumor, retinoblastomas, and tumors of the central nervous system in children. Repeat sessions are typical, requiring reliable motionlessness in order to precisely aim the beam at malignant cells while sparing healthy cells. A planning session in a simulator is often scheduled prior to the initiation of radiotherapy so that fields to be irradiated can be plotted and marked.

Radiotherapy

Radiotherapy is usually very brief and non-painful. The key issue is the anesthesiologist's limited access to the patient. Remote video monitoring as well as ECG and pulse oximeter use is crucial. Two, or in some locations, three video cameras are used to look at the monitors, the chest, and the face of the patient. Central access in young children helps immensely. It is important to remember that babies undergoing radiotherapy following a prolonged fast are at risk for hypoglycemia; delayed awakening or tremulousness should prompt a glucose determination.

Fractionated radiotherapy divides the total radiotherapy course into discrete daily sessions, allowing normal tissue repair between sessions while the tumor burden is lessened or destroyed. *Hyperfractionated* or multiple session daily radiotherapy is a modality reported primarily in adults for head and neck cancer. The rationale for twice-daily fractionation in children is that fractionation to growing bone in rats reduces the growth deficit by 25–30%; the hope is that other normal tissues may be similarly spared during growth [121,122]. While one successful approach has been to give infants an initial formula feeding 6 h before their first treatment and keep them NPO until recovery from their second anesthetic 6 h after the first [123], with the current liberalization of NPO guidelines we prefer to give children clear liquids during their recovery from the first anesthetic and keep them NPO thereafter for 4 h prior to the second anesthetic.

Stereotactic radiosurgery

Stereotactic radiosurgery (gamma knife) is a major advance in the treatment of selected intracranial arteriovenous malformations and tumors in children [124]. A focused, single, large fraction of radiation is used instead of smaller, daily fractions. Stereotactic radiosurgery uses relatively weak-intensity γ-rays produced by 201 cobalt-60 (^{60}Co) sources which intersect at a single point where all 201 beams converge to destroy tumors, vascular malformations, or abnormal tissue sites within the brain. Normal brain tissue surrounding the abnormality is therefore relatively protected from radiation effects. For optimal results, tumor volume ideally has to be small (≤14 cm^3) [125].

The stereotactic procedure begins with a CT scan or MRI, followed by computer calculations for dose and the 3D coordinates for the beam. The child is placed in a stereotactic headframe which is screwed into the cranium. Most adults are able to tolerate the entire procedure with local anesthesia or sedation. Adults and older children who tolerate this procedure with sedation alone may vomit as a result of the anxiety, the headache, or the location of the tumor itself. Once the calculations are complete, the patient is transferred to the radiosurgery suite. Following the irradiation, the patient is allowed to emerge from the anesthetic [124]. The most common perioperative problem is nausea and vomiting, probably due to radiation sensitivity of the chemoreceptor trigger zone. Because the headframe is heavy and cumbersome, it is difficult for the vomiting patient to turn their head in order to protect their airway. Children (including most adolescents) typically require a general anesthetic. General anesthesia with tracheal intubation is induced prior to placement of the headframe. The key for removal of the headframe is taped to the frame itself. A nasogastric tube is placed for the day's anesthetic.

Stereotactic radiotherapy

Stereotactic radiotherapy is more precise localization of the fractionated radiation dose over the same duration of time as conventional radiotherapy, with the adjunctive use of a headframe. Considerations for the headframe include ease of application, reliability, ability to deliver supplemental oxygen and support the airway with a facemask if needed, and rapid removal of the facial restraint should it become necessary.

Total body irradiation

Total body irradiation (TBI) is generally performed twice a day over a 6-week period, usually in preparation for a bone marrow transplant. As these patients progress with their TBI treatment and become more immunocompromised, there is an increased risk of acquiring an illness during the course of treatment. Vomiting, respiratory illness, poor nutrition, or hypovolemia are all possible. Cancellation of a TBI treatment because of an associated illness is discouraged because it disrupts the course of treatment and could compromise their overall prognosis. Ondansetron in combination with dexamethasone or propofol has been found to be beneficial as a prophylactic for nausea and vomiting in children undergoing TBI and should be considered for first-line antiemetic therapy [126]. Although anesthesiologists are wary of the risks of aspiration, both sedation and general endotracheal anesthesia have been found to decrease the incidence of vomiting with TBI [127,128].

Proton radiotherapy is a newer modality thath can limit irradiation of normal tissues, because the proton is a charged particle and the radiation dose can be directed to a smaller area and there is a minimal exit radiation dose. As of 2017, there are approximately 60 of these centers in operation worldwide, including 20 in the USA [129]. Pediatric cancers amenable to treatment with this modality include intracranial tumors, sarcomas, ependymoma, neuroblastoma, and retinoblastoma [130]. Treatments commonly require 30–90 min, and children age 4 years and under usually require anesthesia or sedation. A survey of 17 centers documented that total IV

anesthesia with propofol, with nasal cannula, or facemask was utilized for 57% of anesthetics, general anesthesia with sevoflurane and LMA in 36%, and intubated general anesthesia in 7%. Of note, 43% of proton therapy centers had no anesthesia waste gas evacuation capability [131]. Complicating delivery of anesthesia care in this population is that many proton radiation centers are freestanding facilities, often at some distance from the hospital or surgery centers.

Dental and oral surgery

The high prevalence of pediatric dental disease, breadth of options available for difficult child behavior, and parental expectations will generate and maintain the need for sedation/anesthesia services in children who presented for dental procedures [132,133]. Oral sedation ± nitrous oxide inhalation have been the mainstays of pediatric dental sedation for many years; however, recently parents and practitioners have become accustomed to outpatient general anesthesia for children [134]. Moderate or deep sedation or general anesthesia are required for patients who have special needs, or when the dental or surgical requirements become more complex [135].

Midazolam alone may not provide sufficient sedation and the addition of an opioid can increase the risk of respiratory depression or vomiting. Dexmedetomidine appears to provide a good alternative for successful dental sedation due its analgesic effects, antisialogog properties, anxiolytic and sympatholytic effects, and lack of respiratory depression [136].

Recent reports have pointed to the highest adverse event risk group as being children less than 6 years of age and being cared for by a general dentist [137,138]. No single sedative was implicated in these reports. These findings have led to increased scrutiny of pediatric dental sedation by the public and the medical community. Each US state has unique requirements for a dentist to perform procedural sedation, with considerable variations among states regarding training standards, education, and credentials.

The equipment requirements for dental surgery in NORA locations are identical to those for the operating room. Supplies, drugs, and equipment necessary for the administration of anesthesia and emergency management should be immediately available in a designated cart in these locations. The ASA issued a statement on NORA locations in October 2003, which was last amended in October 2013 [139]. If a central fresh gas supply is not available, portable cylinders can be used. Additional considerations for the medically complex patient undergoing dental rehabilitation are necessary, e.g. congenital heart disease patients before surgery or transplant, patients with craniofacial anomalies and difficult airways, or patients with complex genetic or metabolic syndromes. Adequate preoperative planning, equipment and drugs for emergencies, and plans for postoperative admission are often necessary in NORA locations.

Clinic and office procedures

Endoscopy

Gastrointestinal endoscopy constitutes the bulk of procedures performed by a pediatric gastroenterologist [140]. Depending upon the patient and the type of procedure contemplated (therapeutic versus diagnostic), children may require no sedation, minimal to moderately deep sedation, or general anesthesia. Over the past 20 years, the volume of endoscopic procedures has increased by 2–4-fold in the adult community, and has most likely increased at a similar rate in children [141].

Although some recommend that deep sedation be limited to anesthesiologist delivery only [142–148], gastroenterologists have reported that they too are able to safely administer and/or supervise sedation [149]. The ASA's statement on the safe use of propofol makes the point that when it is not possible to have an anesthesiologist involved in the care of a patient then "non-anesthesia personnel who administer propofol should be qualified to rescue patients whose level of sedation becomes deeper than initially intended and who enter, if briefly, a state of general anesthesia" [150]. It is estimated that one-quarter of all adult endoscopies are performed with propofol sedation [141], although there is a wide variation in pediatric practice [151]. Children with more complex medical problems, anticipated airway difficulties, morbid obesity, or behavioral problems can undergo their procedure in the operating room. Regardless of the site of the procedure, all patients scheduled for sedation for endoscopy should be evaluated beforehand to confirm that they are appropriate candidates. In addition, the anesthetic technique depends on the procedure, the patient, and the skill of the endoscopist as well as the limitations and capabilities of the endoscopy suite.

Esophagogastroduodenoscopy

Access to the airway is limited once a transoral endoscope is in place. It is important to maintain spontaneous ventilation during deep sedation because any airway intervention needed typically requires the removal of the endoscope. The two most stimulating portions of esophagogastroduodenoscopy (EGD) are transoral and transpyloric passage of the endoscope. A smooth endoscope insertion can be aided by topical spray of local anesthesia to the oropharynx to help eliminate coughing and gagging.

Currently there is no standard airway technique that can offer the best balance of minimizing respiratory complications and maximizing efficiency during EGD. Insufflation of sevoflurane through a nasopharyngeal airway has been associated with an increase in airway complications without benefitting efficiency [152]. Maintenance of anesthesia with propofol using the native airway was associated with a higher incidence of respiratory complications compared with techniques including endotracheal intubation, without any improvement in efficiency [153]. Recent studies have shown that using propofol without airway intervention during EGD is feasible, without increasing the risk of respiratory complications [154]. LMAs also appear to be an acceptable and safe airway technique for otherwise healthy children undergoing routine EGD [155].

Most endoscopy-related respiratory complications occur during EGD, especially in infants and younger children, when compared with colonoscopy. A combination of factors, including the large size of the endoscope, partial airway obstruction, and abdominal distension due to air introduced into the stomach as well as sedation, may contribute, leading to hypoventilation. This has led several groups to select 6 months of age as the time prior to which general anesthesia with endotracheal

intubation is required for the procedure, due to the higher respiratory complication rate in this age group [145,147]. Targeted controlled intravenous infusions of propofol, with or without dexmedetomidine, have been used effectively in children (3–10 years) who underwent EGD with spontaneous ventilation without endotracheal intubation. In the presence of dexmedetomidine, the dose–response curve of propofol appeared unaffected [156].

Colonoscopy

Access to the airway is unimpeded during a colonoscopy. Deep sedation can be achieved more readily, and if respiratory problems occur, airway interventions are straightforward to manage. Patients undergoing colonoscopy will experience increased stimulation during certain parts of the procedure such as traversing the colon to the splenic flexure and the ileocecal valve. At times, abdominal pressure is applied to help advance the colonoscope. The depth of the anesthetic should be adjusted accordingly.

Endoscopic retrograde cannulation of the pancreas

Many institutions report success of procedural sedation in pediatric patients undergoing endoscopic retrograde cannulation of the pancreas [157,158]. However, general anesthesia with endotracheal intubation may make the procedure easier to perform, especially if it is of long duration, the patient has significant co-morbid diseases, or the procedure is performed with the patient in the prone position.

KEY POINTS: CLINIC AND OFFICE PROCEDURES

- Currently, there is no standard airway technique that can offer the best balance of minimizing respiratory complications and maximizing efficiency during EGD
- Most endoscopy-related respiratory complications occur during EGD when compared with colonoscopy, especially in infants and younger children
- The laryngeal mask airway appears to be an acceptable and safe airway technique for otherwise healthy children undergoing routine EGD

Anesthetic management of NORA procedures

In the several decades since the initial guidelines for pediatric sedation outside the operating room [159], not only have numerous organizations taken it upon themselves to fashion standards of practice, they have variously acknowledged and in many cases overtly approved the practice of non-anesthesiologist-administered sedation and analgesia medications, creating their own standards, guidelines, and policy statements, sometimes reinforced by citing relevant peer-reviewed literature. Furthermore, the regulatory environment is different for every state in the USA (Table 41.5). As experts in the continuum of sedation and anesthesiology, we sometimes find ourselves in a cognitively, clinically, and diplomatically tense and uncertain situation, which ultimately can only be answered through education, collaboration, and consistency of policy at least at the institutional level. The breadth of these regulations, nevertheless, is staggering.

Standards

Until the 1990s, sedation in the USA was limited predominantly to delivery by anesthesiologists, radiologists, dental medicine, and emergency medicine physicians. It now encompasses other specialties which include gastroenterology, intensive care medicine, hospital medicine, pediatric medicine, and nursing [160–162]. Worldwide, however, the majority of pediatric sedation is still administered by anesthesiologists. The challenge facing sedation care providers is the lack of consensus on sedation standards with respect to skills, training, qualifications, sedatives, physiological monitoring, NPO guidelines, routes of delivery, and emergency preparedness. A global look at sedation guidelines reveals that there is lack of consistency not only between the specialties within a single continent, but also between the continents. Different specialty societies as well as institutions in the USA and worldwide have published guidelines, policies, and recommendations, many of which do not agree [163]. In the USA, in response to the deaths of dental patients after sedation with midazolam, the National Institutes of Health and the American Academy of Pediatrics published two nearly identical consensus documents on sedation in 1985 [164–167]. Depth of sedation was introduced as a continuum, consisting of three levels: conscious sedation, deep sedation, and general anesthesia. Recently, the terminology has evolved to include four depths (minimal, moderate, deep sedation, and general anesthesia) and to eliminate the term "conscious sedation" [4,168,169]. This terminology has been adopted by the Joint Commission and specialty societies worldwide. Limitations of the sedation continuum have been recognized, particularly the subjective determinants of using patient response to verbal and tactile stimulation in order to determine the sedation depth. Future efforts should be made to identify objective criteria in order to determine depth of sedation and, more importantly, the risk of adverse events [170].

Organization

At a minimum, safe patient care requires appropriate anesthesia equipment and monitors and adequate space and experienced ancillary providers who are knowledgeable and facile in providing assistance if needed. Each off-site area has its own needs, goals, and guidelines. It is ideal to designate a team of anesthesiologists committed to providing NORA anesthesia care and troubleshooting the logistical challenges in the various locations. Each member should rotate regularly through the different NORA sites in order to maintain familiarity with the procedures, to foster a relationship with the physicians and ancillary personnel, and to understand the anesthesia demands unique to each site including ongoing advances. Technological advances are expanding in the field of radiology, and complicated imaging studies challenge the anesthesiologist to have an understanding of the unique conditions which the study requires.

Table 41.5 Documents from various societies about sedation services

State regulations for nurses in all 50 states	http://www.sedationfacts.org/sedation-standards/nursing-sedation-regulations
American College of Gastroenterology (ACG) Practice Guidelines	https://gi.org/guidelines
American Gastroenterological Association	www.gastro.org
Endoscopic Sedation (8/07) (Medical Position Statement)	
Endoscopic Sedation, Administration of Propofol by a GI, Nonanesthesiologist (4/10) (Medical Position Statement)	
American Gastroenterological Association (AGA) Institute Review of Endoscopic Sedation	Gastroenterology 2007; 133: 675–701
AGA Standards for Office-based Gastrointestinal Endoscopy Services	Gastroenterology 2001; 121: 440–3
American Society for Gastrointestinal Endoscopy (ASGE) Practice Guidelines	
Guideline for sedation and anesthesia in GI endoscopy	Gastrointest Endosc 2008; 68: 815–26
Position statement: nonanesthesiologist administration of propofol for GI endoscopy	Gastrointest Endosc 2009; 70: 1053–9
Society of Gastroenterology Nurses and Associates	Position Statement: Statement on the Use of Sedation and Analgesia in the Gastrointestinal Endoscopy Setting (2007)
Guidelines for the Use of Sedation and General Anesthesia by Dentists	October 2007 ADA House of Delegates Guidelines for the Use of Sedation and General Anesthesia by Dentists Adopted by the ADA House of Delegates, October 2016
American College of Emergency Physicians: Clinical policy for procedural sedation and analgesia in the emergency department	Ann Emerg Med 2014; 63: 247–58
Pediatric Committee of the American College of Emergency Physicians. pediatric analgesia and sedation	Ann Emerg Med 1994; 23: 237–50
Joint Commission: Moderate Sedation Medication and Patient Monitoring	https://www.jointcommission.org/standards_information
American College of Cardiology: Clinical Expert Consensus Document on Cardiac Catheterization Laboratory	J Am Coll Cardiol 2001; 37: 2170–4
American College of Radiology: Practice Guideline for Pediatric Sedation/Aanalgesia	Revised 2005 (Res. 42)
American College of Surgeons [ST-46]: Statement on patient safety principles for office-based surgery utilizing moderate sedation/analgesia, deep sedation/analgesia, or general anesthesia	Bull Am Coll Surg 2004; 89(4)

All websites accessed May 2019.
GI, gastrointestinal.

In the past, NORA locations were not designed with the anesthesiologist in mind. The need for anesthesia had not been anticipated when off-site locations were planned. It is only within the past few decades that the demand for anesthesia services in these sites has substantially expanded. Thus, most NORA locations have not been configured to support an anesthetic. Ideally, anesthesiologists should be involved in the early stages of site design to ensure that minimum standards for anesthesia delivery are met and to troubleshoot engineering issues and advocate for adequate space for anesthetic induction and emergence [159,171]. Physical plant considerations for MRI site planning have been previously described [160]. When anesthesia services are requested, these sites may not meet minimum standards [161] and will require reengineering to meet minimum requirements of the ASA. The anesthesia machine should be equipped with back-up supplies of E cylinders filled with oxygen and nitrous oxide. If pipeline oxygen is not available, then oxygen should be supplied from H cylinders (6600 L) rather than the smaller E tanks (659 L). For MRI locations in particular, induction of anesthesia or sedation is often best accomplished in an induction area, outside the scanner room, to allow full access to the patient and the use of non-MRI-compatible equipment such as laryngoscopes. Issues such as airway obstruction, emergence, or need for resuscitation are best addressed in such a location.

Scavenging systems should be carefully evaluated in the NORA location. Unlike the operating room, passive scavenging systems may not always be possible. A safe means of active scavenging may be provided by the vacuum at the wall or wall suction canisters. A scavenging system should be dedicated solely to waste gases. Many MRI scanners do not have wall suction because MRI-compatible wall suction is not widely available. If the suction is located outside the MRI suite, then a mouse-sized hole may be created in the suite's wall to allow suction tubing to be passed inside [172]. A standard anesthesia cart at each anesthetizing location should be fully stocked with essential medications, necessary additional equipment, a spare self-inflating (Ambu®) bag, endotracheal tubes, LMAs, suction catheters, intravenous supplies, laryngoscope handles and blades, and a variety of oral and nasopharyngeal airways (Fig. 41.8).

Electrical circuitry and lighting in NORA locations may not be up to operating room standards even if the outlets are grounded and up to hospital grade. Although some NORA locations carry minimal risk of electrical shock or electrocution, these sites do not have line-isolation monitors and will not warn of excess leakage of current. Supplemental lighting for recordkeeping, label verification, establishment of IV access, and visualization of the patient is critical. Even under the best circumstances, for example, lighting is dim in the MRI scanner and monitoring by simple clinical observation can be limited. Video monitoring or hardwiring through reinforced walls can allow remote video display of the patient and physiological monitors within.

A storage area large enough to stock anesthesia equipment and supplies must be easily and quickly accessible. This area

Figure 41.8 MRI-safe anesthesia cart. The contents include nasal airways, oropharyngeal airways, laryngeal mask airways, oxygen nasal cannulas, facemasks, and suction catheters.

should be routinely checked, restocked, and kept locked when anesthesia services are not required. The need for redundancy of non-disposable supplies is a matter of philosophy. Are two laryngoscopes enough, or should there be a third? Is one ECG monitor enough, or should there be a battery-operated monitor for back-up and transport? Drugs should be checked per the usual operating room routine and expired medications replaced. Gas cylinder supplies must be reliable, especially in areas without piped oxygen. A code cart should be conveniently located in an area known to all physicians and ancillary personnel. This cart should be routinely checked and restocked. With ever-larger volumes of patients using these sites, strong consideration should be given to having a difficult airway cart available close by.

Finally, NORA locations are often distant from the operating room. Patients may need to remain anesthetized during transport to or from the NORA location. For these circumstances, assured elevator access with key-controlled emergency over-rides is a must. All anesthesiologists who deliver NORA services should be familiar with their surroundings. Checklists are invaluable to guarantee consistent patient care, anesthesia monitoring, equipment, documentation, and back-up assistance.

Practitioners

Interdisciplinary skepticism is abundant and the need for leadership remains crucial; a director of anesthesia and sedation at a NORA location can orchestrate, facilitate, and coordinate these services as well as educate all clinical stakeholders and the public. Specific guidance is provided in several standards from the ASA, especially the "Statement on Granting Privileges for Administration of Moderate Sedation to Practitioners Who Are Not Anesthesia Professionals" and further in "Continuum of Depth of Sedation: definition of general anesthesia and levels of sedation/analgesia." By being available to answer questions, provide on-site consultation, examine patients, and provide support or emergency airway expertise, the anesthesiologist can also guide a nurse-administered sedation program. Nurses who provide sedation under the supervision of the ordering physician should be Pediatric Advanced Life Support and Basic Life Support

certified. In October 2012, the ASA passed an amendment to the advisory on deep sedation by non-anesthesiologists: "because of the significant risk that patients who receive deep sedation may enter a state of general anesthesia, privileges for deep sedation should be granted only to non-anesthesiologist physicians who are qualified and trained in the medical practice of deep sedation and the recognition of and rescue from general anesthesia." The Joint Commission advocates that anesthesiology departments play a role in the development of training and privileging programs for sedation but they no longer hold the role of being "in charge" of sedation services. The Joint Commission also requires that individuals who administer sedation are able to rescue patients from whatever level of sedation or anesthesia is achieved, *whether intentional or unintentional* [39]. This is the context within which the ASA documents were created. Attention to the sedation continuum and a paean for translating subjective assessments to more consistently measureable physiological endpoints has recently been published [173]. Regardless of the intended level of sedation or route of drug administration, the sedation of a pediatric patient may result in respiratory depression, laryngospasm, impaired airway patency, apnea, and cardiovascular instability (Table 41.6). Sedation-related safety and effectiveness are determined by the circumstances and professional skills rather than by the chosen sedative-specific pharmacological characteristics. Consequently, it is wise to formulate separate recommendations regarding professional skills and competence for different levels of sedation (mild sedation on one hand and moderate to deep sedation on the other hand) [174].

As recommended by the Joint Commission, sedation-related policies and procedures should be part of a quality assurance initiative that should accompany all sedation programs. Ideally, adverse events such as failed or prolonged sedations, paradoxical reactions, hypoxia, emesis, unscheduled admission, and cardiac or respiratory events should be identified and entered into a computerized database. In addition, the NORA nurse should call all patients and families within 24 h in order to follow-up on patient outcome and identify any delayed adverse events.

Scheduling and preparation of patients

Appropriate planning for an anesthetic begins with familiarity with the procedure. The requesting service (e.g. neurology, surgery) orders the procedure and then leaves the logistics of scheduling to the NORA service (e.g. radiology, anesthesiology). Radiologists recognize that the administration of an anesthetic will lengthen their total time commitment to a patient and potentially limit the number of procedures accomplished in a day [175,176]. A well-coordinated system to screen patients on the day of the procedure is important. Experienced personnel, ideally a certified pediatric nurse practitioner, should be designated to take initial vital signs, review recent medical history, begin IV lines if necessary, and familiarize the family with the upcoming procedure including anesthesia.

Screening patients for NORA procedures may be challenging and time consuming. Many children are chronically ill, nutritionally impaired, and medically complicated. These issues must be carefully addressed through attention to the patient's history, physical examination, old medical records, outside consultations, and close communication with other medical colleagues. Several consultants may need to confer in

Table 41.6 Continuum of depth of sedation: definition of general anesthesia and levels of sedation/analgesia*

	Minimal sedation anxiolysis	Moderate sedation/analgesia ("conscious sedation")	Deep sedation/analgesia	General anesthesia
Responsiveness	Normal response to verbal stimulation	Purposeful† response to verbal or tactile stimulation	Purposeful† response following repeated or painful stimulation	Unarousable even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired

* Monitored anesthesia care does not describe the continuum of depth of sedation, rather it describes "a specific anesthesia service in which an anesthesiologist has been requested to participate in the care of a patient undergoing a diagnostic or therapeutic procedure." Because sedation is a continuum, it is not always possible to predict how an individual patient will respond. Hence, practitioners intending to produce a given level of sedation should be able to rescue patients whose level of sedation becomes deeper than initially intended. Individuals administering moderate sedation/analgesia ("conscious sedation") should be able to rescue patients who enter a state of deep sedation/analgesia, while those administering deep sedation/analgesia should be able to rescue patients who enter a state of general anesthesia.

† Reflex withdrawal from a painful stimulus is NOT considered a purposeful response.

Minimal sedation (anxiolysis) is a drug-induced state during which patients respond normally to verbal commands. Although cognitive function and physical coordination may be impaired, airway reflexes and ventilatory and cardiovascular functions are unaffected.

Moderate sedation/analgesia ("conscious sedation") is a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.

Deep sedation/analgesia is a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully† following repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.

General anesthesia is a drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.

order to fully understand the patient's current state of health. Not every procedure is elective. Urgent procedures may be required *despite* an upper respiratory tract infection, ongoing pneumonia, deteriorating physical status, untreated gastroesophageal reflux, sepsis, or hemodynamic instability. In these situations, consultation between the anesthesiologist, the requesting physician, and the radiologist should confirm urgency. Anesthesia plans should be adjusted to accommodate the requirements of the procedure (e.g. breath holding for chest CT scan) and the patient's medical condition.

It is not always possible for an anesthesiologist to provide sedation and anesthesia for all children when there is a large volume of cases. A structured nursing sedation program can provide safe and effective sedation. In many hospitals, the requesting department "outsources" responsibility for sedation to another department which could include pediatrics, hospital medicine, anesthesiology, intensive care, or emergency medicine. After patient screening, an appropriate referral for either general anesthesia or procedural sedation is the usual result. Because MRI is performed in a unique environment, it is more efficient to have the MRI nurses screen the patient prior to and on the day of the procedure. To ensure consistent decision making, the departments of anesthesiology and radiology should develop a set of guidelines and easily identifiable "red flags" (Table 41.7) to help in this triaging process. If there are any questions or need for additional medical history or studies, the nurse and anesthesiologist must confer before making the final decision regarding general anesthesia or procedural sedation. In addition, chronically ill children often have electrolyte disturbances, coagulation and hematological abnormalities, and hemodynamic instability. A consent for the administration of general anesthesia or procedural sedation must be obtained, in parity with policies established for anesthesia in the operating room.

Because gastroesophageal regurgitation is common in infants, a detailed clinical history should be taken with regard to the incidence and timing of the regurgitation. If the reflux is predictable (e.g. only associated with mealtimes or soon thereafter) children are usually approved for procedural sedation. NPO guidelines are adjusted to minimize the risk of reflux. For example, if the baby refluxes within 2 h of solid feeds, but never after 3 h, then the NPO guidelines for this infant may be extended to 6 h for solids.

Postanesthesia care

Recovery criteria and the postanesthesia care unit (PACU) environment in NORA locations must be no different than the postanesthesia care delivered to children following an operative procedure. Each site must have sources of supplemental oxygen, the ability to deliver positive pressure ventilation, the availability of suction and monitoring equipment, and a nursing staff trained in postanesthesia care. Specific antagonists of opioids and benzodiazepines should be available. If the administration of an antagonist is necessary, continuous and prolonged monitoring is needed. Discharge criteria should be established by an anesthesiologist in conjunction with the NORA service and its nursing staff. The American Society of Anesthesiologists issued a statement on NORA locations in an October 2013 update, recognizing the importance of the recovery period – with the expectation that there will be a designated postanesthetic recovery area with qualified personnel for the transport and recovery of these patients [139].

Analgesic requirements postprocedure are extremely variable. While groin puncture may be only mildly annoying for adults, the inability to move about and the ache of blood dissecting subcutaneously causes considerable discomfort in children. Following angiography, all children require a minimum PACU stay of 4 h to ensure that the puncture site does not bleed or develop a hematoma. Ideally, the patient should be pain-free and resting supine and motionless in order to minimize the risk of a groin-puncture bleed or hematoma. Experienced nursing staff will be able to recognize, manage, and call for extra help when they encounter unexpected

Table 41.7 "Red flags" for sedation

1	Apnea	If documented by sleep study, strong clinical history, or routine use of an apnea monitor, with significant likelihood of respiratory risk – availability of ICU must be considered
2	Unstable cardiac disease	If cyanotic, depressed myocardial function, or significant stenotic or regurgitant lesions – will likely require substantial planning, often in coordination with a cardiologist or cardiac anesthesiologist, and availability of ICU
3	Respiratory compromise	Recent (<8 weeks) pneumonia, bronchitis, asthma, or respiratory infection – if necessary to proceed, may require general endotracheal anesthesia to control coughing, and availability of ICU
4	Craniofacial defect	Potential for airway difficulty – availability of difficulty airway equipment or airway procedures (intubation and extubation) in the OR
5	History of a difficult airway	Potential for airway difficulty – availability of difficulty airway equipment or airway procedures (intubation and extubation) in the OR
6	Active gastroesophageal reflux or vomiting	If in poor control, with or without medical or surgical treatment – may require general endotracheal anesthesia with a rapid-sequence induction
7	Hypotonia and lack of head control	If patient is unable to maintain their own airway without assistance – appropriate perioperative planning must include airway support and ICU. Patients with underlying muscular or mitochondrial disorders may have specific anesthetic risks
8	Allergies to barbiturates	Usually the mainstay of a sedation protocol – cross-allergies must be considered
9	Prior failed sedation	Previously unable to be sedated or unsuccessful imaging study because of excessive movement – may require general anesthesia for an optimal study
10	Tremors	Unlikely to be ablated with sedation – may require general anesthesia for an optimal study

ICU, intensive care unit; OR, operating room.

agitation, delirium, or an unanticipated/undesired change in mental status.

Following embolization procedures, patients frequently experience pain or swelling, the severity depending upon the extent of embolization, the agent used for embolization, postembolic swelling and amount of tissue necrosis. A variety of analgesic techniques are available, and the use of steroids perioperatively, while not directly decreasing pain, may be of benefit in reducing edema and postembolic neuritis. Postembolic swelling will influence perioperative airway management for procedures in the head and neck. Pediatric patients may need to remain intubated following such procedures, particularly when edema in the floor of the mouth, tongue, hypo- or oropharynx, or anterior neck could compromise the airway.

Nausea or vomiting may increase venous blood pressure because of the Valsalva maneuver, which can aggravate bleeding and swelling in puncture sites or following head and neck procedures. Hypothermia is a risk at some NORA locations because the MRI, CT, and interventional radiology equipment requires a cool environment. Heating lamps and forced-air heaters may be utilized when safe and appropriate. Finally, with the use of iodine-containing radiocontrast media and sclerosing and embolizing agents, consideration must be given to adequate volume resuscitation, the risk of a contrast reaction, as well as bladder catheterization for the detection of oliguria, polyuria, or hematuria.

KEY POINTS: ANESTHETIC MANAGEMENT OF NORA PROCEDURES

- Sedation-related policies and procedures should be part of a quality assurance initiative which should accompany all sedation programs
- Sedation-related safety and effectiveness are determined by circumstances and professional skills rather than by the chosen sedative agent's pharmacological characteristics.
- There is still need for evidence-based guidelines that address current discrepancies in fasting guidelines, measurement of sedation depth, and standardization of definitions of adverse events among specialty groups
- Recovery criteria in NORA locations must be no different to those of the surgical postanesthesia care unit

Resuscitation

Each NORA location is unique with regard to conducting resuscitation. Redundancy of monitoring devices and equipment is important; one should not be limited to a single item that could malfunction at the time of resuscitation. Patients with multiple allergies, shellfish allergies, or atopic disease are at increased risk of exhibiting anaphylaxis to iodine-containing contrast. These patients may benefit from pretreatment with steroids and antihistamines. Areas with restricted access, MRI areas in particular, should have designated adjacent locations to perform full resuscitation. These areas should be equipped with wall oxygen, suction, and full monitoring and resuscitation capability. A self-inflating silicone bag (no ferromagnetic working parts) or non-ferrous Jackson Rees circuit should always be kept inside the MRI suite.

The physicians, nurses, anesthesiologists, technologists, and support personnel must know the location of a readily accessible code cart. In addition, a hard board to be placed under the patient during resuscitation should be available. Mock codes should be performed regularly to ensure adequate flow, teamwork, and delineation of responsibilities in the event of an emergency. The MRI scanner poses a special problem in the event of cardiorespiratory arrest. To date, there is no defibrillator that has met FDA approval for entering the MRI environment. Rather, the ASA Task Force on Anesthetic Care for MRI Practice advises that resuscitation be initiated in the MRI scanner as the patient is being removed from the MRI environment to an adjacent area equipped with a defibrillator, physiological monitor, and code cart [38]. Protracted resuscitation should never be conducted in the scanner because as support personnel rush inside to assist, unremoved ferrous materials will become projectiles and create an even more hazardous situation. Quenching a magnet should not be an alternative, because it requires a minimum of 3 min to eliminate the magnetic field. In addition, inadequate exhaust during a quench has been known to produce hypoxic conditions in the scanner and has resulted in a patient death. A "black quench" (loss of liquid coolant with resulting coil meltdown) could require replacement of the scanner, a costly and time-consuming undertaking.

Difficult airway management in NORA sites

If a child with a known difficult airway requires endotracheal intubation in order to complete the scheduled procedure, then it is wise to perform the anesthetic induction in the operating room, an area where access to difficult airway equipment and extra help is readily available. Regardless of an anesthesiologist's comfort level and familiarity with NORA environments, the same depth of back-up coverage is simply not available. It is also important to jointly discuss the plan for airway management in patients with a difficult airway and have a clear plan before anesthesia induction. The availability of a fiberoptic bronchoscope, video laryngoscope, and the difficult airway cart should be confirmed.

The unanticipated difficult airway is problematic in a remote location. Therefore, it is important to confirm that appropriate airway management instruments including different sizes of facemasks, oral and nasopharyngeal airways, endotracheal tubes, laryngoscope blades and handles, and appropriately sized LMAs are stocked in all NORA anesthesia carts. If the trachea cannot be intubated and the lungs cannot be ventilated with a mask, LMAs can provide a successful alternative. Many case reports describe the successful use of LMAs in children with difficult craniofacial anomalies such as Goldenhar syndrome [177,178] and even Pierre Robin sequence [179]. Similarly, a lightwand may facilitate endotracheal intubation in the child with a difficult airway [180]. Recently introduced video laryngoscopes (e.g. Glidescope®), in infant through pediatric sizes, should be strongly considered for availability in NORA locations.

It is important to recognize that the airway that had not been difficult on induction may become difficult on emergence following sclerotherapy with alcohol and subsequent tissue edema, particularly at the base of the tongue, the neck, or the mediastinum [181–183]. These patients will often require several days of airway support and ongoing evaluation in the intensive care unit until tissue swelling and airway compromise is no longer a concern.

Blood loss management outside the operating room

Transfusion requirements are rare in NORA locations, yet preprocedural anemia, accidental perforation of vascular structures, or medical transfusion requirements such as sickle cell disease or prematurity may require transfusion therapy. Equipment familiar to the anesthesiologist and identical to that available in the operating room is a welcome sight in a life-threatening emergency. Calling for additional help, establishing additional vascular access, and coordinating with the blood bank is crucial. Having a runner available may be critical when there is no equivalent to a circulating nurse. It may become necessary to involve a surgeon urgently and transport the patient to the operating room, in which case another anesthesia team setting up the operating room while the patient is being prepared for transport would be optimal.

Selection of anesthetic technique and agents

The selection of an anesthetic technique, as in any circumstance, depends on the patient's underlying medical condition, age, drug tolerance, and anticipated procedure. The assistance of the anesthesiology department is often sought when prior sedation has failed [184] and an anesthetic or deep sedation is needed to provide ideal conditions and allow successful completion of the procedure. The anesthetic care plan will ultimately be a product of institutional expectations, the patient's co-morbidities, and the anesthesiologist's preference.

Preparation of the stomach and aspiration prophylaxis are of particular concern for urgently scheduled cases (outside of NPO guidelines) or when the medical history suggests aspiration risk. If using H2 receptor antagonists, bronchospasm may occur in asthmatic patients because of the relative increased availability of H1 receptors. H2 blockers may also inhibit the metabolism of other concurrently administered medications. Metoclopramide accelerates gastric emptying and increases tone in the lower esophageal sphincter, but is associated with a significant incidence of extrapyramidal side-effects in children. Ondansetron works synergistically with other agents through its vagal blocking actions in the gastrointestinal tract as well as through its inhibition of the chemoreceptor trigger zone via serotonin receptor antagonism, particularly for patients undergoing radiotherapy with pulses of chemotherapy. [185,186].

The airway management may be influenced by the procedure itself as well as anticipated postprocedure requirements. Access to the patient's airway in locations outside the operating room is often limited – MRI scanners have a long bore with the patient out of the line of sight of the anesthesiologist. Radiotherapy accelerators and TBI machines are sited within a locked room. Interventional procedures are often performed so that the patient can be imaged with biplane fluoroscopy and therefore the physical plant is designed to accommodate the imaging equipment and not the needs of the anesthesiologist. Airway obstruction, laryngospasm, and the presence of secretions may all be difficult to determine. Hypoventilation and apnea are difficult or impossible to determine by direct observation. As long as an appropriate plan is chosen and appropriate monitoring is used, there is no evidence to support a specific standard for airway management.

Appropriate drug selection for the intended procedure includes a clear understanding of the pharmacokinetics and pharmacodynamics of the chosen sedative/anesthetic agent and drug interactions and is imperative for safe pediatric procedural sedation practice. We will focus below on the current sedation/anesthetic agents currently used by sedationists.

Barbiturates may be useful as a sole method of providing sedation. Pentobarbital (Nembutal), for example, has the advantage of providing sedation, minimal respiratory and circulatory depression, and is rarely associated with adverse events [187]. Barbiturates have no analgesic properties, and can produce paradoxical reactions, especially in children. Furthermore, no antagonist to barbiturates is available, thus dosing should be carefully titrated. Intravenous pentobarbital by titration has been used successfully by radiologists while monitoring oral and nasal air flow, oxygen saturation with a pulse oximeter (SpO_2), end-tidal carbon dioxide, and cardiac rate and rhythm. Transient decreases in SpO_{2in} up to 7.5% of patients have been reported; interventions have included stimulation and head repositioning [188,189]. Other studies have described the use of pentobarbital both in the oral and intravenous form [104,190]. For infants less than 1 year of age, oral pentobarbital is more successful and carries a lower rate of adverse events compared with chloral hydrate [190]. The long half-life of pentobarbital (approximately 24 h) requires careful and conservative recovery and discharge guidelines. The dosage of pentobarbital is 2–6 mg/kg PO, up to 9 mg/kg in patients who are receiving barbiturate therapy.

Propofol (2,6-diisopropylphenol) is an intravenous hypnotic agent approved by the FDA in the United States for the induction and maintenance of anesthesia. Its package insert specifies that it "be administered only by persons trained in the administration of general anesthesia" [191]. Although propofol does not have a labeled indication for children less than 3 years of age, it has been used extensively in this age group as a means of providing sedation or anesthesia. Propofol sedation by bolus or continuous infusion for brain MRI can provide successful imaging conditions but with the risk of need for airway intervention and respiratory compromise [192]. A recent comparison of dexmedetomidine with propofol in children with and without obstructive sleep apnea suggests that dexmedetomidine offers the benefit of preserved respiratory drive, less need for artificial airway support, and fewer incidences of airway compromise [31,193].

There is a rare, often fatal complication known as propofol infusion syndrome (PRIS) most often seen with prolonged propofol administration (>48 h) at high doses (>4 mg/kg/h). PRIS is characterized by metabolic acidosis, rhabdomyolysis of skeletal and cardiac muscle, arrhythmias (bradycardia, atrial fibrillation, ventricular and supraventricular tachycardia,

bundle branch block, and asystole), myocardial failure, renal failure, hepatomegaly, and death [194–198]. In 1992 the deaths of five children who had received long-term, high-dose propofol infusions were reported. These children died from myocardial-related causes, presumed to be related to propofol, in conjunction with lipemic plasma, metabolic acidosis, and an enlarged or fatty liver [199]. This syndrome arises from interference with the electron transport chain and derangement of mitochondrial metabolism. Propofol should be used with caution for sedation in critically ill children and adults, as well as for long-term anesthesia in otherwise healthy patients, and doses exceeding 4–5 mg/kg/h for long periods (>48 h) should be avoided [200–202]. There are now over 150 published case reports of PRIS, with 36% of cases in children [203]. PRIS can occur during anesthesia, and more recently, cases have been seen with lower doses, and with shorter duration of infusion; 20% of cases had propofol infusions of less than 20 h. Metabolic acidosis was observed in 77% of patients, and ischemic changes on ECG and arrhythmias in two-thirds of patients. Rhabdomyolysis is observed in 56%. The mortality rate has decreased in recent years and was 51% for the entire series [203]. Vigilance for this rare but devastating complication is necessary with prolonged propofol infusions of >6–8 h.

Propofol administration by non-anesthesiologists has generated tremendous controversy. The ASA guidelines specifically state that only personnel qualified to provide general anesthesia should administer this medication. Sedation providers administering propofol must be able to recognize respiratory depression and be skilled in advanced airway management. Recent large, prospective, observational studies in nearly 100,000 children showed that administration of propofol was safe in a variety of settings by sedation providers well versed in sedation management and airway rescue [204–206]. Another recent multicenter study examined the safety and efficacy of pediatrician-administered propofol in 36,516 procedural sedations, showing that pediatricians can administer propofol safely. The study also highlighted the importance of appropriate training to increase the safety of procedural sedation in children [207].

Opiates reduce anesthetic and pre- and postprocedure analgesic requirements. They are reversible with naloxone. While opioids may be unnecessary for non-painful diagnostic procedures, they may be very useful for therapeutic interventions, especially for those patients with postprocedural pain. They are also useful following anthracycline chemotherapy, when patients have documented impaired myocardial function [208]. Because opioids depress the ventilatory response to CO_2, this respiratory depression may be of particular concern for children with increased intracranial pressure. Opioids may also worsen pre-existing nausea and vomiting, particularly common for children undergoing cancer treatment. Caution should be exercised when opiates are combined with other sedatives as the risk of respiratory depression is substantial.

Benzodiazepines have the advantage of anxiolysis with minimal vomiting and cardiorespiratory depression. Diazepam (Valium®) is painful during intravenous injection and may lead to thrombophlebitis; midazolam (Versed®) is water soluble, and therefore may be more suitable intravenously or intramuscularly. The elimination half-life of midazolam averages 2.5 h compared to 20–70 h for diazepam [209,210]. Young patients or patients with significant liver disease may have prolonged duration and exaggerated effect of the benzodiazepines.

Ketamine has enjoyed great popularity during the past 30 years or more for sedation, analgesia, or anesthesia outside the operating room due to its support of the cardiovascular and respiratory systems. Ketamine-induced nightmares, hallucinations, delusions, and agitation are rare in children [211,212]. The combination of ketamine and propofol ("ketofol") is being administered with increasing frequency. Ketamine with propofol blunts the emetogenic and psychocognitive effects of ketamine, while the synergistic effect of ketamine tends to decrease the risk of propofol-associated respiratory depression and hypotension [213]. Ketamine sedation programs, administered by registered nurses and supervised by interventional radiologists, have been developed by anesthesiologists for selective patients and procedures [187,214]. This protocol has allowed painful procedures, and even organ biopsies, to be tolerated by patients who previously would have required general anesthesia [187,215].

Dexmedetomidine (DEX), a highly selective α2-adrenergic agonist, offers some unique and unmatched qualities. DEX is approved for adult sedation via intravenous infusion or bolus (labeling only in the USA) and infusion (labeling in USA and European Union) [216,217]. Despite the lack of pediatric labeling, DEX administration has been described via a variety of routes for sedation, anxiolysis, analgesia, and as an anesthetic adjunct. An extremely important advantage of this novel sedative agent is its potential for neuroprotection particularly in children [218]. DEX is unique in that it produces a state that resembles natural sleep [219,220]. Animal model studies demonstrated that this sedation mimics the endogenous sleep pathway, stimulating the locus coeruleus [221]. Studies in children suggest that the endogenous sleep pathway may be similarly stimulated. The electroencephalograms of children sedated with DEX have been shown to resemble those of natural non-rapid eye movement sleep [222]. Particularly for pediatric sedation for radiological imaging studies, DEX alone can, in high doses, achieve immobility for MRI and CT examinations [223–225]. While it appears to have minimal effects on respiratory drive and the CO_2 response curve, DEX administration may be accompanied by bradycardia, hypotension, and hypertension [223,224,226].

With DEX administered at induction doses of 2–3 mg/kg/min over 10 min followed by an infusion of 1.5–2 mg/kg/min, success rates have been reported of up to 97.6% for MRI scans. In this dose range, the incidence of bradycardia was 16%, with a mean arterial pressure within 20% of age-adjusted normal ranges [226]. Extreme bradycardia can occur if administered to a patient receiving digoxin and syncope, likely from a vasovagal response, which has been reported in the literature as well as in the package insert [227–229]. Moreover, the use of glycopyrrolate to treat the bradycardia is discouraged, as it may result in extreme hypertension [230]. A recent retrospective study showed that the administration of a prophylactic anticholinergic prior to DEX in pediatric imaging studies did not show any advantage other than a transient clinically insignificant increase in heart rate and systolic blood pressure [231]. Combining DEX with IV ketamine has been successfully described for invasive procedures, with fast onset and amnesia, sedation, analgesia, and hemodynamic stability

[232,233]. This combination has been described in adults and children for extracorporeal shock wave lithotripsy [234], lumbar puncture [235], bone marrow biopsy, burn dressing changes [236,237], chest tube insertion, and femoral cut-down for tunneled central venous catheter placement.

Currently, all standard anesthetic and sedative agents used for pediatric sedation including propofol, etomidate, sevoflurane, desflurane, isoflurane, and ketamine produce profound neurotoxic effects in laboratory animals [238]. DEX has not been shown to be neurotoxic in animal studies [239]. Future studies are still required to examine the effect of DEX on neurodevelopmental outcome. Another important question that remains to be answered is the use of combinations of sedatives and neurocognitive outcome.

Transmucosal sedative agents and new methods of drug delivery

The rapid delivery of drug to the bloodstream and the central nervous system after intranasal (IN) administration offers unique advantages that may allow a rapid onset of sedation and greater patient and provider satisfaction [240]. Currently IN midazolam is the most commonly studied medication by this route, although recent data on fentanyl, ketamine, sufentanil, DEX, and combinations of these drugs are available [241]. Reports show that IN midazolam produces nasal burning and irritation in up to 66% of patients. Intranasal DEX seems to be devoid of this discomfort, rendering it a very attractive alternative. The use of non-traditional routes (nasal and buccal) of DEX has been described in recent years. Intranasal DEX bioavailability approximates 65% (35–93%) while buccal DEX approximates 81.8% (72.6–92.1%) [242,243]. In children, IN DEX has been utilized for sedation in doses ranging from 1 to 4 μg/kg [244,245]. A nebulized combination of low-dose ketamine and DEX (1 mg/kg + 1 μg/kg) has been shown to provide more satisfactory sedation and smoother induction of general anesthesia than nebulized ketamine (2 mg/kg) or DEX (2 μg/kg) alone in children [246]. There is wide dose range of IN ketamine used in clinical practice. More research is required to determine the optimal dosing range and to identify patient populations who might require high ketamine doses in order to produce adequate sedation or amnesia [247].

Target-controlled infusion (TCI) systems are intended to more precisely deliver sedation using pharmacokinetic models specific for a particular medication such as propofol or remifentanil. TCI devices administer a bolus followed by a decline in infusion rate to rapidly achieve and maintain a steady-state drug concentration in the plasma or at the site of drug effect [248]. This method of drug delivery contrasts with non-modeled infusion schemes where constant rates result in a rise in blood concentration rather than a steady-state plasma concentration. TCI delivery systems are currently used worldwide but are not widely available for pediatric use. TCI is currently not approved or available in the USA. It is important to recognize that no new technology can replace the role of a capable and vigilant sedation provider monitoring a sedated patient.

Some patients will require general anesthesia because of previous sedation failures, the need for a secure airway, or procedural logistics. Newer, less soluble anesthetic agents such as sevoflurane and desflurane have pharmacokinetic profiles that compare favorably with propofol in adults [249]; there seems little reason to think that would not be the case with children, although pediatric anesthesiologists often avoid using desflurane because of its pungency and associated airway irritability. Since its introduction to clinical practice is the mid-1990s, sevoflurane has become the volatile anesthetic of choice in children. Its lack of airway irritability and its ability to provide children with stable hemodynamic function coupled with its rapid onset and offset make sevoflurane a useful agent [187].

Volatile agent vaporizer performance in the MRI suite has been studied. The output of a Fortec II® vaporizer (Fraser Harlake, Orchard Park, NY, USA) was variable according to the vaporizer's location and the orientation of the bimetallic strip within the magnetic field [250]. The movements of the bimetallic ferromagnetic temperature compensator within the MRI magnetic field altered vaporizer output by as much as 91% of the dialed output concentration. Several other vaporizers examined (Ohio Forane®, Ohio Medical Products, Madison, WI, USA; Ohmeda Isotec IV® vaporizer, Ohmeda, Steeton, UK; and the Forane Vapor 19.1®, Dragerwerk AG, Lubeck, Germany) were incompatible with the MRI environment because of stronger ferromagnetic internal component content or the location of a ferromagnetic spring within the temperature compensator. Measuring inspired and end-tidal levels of volatile agents when delivering a general anesthetic in the MRI environment may provide reassurance. Modern MRI-compatible anesthesia systems have magnetic field detector systems that inform the anesthesiologist when the machine is within a magnetic field strong enough to affect vaporizer and machine performance. In general, situating the machine and vaporizers as far from the magnet as practically possible within the scan room, and following the manufacturer's instructions as to machine operation, will optimize conditions and ensure accurate volatile anesthetic delivery.

Regional anesthesia, rarely administered outside the pediatric operating room, nevertheless remains a valid choice in some circumstances. Intercostal nerve blocks may be very useful for lung or rib biopsies, chest tubes, biliary or subphrenic drainage procedures, and insertion of biliary stents. Nerve block of the brachial plexus by the axillary, interscalene, or supraclavicular route has been reported for the brachial approach to catheterization [251,252] and neuraxial block of the lower extremities for femoral catheterizations and percutaneous approaches to the kidney [253]. Spinal anesthesia has been successfully used for repeat painful radiotherapy on lower extremities, in conjunction with regional hyperthermia and limb exsanguination [254].

Indwelling central catheters are implanted in the majority of radiotherapy patients and can be utilized for induction and maintenance of anesthesia, blood draws, intravenous fluid administration, and chemotherapy. Dressing changes are often accomplished in conjunction with the sedation or anesthesia. Antiseptic preparation of all injection sites is critical. At the end of the session the catheter should be carefully flushed with heparinized saline. An alternative to central lines is the use of a heparin lock peripheral IV line, changed weekly, with careful parental instruction. Smoothness of emergence is particularly important following angiographic procedures because of the risk of dislodging a clot or bleeding at the

puncture site. Some of these patients have been heparinized without protamine reversal. Unlike adults, sandbags and weights are not routinely applied to angiographic cannulation sites of children.

Finally, on occasion, the loss of self-control with sedation results in dysphoria, and some patients fare better when completely awake. Minimal medication may be preferable in patients with complicated and unstable medical conditions who may not tolerate the anesthesia or sedation. Some procedures (unilateral carotid barbiturate injection or Wada test) may require conversation, interaction, and responsiveness of the patient. Cooperation required during these procedures can be challenging especially with traditional sedatives such as fentanyl, midazolam, and/or propofol. In addition, these agents have well-known respiratory depressant effects. Dexmedetomidine provides sedation that parallels natural sleep, sympatholysis, and an anesthetic-sparing effect without relevant respiratory depression [216,217].

KEY POINTS: SELECTION OF ANESTHETIC TECHNIQUE AND AGENTS

- The ASA guidelines specifically state that only personnel qualified to provide general anesthesia should administer sedating medications
- Combining dexmedetomidine with ketamine can be an attractive sedation choice
- Intranasal dexmedetomidine seems to be devoid of the discomfort frequently associated with nasal midazolam, rendering it a very attractive alternative for non-invasive pediatric procedural sedation
- Dexmedetomidine is an emerging alternative for sedation in variety of pediatric procedural settings

Safety issues

As anesthesiologists find themselves participating in the care of patients requiring increasingly sophisticated imaging technology, it is appropriate to examine the risks for patients and staff exposed to the types of high energies and contrast agents used.

Ionizing radiation

Radiation exposure is directly proportional to the duration of the procedure and inversely proportional to the square of the distance from the source. Henderson et al monitored the radiation exposure of 16 pediatric anesthesia fellows during a 2-month period [255]. Fellows assigned to the cardiac catheterization lab had fluoroscopy exposure time of 14–85 min per case, typically for 2–3 cases per day. For these anesthesiologists, badge readings ranged from 20 to 180 mrem/month. All non-cardiac anesthesia fellows had undetectable (<10 mrem/month) levels. All fellows wore lead aprons, 50% wore a thyroid shield, and one stepped at least 3 m away from the source during every exposure; this latter fellow had a reading of 30 mrem, despite having spent 26 h in the catheterization lab. The annual maximum permissible dose (MPD) for non-radiation workers (including anesthesiologists) is 100 mrem or 1 mSv. For comparison, the MPD for radiation workers is 50 mSv annually, and 10 mSv times age cumulatively. MPD during pregnancy for radiation workers (per gestation) is 5 mSv. Safety precautions for all anesthesia practitioners include strict requirements to wear lead aprons and thyroid shields in fluoroscopy areas, to wear radiation detection badges and have them measured at regular intervals, step as far away as possible and out of the direct line of radiation, and use mobile, transparent, lead-impregnated plastic "walls" as an extra source of protection (Fig. 41.9).

The American College of Radiology has raised public and professional awareness about the risks of ionizing radiation and the importance of tailoring the dosing to the needs of the child. The Society of Pediatric Radiology established the Image Gently campaign to seek alternative methods of lowering radiation exposure to children during imaging studies (www.imagegently.org). This has expanded from radiation during CT imaging to include procedures in interventional radiology [256–258]. Web-based training and education has been developed to offer a quality improvement module for CT safety in children [259].

High-intensity magnetic fields

Magnetic resonance imaging exposes the patient (and the healthcare workers surrounding the patient) to a static magnetic field, a rapid switched spatial gradient magnetic field,

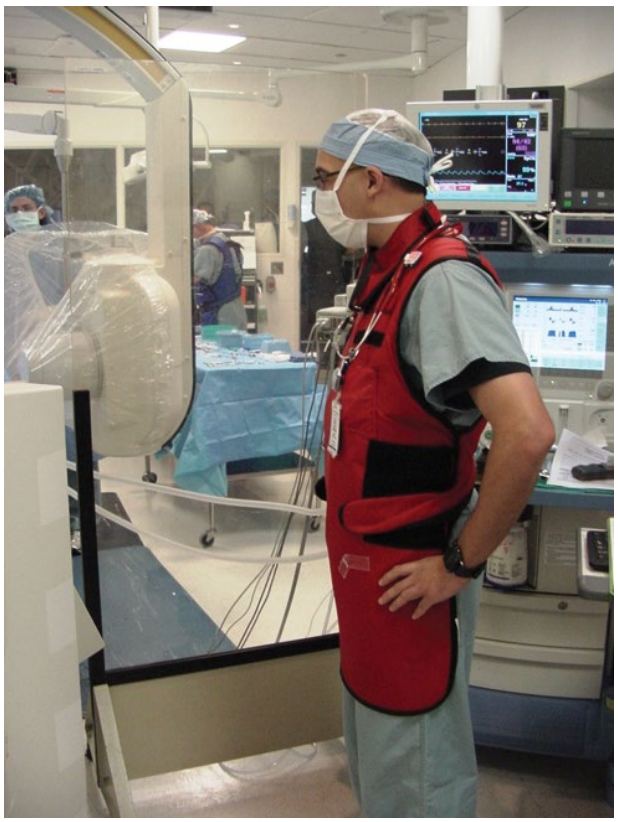

Figure 41.9 Anesthesiologist with proper ionized radiation shielding and safety precautions in a cardiac catheterization laboratory. Note the full lead apron with thyroid shield, radiation detection badge, and lead-impregnated plastic wall. He is also standing at some distance away from the cameras, and not in the direct line of radiation emission.

and radiofrequency magnetic fields. The static magnetic field, which causes alignment of unpaired tissue protons, may cause movement of ferromagnetic devices such as vascular clips, ventricular shunt connectors, casings for pacemakers, and control devices for pacemakers. Metallic devices in other areas, particularly when invested with fibrous tissue are less problematic [61,260]. As mentioned previously, tissue expanders may have magnetic ports to facilitate identification of the injection site. Despite their low mass, such ports have a potential for torque and movement in the presence of a strong magnetic field, therefore the specific type of tissue expander should be identified prior to patient evaluation in an MRI scanner [53]. Assessment of risk in patients with implants or other possibly ferromagnetic devices or objects consists of a careful history including penetrating wounds, physical examination to look for scars, and possibly a plain radiograph of the region in question [261]. Other concerns have been increased blood pressure, cardiac arrhythmias, and impaired mental function. While described or theorized on an experimental basis, little clinical documentation is available.

The magnetic field generates an electric current 2–3 orders of magnitude less than a defibrillator (10 mA/m^2, compared to 1,000–10,000 mA/m^2). This current strength may nevertheless reprogram a programmable pacemaker and interfere with its function [56]. Exposure to a strong external magnetic or electromagnetic field can lead to conversion of a demand pulse generator from synchronous to asynchronous mode, damage to the reed switch (which activates the fixed rate pulse generator), reprogramming of pacemaker parameters, induction of currents in the electrode wires, or to displacement of the generator itself. Indeed, it is the sensitivity of some reed switches that has determined the "safety boundary" of magnetic resonance devices as being 5 G (5×10^{-4} T). Patients with implantable defibrillators/cardioverters, implantable infusion (e.g. insulin) pumps, cochlear implants and neurostimulators, are all at risk for having the implant device reprogrammed upon exposure to the magnetic field. Defibrillator failure has been reported in the MRI environment [262]. As noted earlier, MRI-compatible, conditionally safe pacemakers are now available [58].

Radiofrequency pulses cause heat production in metallic implants and coiled wires such as ECG cables or pulse oximeter cables if looped and laying on the patient's skin. Patients with compromised thermoregulatory abilities, such as those with cardiac problems, fever, or taking certain drugs, may be at particular risk. Included in this group are infants, whose SAR is greater than that of adults because of the greater ratio of body surface area to body mass, and whose thermoregulatory abilities may be interfered with during a general anesthetic [76]. SAR refers to the energy absorption (e.g. increasing body temperature) with an increase in the total amount of RF energy absorbed [263].

Increased reports of vertigo, nausea, and a metallic taste have been found in a study on human exposure to a 4 T magnetic field (whole-body scanner) [264]. Fertilized frog embryos exposed to a 4 T magnetic field did not demonstrate any adverse effects on early development [52]. An increase in cardiac cycle length of 17% was found in healthy volunteers in a 2 T environment after 10 min of exposure, causing speculation about the effect of the 2 T environment on the sinus node [67] This may be of particular concern in patients with a pre-existing arrhythmia history. Of more significant concern in pediatric patients is the potential for hypothermia because of the air flow directed through the scanner cavity and the inability to control room temperature or use radiant warmers. The use of warm IV fluid bags, thermal packs, and blankets can decrease heat loss. Excellent reviews of monitoring considerations and equipment choices in the MRI environment as well as patient safety principles are available [46,70,261,263,265,266] and the American College of Radiology (with a representative from the ASA) has published a white paper on magnetic resonance safety [37].

Magnetic resonance imaging and spectroscopy do not employ ionizing radiation. However, secondary harmful effects, such as magnetic objects becoming projectiles within the magnetic field as they approach the bore of the magnet and potentially causing injury, are a consideration [267,268]. Patients (and anesthesiologists) with metallic implants such as vascular clamps, hemostatic clips, dental devices, heart valve prostheses, intravascular coils, filters and stents, ocular implants, orthopedic implants, otological implants, shrapnel, penile implants, and vascular access ports must be individually evaluated for their risk in the MRI environment [269,270].

Use of intravascular contrast media

In a comprehensive review, Goldberg noted approximately 5% of radiological exams with radiocontrast media (RCM) are complicated by adverse reactions, with one-third of these being severe and requiring immediate treatment [271]. Anaphylaxis during anesthesia has recently been the subject of several consensus conferences [272–274]. Reactions occur most commonly in patients between 20 and 50 years of age, and are relatively rare in children. The male : female ratio is about 1:2.5, not dissimilar to the gender distribution of other allergies such as to latex, aspirin, and neuromuscular blocking agents. With a history of atopy or allergy, the risk of a reaction is increased from 1.5- to 10-fold. Reactions vary from mild, subjective sensations of restlessness, nausea, and vomiting to a rapidly evolving, angioedema-like picture accompanied by respiratory distress, bronchospasm, arrhythmias, and cardiac arrest. Because of the high molar concentration of contrast media (often >1000 mOsm, and sometimes >2000 mOsm), caution should be exercised with patients who have a limited cardiovascular reserve such as patients in congestive heart failure or those with cardiomyopathy. In addition, volume-depleted young children (NPO for prolonged intervals, bowel preps) should be pre-hydrated prior to RCM administration. Because contrast agents are hypertonic, the initial hypertensive response is usually followed by equilibration with the extracellular fluid compartment within 10 min, heralded by the onset of diuresis. Special attention should be paid when administering iodine RCM to any child with a history of congestive heart failure. Patients with hepatic or renal dysfunction should be observed closely for signs of impaired excretion of the RCM. In sickle cell disease, the increase in blood osmolarity may precipitate shrinkage, clumping, and, ultimately, sickling of erythrocytes and vascular occlusion. Sickled cells are known to align with external magnetic fields to which they are exposed; it is unknown how this theoretical concern compares, for example, with the normal forces of deformation imposed on red cells of patients

with sickle cell disease in their normal course through the vascular tree [70]. Those patients dependent on a full intravascular volume status (patients with sickle cell disease, cyanotic congenital heart disease with a restricted pulmonary circuit volume, patients with arteriovenous shunts, etc.) should be monitored carefully for an initial rise in filling pressures and intravascular volume and subsequent diuresis following an osmolar load. Patients with impaired excretory mechanisms, such as those in renal failure, must be monitored closely following high osmolar loads. Low osmolar RCM are relatively safe with regard to life-threatening reactions, but moderate non-life-threatening reactions requiring some treatment occur 0.2–0.4% of the time, and a severe life-threatening reaction can occur in 0.04% of patients [275]. The risk of contrast reaction to non-ionic contrast media is rare. A recent review of 12,494 patients reported overall a 0.46% incidence of contrast reaction, all being mild or moderate and none classified as severe [276].

Gadolinium dithylenetriaminepenta-acetic acid is a low osmolar ionic contrast medium used for MRI, with a slower clearance in neonates and young infants than in adults, yielding longer windows for imaging [277]. Free gadolinium has a biological half-life of several weeks with uptake and excretion taking place in the kidneys and liver. Unfortunately, free gadolinium is quite toxic and is therefore chelated to another structure that restricts the ion and decreases its toxicity. The most common adverse reactions are nausea, vomiting, hives, and headache. Local injection site symptoms include irritation, focal burning, or a cool sensation. Transient elevations in serum bilirubin (3–4% of patients) have been reported and a transient elevation in iron for Magnevist® and Omniscan® (15–30% of patients) occurs, which tends to reverse spontaneously within 24–48 h [278]. Anaphylactoid reactions occur in the order of 1:100,000 to 1:500,000 and are more rare (<1:100,000 doses) in children.

The older literature states that patients who have had anaphylactic reactions to shellfish are at increased risk of anaphylactoid reaction to RCM. The irony of the statement is that it may be correct, but for non-obvious reasons. The original rationale was that shellfish contain high quantities of iodine and therefore it was assumed that there would be a risk of cross-reactivity. However, neither shellfish allergy nor RCM reactions are due to iodine. Atopy per se is a risk factor; therefore, the association between atopy and anaphylactic reactions to shellfish and a possible predisposition to a RCM reaction may indeed be valid.

The treatment of severe allergic reactions, whether anaphylactoid or anaphylactic, is no different than for any other allergic reaction. Epinephrine, aminophylline, atropine, diphenhydramine, and steroids have all been employed in order to control varying degrees of adverse reactions. A patient who requires RCM administration and who has had a previous reaction to RCM has an increased (35–60%) risk for a reaction on re-exposure. Pretreatment of these high-risk patients with prednisone and diphenhydramine 1 h before RCM administration reduces the risk of reactions to 9%; the addition of ephedrine 1 h before RCM administration further reduces the rate to 3.1% [279–281].

Allergic reactions rarely occur with oral agents. The incidence of severe anaphylactoid reactions to gastrointestinally administered agents is approximately 0.004:10,000 and the causes remain unknown. Gastrointestinal complications include nausea, vomiting, and diarrhea. One of the factors that may protect against having an allergic reaction is the poor absorption of oral iodinated contrast agents. Indeed, disruption of the gastrointestinal mucosa is recognized as causing an increase in absorption of oral contrast and the urinary excretion of contrast in a gastrointestinal study is a well-recognized sign. Yet rarely will they be associated with bronchospasm, flushing, periorbital edema, pruritis, rash, rhinitis, and urticaria.

Potential anesthetic and sedative neurotoxicity

Animal models of anesthetic and sedative exposure in the neonatal and early infancy age periods consistently demonstrate increased neuroapoptosis and other types of neurodegeneration, and long-term neurobehavioral effects of exposure to all common anesthetics and sedative agents that bind to γ-aminobutyric acid and N-methyl-D-aspartate receptors to produce their effects. This includes all volatile anesthetic agents, propofol, barbiturates, ketamine, benzodiazepines, and etomidate [282]. The human data are less convincing, and a short single exposure to anesthetics does not appear to have an effect on longer term neurodevelopmental outcomes [283,284]. However, some retrospective cohort studies demonstrate an association with repeated or prolonged anesthetics and higher incidence of learning disability, cognition and language problems, and other neurodevelopmental outcome problems [285,286].

In 2016 the US FDA issued a drug safety communication, warning that "repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains" [287]. The FDA has directed physicians to communicate with parents about this potential problem, and to discuss whether a procedure with sedation or anesthesia should be done now or can be postponed until after age 3 years. In addition, the duration of the anesthetic, and the potential need for repeat anesthetics, should be discussed, according to the FDA. This warning has generated considerable controversy [288], and also has led to evaluation of some procedures for medical necessity, including brain MRI for developmental delay in an otherwise asymptomatic patient [24]. A recent systematic review of 29 studies in 2299 children with developmental delay who had brain MRI found that only 7.9% of MRI scans led to an etiological diagnosis of the developmental delay [289]. More data are needed in this area before changing practice since recommendations for diagnostic testing for developmental delay emphasize brain MRI as a primary modality [290]. Chapter 46 has an extensive discussion of anesthetic neurotoxicity.

A strategy to avoid sedation in young infants up to the age of about 3 months is the "feed and swaddle" technique, which involves coordinating the scan time after a feed, and wrapping the infant in a blanket, using noise attenuation, and gentle restraint with a vacuum bean bag (Fig. 41.10) [291]. Shorter scans in younger infants are most amenable to

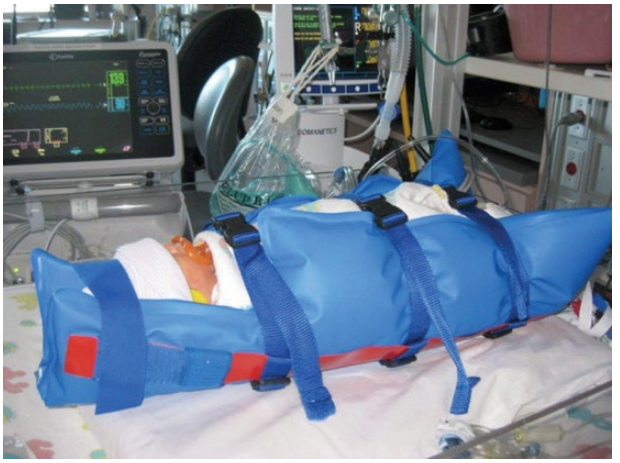

Figure 41.10 Feed and swaddle technique for non-sedated MRI in young infants. The neonate is wrapped in blankets and a vacuum bean bag, with noise attenuators in place, ready for transport to the MRI scanner suite. *Source:* Reproduced from Barkovich et al [291] with permission of Springer Nature.

this technique, which requires coordination and cooperation among MRI technologists, parents, and nursing staff. Noise reduction is crucial for this approach. Other measures increasing success are reducing scan time by focusing on the clinical question and tailoring sequences to reduce time, and using motion correction software. This approach has become more common in order avoid the risks of sedation and anesthesia, including respiratory and cardiovascular risk, and the potential but as yet unproven risk of neurotoxicity in young infants.

Quality improvement and simulation in NORA locations

With increasing economic pressure for cost containment and efficiency in the context of quality care, sedation/anesthesia providers should not only focus on medical knowledge but also on the application of quality improvement principles in NORA locations. Improvement requires leadership support and a team approach embracing transparency and open communication. In several pediatric centers, applied quality improvement methodology in NORA locations has been recently reported to improve work flow and safety for patients requiring anesthesia for radiological procedures. In the first quality improvement project, the percentage of successful start on time for the first patient scheduled with general anesthesia in MRI was 36% prior to starting the improvement project. At the conclusion of the project the on time start had improved to 84%. The key interventions of this project primarily focused on standardizing the processes for completing the preimaging evaluation and for anesthesia induction [292].

Many of the infusion medications used in radiology (propofol, dexmedetomidine, etc.) are used for sedation/anesthesia and the errors related to programming and operation can be catastrophic [293]. The common reasons for intravenous medication infusion errors are incorrect programming of weight or dose, programming a wrong medication, and over-ride of alerts by providers without recognizing an error. By using plan–do–study–act cycles, the second quality improvement project showed that utilizing a brief two-person verification approach in the radiology department can reduce medication errors due to wrong infusion pump programming [294].

The willingness of personnel to speak up about a patient safety concern is an important part of safety and is equally important in the operating room and outside the operating room. The third project examined the concept of doing a challenge and response checklist to prevent errors in pediatric freestanding ambulatory surgery centers for patients undergoing MRI. The authors concluded that this approach can dramatically improve teamwork and patient safety in the operating room and in the radiology suite [295].

Finally, a recent quality improvement project examined the variables associated with postscan hypothermia in neonatal intensive care unit infants undergoing MRI and concluded that applying quality improvement principles minimizes hypothermia in this challenging patient population [296].

Medical simulation is emerging as a powerful educational tool capable of exploring technical, behavioral, and systems issues within healthcare [297,298]. Simulation enacts a participative clinical event for the purpose of learning, practicing, evaluating, testing, and understanding human actions [297]. Practitioners can learn in simulation without putting patients at risk and can also incorporate a review of educational content and debriefing by an expert facilitator to drive learning [297]. Recent studies have explored how simulation enhances pediatric sedation practice. A recent study supported the notion that patient safety was enhanced when simulation was incorporated into training for pediatrician-administered sedation [299]. Simulation can also address "latent error" identification such as patient vulnerabilities in complex healthcare environments [300]. Studies evaluating performance among pediatric trainees demonstrated clear deficiencies in life-saving skills such as resuscitation and airway management [301,302].

KEY POINTS: QUALITY IMPROVEMENT AND SIMULATION IN NORA LOCATIONS

- Improvement requires tremendous leadership support and a team approach, which embraces transparency and open communication
- The use of quality improvement methodology in NORA locations can improve work flow and safety
- Simulation can address systemic failures that undermine patient safety and may provide a unique tool capable of exploring patient vulnerabilities in complex healthcare environments

Future directions of pediatric sedation

The provision of pediatric sedation will likely change qualitatively as well as quantitatively in the future in response to changes in imaging technology and non-invasive or minimally invasive procedures outside the operating room. This will occur within the environment of a growing emphasis on

cost, efficiency, safety, and patient satisfaction. New and safer sedative agents, innovative delivery systems, broadening of non-anesthesiologist practitioners and their training, increased deployment of high-quality databases informing quality improvement methodology, standardized definitions of adverse events amongst multiple practitioners in multiple sites, and evolving requirements for credentialing are expected changes in the future practice of pediatric sedation.

The last decade has seen a significant growth of interventional procedures that are replacing many surgical procedures. More and more care in NORA locations is expected and some of this care will be provided by non-anesthesia providers in the future. Pediatric anesthesiologists should play a critical role in collaborating with non-anesthesiologists in examining practice and outcomes. The results will inform and advance sedation practices. For example, a successful collaboration among anesthesiologists, intensivists, emergency physicians, and hospitalists working with over 130,000 patients showed no difference in complications between specialists [303,304].

Previously, depth of sedation was defined based on a patient's response to verbal or tactile stimuli. Recently, the International Sedation Task Force (World Society of Intravenous Anaesthesia) created a sedation reporting tool that is open access, on-line, free of Health Insurance Portability and Accountability Act identifiers, and a means of collecting and sharing data worldwide among all specialists (www.AESedationReporting.com) [305]. This AE Sedation Reporting Tool has already been adopted and promoted by specialists in multiple disciplines worldwide for sedation studies of both adults and children [306–308].

KEY POINTS: FUTURE DIRECTIONS OF PEDIATRIC SEDATION

- Large, prospective outcome studies are necessary to determine optimal sedation practices
- As the demand for procedural sedation continues to expand, sedation providers must continue to be creative in their search for novel, safe, effective, and efficient methods to deliver care
- There is a need for multispecialty groups to share results and devise evidence-based guidelines that address current discrepancies in training, equipment, techniques, and outcomes

Summary

The demand for anesthesia and sedation services in sites distant to the operating room is continuing to increase. Providing patient services in NORA locations can be challenging and can pose risks that may not exist in the operating room. As technology advances, the anesthesia/sedation providers must maintain an understanding of the procedures in order to tailor the anesthetic/sedative appropriately. Versatility must be maintained to adapt to the different clinical situations required for delivering anesthesia/sedation in NORA locations. All stakeholders in the provision of NORA sedation and anesthesia services must recognize that as the demand for these services grows, so also should their ability to understand the specific environment and to do careful risk analysis when selecting patients and formulating an individual as well as an institutional plan of care.

CASE STUDY

An 18-month-old, 18 kg boy is scheduled for an MRI of the brain to evaluate new onset of grand mal seizures, photophobia, and increasing irritability. He has been well previously. He is currently taking phenobarbital and phenytoin.

The evaluation of children presenting for imaging studies is very similar to the evaluation of children requiring surgery. This rather large toddler's preanesthetic evaluation has to consider the efficacy of his anticonvulsant therapy because he is on two medications. Grand mal seizures of the tonic-clonic variety are usually the easiest to control, particularly if they originate from a single seizure focus, but generalized tonic-clonic seizures associated with a progressive metabolic disease, or complex partial seizures, are more difficult to control. Multimodal therapy is often required in these circumstances. The history is important here because seizure thresholds may be affected by the administration of or the withdrawal from a general anesthetic, in the first case raising the threshold and in the second case lowering it. Therefore, during emergence, the patient may be at increased risk for a seizure.

Many induction plans are acceptable. Intravenous access may be more difficult prior to induction due to the size of the patient (18 kg at 18 months of age, approximately the size of an average 4 year old), multiple attempts, and the increased stress. Crying and aerophagia would be expected. If a general anesthetic were required we would be inclined to proceed with a parent-present mask induction. Most imaging studies only require immobilization and are not stimulating. The sedation level can change rapidly from minimal sedation to general anesthesia; therefore, the expectation of the Joint Commission is that a deeply sedated patient should be able to be rescued from a depth of general anesthesia. If it seemed like deep sedation would be a good strategy and easy intravenous access is likely, we would probably plan on using pentobarbital sedation rather than dexmedetomidine, the other alternative we commonly use. The effect of dexmedetomidine on seizure threshold is controversial; some (early) studies indicated that it may lower the seizure threshold, although in these studies enflurane and sevoflurane were used as part of the anesthetic technique. Pentobarbital, on the other hand, would raise the seizure threshold and perhaps provide a greater margin of safety for this poorly controlled toddler. With this plan, airway management would likely consist of a natural airway with supplemental oxygen, without any adjunctive devices. Use of a divided nasal cannula capable of end-tidal CO_2

monitoring is an important monitoring technique in these patients for early detection of airway obstruction. Video camera monitoring of the patient in the bore of the scanner is useful to detect inadequate sedation with patient movement, or airway obstruction. Minimal obstruction of the natural airway with preservation of pharyngeal muscle tone will allow the procedure to continue with an adequate level of sedation. If significant upper airway obstruction occurs, the rocking motion of the head, neck, and chest may interfere with the quality of the scan, and therefore the anesthetic plan would need to be modified because the study requires a motionless patient.

A total intravenous anesthetic (TIVA) technique with propofol may also be chosen. Supplemental oxygen is provided with a nasal cannula. Placement of a shoulder roll and/or an oral airway is helpful in maintaining patency of the airway. If the airway remains obstructed, then a general anesthetic (intravenous or inhalational) can be employed with a laryngeal mask airway or endotracheal tube.

Safety concerns in the environment of the magnet are critical. It is important to remember that the magnet is always on, and the dangers of the electromagnetic field are ever present. Ferrous-containing elements of the anesthetic equipment have to be eliminated for the sake of patient safety as well as the test results. Iron-containing materials become missiles in the MRI scanner, depending on iron content and mass, but magnetic attraction obeys the inverse square law such that the closer it gets to the bore of the magnet the greater the attraction becomes. Oxygen tanks, tables, and anesthesia machines have been "sucked into" the bore of the magnet. For the anesthesiologist and other medical personnel, anything containing iron in their pockets can become projectiles as well, such as stethoscopes or scissors. In addition, personal identification cards such as hospital ID cards and credit cards can have their information rendered useless; beepers and telephones will also have their radiofrequency chips scrambled to the point of uselessness. In the event of an emergency, removing the patient from the magnet room to a less hostile environment is the preferred initial course of action.

The duration of PACU stay will depend on how many seizures the patient ordinarily has per day, the competence of the parents in dealing with these seizures, and to some extent the risks of driving home (e.g. distance to home, distance to closest hospital). We would probably keep the patient for 4–6 seizure-free hours in the PACU, with the resumption of his previous oral medications, consultation with his neurologist, and postoperative blood levels, which should be easy to obtain. We would restart his anticonvulsants following the scan. The half-lives are drawn out enough and the onset is long enough that his level will neither decline nor be increased drastically if he resumes his usual oral schedule a few hours later. It will probably be unnecessary to give him any intravenous equivalent doses of his phenobarbital or phenytoin.

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 42
Pediatric Intensive Care

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Pediatric intensive care unit team

The pediatric intensive care unit (PICU) is a complex system of multidisciplinary care delivery for many different medical and surgical diagnoses. The care team is large and diverse, including but not limited to physicians, nurses, respiratory therapists, social workers, discharge planners, nutritionists, child life specialists, and family members. Subspecialization of pediatric critical care is increasing, including cardiac and neurological critical care. The number of pediatric critical care beds is increasing while numbers of general inpatient care beds are decreasing, reflecting the rising inpatient complexity and illness. The majority of patients in the PICU are straightforward medical and surgical patients with single-system organ dysfunction, although children who are chronically critically ill with long-term organ system failure are present as well. Because of the paucity of rehabilitation, chronic care, and hospice options for children in the community, the PICU often serves these purposes as well. This chapter provides an overview of disease processes and therapies provided in the PICU that are pertinent to perioperative care of children.

Relationship between the PICU and operating room

The PICU is part of the operative complex that provides perioperative care for children. There is high utilization of anesthesia services by PICU patients, and anesthesiologists and intensivists must work closely together to provide optimum care for critically ill children. Critically ill patients have increased perioperative anesthetic risk by virtue of organ system dysfunction and, in some cases, emergency designation [1,2]. Communication and collaboration between the pediatric intensivist and anesthesiologist is key to patient optimization and surgical and anesthetic decision making. Ideally, anesthesiologists have a working knowledge of issues faced by intensivists and vice versa – thus improving perioperative care.

Patient hand-offs between the anesthesiologist and PICU are common and should be a quality care focus. Standardized pediatric operating room (OR) to PICU hand-offs have been shown to improve quality of information provided, timeliness of antibiotic and analgesic dosing, and to decrease errors and omissions during hand-over [3,4].

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

Family-centered care in the PICU

The Institute for Patient- and Family-Centered Care defines family-centered care as encompassing four core concepts: respect and dignity, information sharing, participation in care and decision making, and collaboration between patients, families, and the healthcare team [5]. In the PICU, these concepts are realized through structural design and systems that prioritize families' needs. Physical plant features such as waiting rooms, bathrooms, kitchen areas, and patient rooms that recognize parent and family function in the PICU are critical [6]. Rounds participation is important to families as a place for information sharing and participation in decision making [7–9]. Particularly for the patient with developmental disability, parental presence, knowledge of baseline or communication strategies, and interpretation of symptoms are important. Recognition and support of the key role that families play in patient care and recovery is central to family-centered care in the PICU.

PICU family-centered care impacts the anesthesiologist's practice as it demands demonstration to the family and patient the collaboration and communication between the OR and the PICU. Anesthesiologists can support PICU family-centered care by allowing the family to participate in perioperative discussion and decision making, demonstrating communication and effective hand-off between environments, and respecting the role that families and patients play in the healing process.

Continuous quality improvement in the PICU

Quality care delivery in the PICU a universal goal, but "quality" is neither well defined nor easily measured. When pediatric critical care was in its infancy, measures of outcome were limited to mortality. As mortality in the PICU has remained low at 2–3.3% for the general PICU population, measurements of quality have turned to morbidities and complications of care [10,11]. Common quality metrics in critical care include hospital-acquired conditions such as central line-associated bloodstream infection (CLABSI), catheter-associated urinary tract infection, ventilator associated events, and pressure ulcers. For each of these morbidities, PICU practice prevention bundles and education strategies have been developed and implemented with varying effectiveness in reduction [12–14]. Electronic medical record triggers have provided another method to monitor and improve quality via dashboards [15,16].

CLABSI is the metric with the highest cost to the patient and healthcare system and the best-studied quality metric; it has significant attributable financial costs and affects length of stay [17]. Risk factors for CLABSI include multilumen central lines and line location; femoral lines have the greatest risk and subclavian lines the least risk [18,19]. Bundling of CLABSI prevention, insertion, and maintenance practices has been shown to decrease CLABSI rates in a large multicenter database review and single-center reports [20]. As anesthesiologists frequently insert and manage invasive devices, awareness and adherence to current practices is critical to the prevention of these costly complications.

Other emerging PICU quality metrics focus on the prevention of delirium and efforts at early mobility and rehabilitation. There is increasing recognition that previous practices of sedation and immobility may have a negative impact on physical and psychological healing and increase the risks for complications, including sleep deprivation and delirium [21,22]. In addition to the classic care bundles for CLABSI and ventilator-associated pneumonia, there are care bundles to reduce delirium and encourage early mobility and rehabilitation [23,24]. Knowledge of these efforts in the PICU impacts anesthesia care by informing choices in anesthetic technique and pain and sedation management.

KEY POINTS: PICU TEAM, OR, FAMILY-CENTERED CARE, AND QUALITY IMPROVEMENT

- The PICU team is diverse and includes physicians, nurses, respiratory therapists, nutritionists, and many other disciplines
- There is high utilization of anesthesia and perioperative services by PICU patients, and excellent communication and collaboration for care and hand-offs is essential
- Family-centered care encompasses respect and dignity, information sharing, participation in care, and collaboration
- Mortality in the PICU has remained low and measurements of quality have turned to morbidities and complications of care, including CLABSI, ventilator-associated pneumonia, and pressure ulcers

Organ system function and failure

Pediatric multiple organ dysfunction syndrome (MODS) represents a continuum of physiological disturbances that are potentially reversible in early stages and appear to become irreversible after a certain tipping point [25]. MODS occurs in more than 25% of PICU patients [26–28] and is more common in neonates and infants compared with older children [29,30]. It represents the leading final pathway to death in children who suffer critical illness triggered by acute insults as diverse as sepsis, trauma, burns, acute respiratory distress syndrome, congenital heart disease, inborn errors of metabolism, transplantation, and others [31,32]. Regardless of the inciting event, children with MODS have mortality rates ranging between 10% to as high as 57% [26,27,29,31,33–35].

First defined in 1986 as the simultaneous presence of two or more organ dysfunctions using the criteria proposed by Wilkinson et al [36,37], the definition criteria and monitoring of pediatric MODS have undergone several transformations over the years [38–41]. A recently published study comparing the two most recent criteria for pediatric MODS, Goldstein et al [41] and Proulx et al [40,42–44], conducted in a cohort of 842 consecutive PICU patients admitted at a single institution between 2009 and 2010, showed that the application of the two definitions in the same population yielded different rates of MODS: 21.4% versus 37.3%, respectively [26]. Applying the two definitions yielded different 90-day mortality rates for patients with MODS at PICU admission (11.5% versus 17.8%,

p = 0.038), but similar 90-day survival of patients without MODS at PICU admission (98.9% versus 98.6%, p = 0.73), using the Goldstein versus Proulx criteria, respectively [26].

While not yet universally incorporated into routine clinical care, serial assessments of pediatric MODS scores have become an integral part of clinical studies in pediatric critical care. New and progressive MODS (NPMODS) has been proposed as the primary outcome in a number of completed and ongoing major clinical studies in pediatric critical care, replacing mortality [45–47], because NPMODS develops in most patients who die and is significantly associated with worse functional outcomes in survivors [31,45,46,48,49]. NPMODS is defined as the development of dysfunction of two or more organ systems after hospital admission, or progression of MODS as evidenced by the worsening of one or more organ dysfunctions [45].

There are three published pediatric MODS scores: the PEdiatric Logistic Organ Dysfunction (PELOD, with the recently updated PELOD-2) score [40,44,50,51], the Pediatric-Multiple Organ Dysfunction Score (P-MODS) [52], and the modified Sequential Organ Failure Assessment (SOFA) scores for children [53,54]. PELOD-2 is comprised of 10 measures within five organ systems, including neurological (Glasgow coma scale (GCS) score, pupillary reactions), cardiovascular (lactatemia, mean arterial pressure), respiratory (PaO_2/FiO_2, $PaCO_2$, mechanical ventilation), renal (creatinine), and hematological (white blood cell count, platelet count) [44]. The score ranges from 0 to 33, measured in integers [44]. P-MODS is comprised of measures from five organ systems, including cardiovascular (lactatemia), respiratory (PaO_2/FiO_2 ratio), renal (blood urea nitrogen (BUN)), hematological (fibrinogen), and hepatic (bilirubin) [52]. Each variable is rated from 0 to 4, and P-MODS is the sum of the five variables [52]. P-MODS was developed and validated using data over the entire PICU course [52]. Lastly, modified SOFA scores for children have been proposed but only evaluated in the postoperative cardiac pediatric population in a small sample size study (n = 142), at admission (initial), 12 and 36 h postoperatively [53], and in the general PICU population at a single time-point at PICU admission as a severity of illness score [54]. Of these scores, PELOD and its updated version, PELOD-2 (Table 42.1), are the only scores validated in prospective multicenter cohorts that can be calculated serially during the PICU stay.

Table 42.1 PEdiatric Logistic Organ Dysfunction 2 (PELOD-2) score elements

System	Score element
Neurological	Glascow coma scale
	Pupillary reaction (both)
Cardiovascular	Lactatemia (mmol/L)
	Mean arterial pressure (mmHg)
Renal	Creatinine (μmol/L)
Respiratory	PaO_2 (mmHg)/FiO_2
	$PaCO_2$ (mmHg)
	Invasive ventilation
Hematological	White blood cell count (× 10^9/L)
	Platelet count (× 10^9/L)

Source: Reproduced from Leteurtre et al [39] with permission of Wolters Kluwer.

Cardiovascular disease

Assessment of cardiovascular function

Evaluation of a patient's cardiovascular state in the intensive care unit (ICU) involves performing a physical examination and evaluating physiological monitors and laboratory values. Evaluation of the electrocardiogram (ECG) for rate, rhythm, morphology, and presence of dysrhythmias can provide clues about myocardial well-being, while tachycardia, frequent premature ventricular contractions, and ST segment depression or elevation depict a more ominous sign of oxygen supply–demand mismatch. Abnormalities in end-tidal CO_2 ($ETCO_2$), pulse oximetry waveform and saturation, blood pressure, pulse pressure, central venous pressure (CVP), and cerebral and somatic oximetry can help elucidate underlying cardiovascular pathology. Signs and symptoms that may suggest poor cardiac output may also be appreciated on physical exam – dyspnea, crackles, depressed liver edge, peripheral edema, weak central and peripheral pulses, delayed capillary refill time, cool and mottled skin, abdominal pain, and abnormal third and fourth heart sounds. Laboratory studies to assess end-organ function can validate the degree of poor perfusion states – international normalized ratio (INR), liver enzymes, BUN, creatinine, lactate, B-type natriuretic peptide, and troponin.

When the underlying etiology is not clearly evident, or further characterization of the mechanism for cardiovascular demise is necessary, echocardiography is needed to gain detailed information about cardiac anatomy and function. Transthoracic echocardiography is non-invasive, does not often require sedation, and may quickly be performed at the bedside. Recent development of point of care ultrasound approaches utilizing portable ultrasound equipment stored in the PICU used by trained intensivists has greatly expanded the availability of this technique [55]. In children, 2D views allow for determination of left ventricule (LV) function – normal shortening fraction of 28–44% and ejection fraction of 55–65%. M-mode echocardiography is more commonly used to assess global right ventricule (RV) function by the tricuspid annular plane systolic excursion, which is the distance of downward movement of the lateral tricuspid valve annulus toward the apex during systole (Fig. 42.1). This has good correlation with isotopic-derived RV ejection fractions [56]. Growth-related changes have been published for children [57]. The pressure gradients across valves and RV pressure may be calculated using Doppler flow analysis. The velocity of blood moving across a valve or chamber can also be determined using Doppler. This velocity (V) in cm/s can then be used to determine the pressure difference (ΔP) in mmHg across the valve or chamber using the simplified Bernoulli equation:

$$\Delta P = 4 \times V^2$$

As an example, if the flow across the aortic valve using Doppler echocardiography is 3 cm/s, then the ΔP across the aortic valve is $4 \times 3^2 = 36$ mmHg. Similarly, the RV pressure can be determined if there is enough tricuspid jet to determine a velocity of blood flow. However, the estimation of RV pressure must take into account the opposing CVP that flows into the ventricle (the tricuspid jet travels from the RV to the

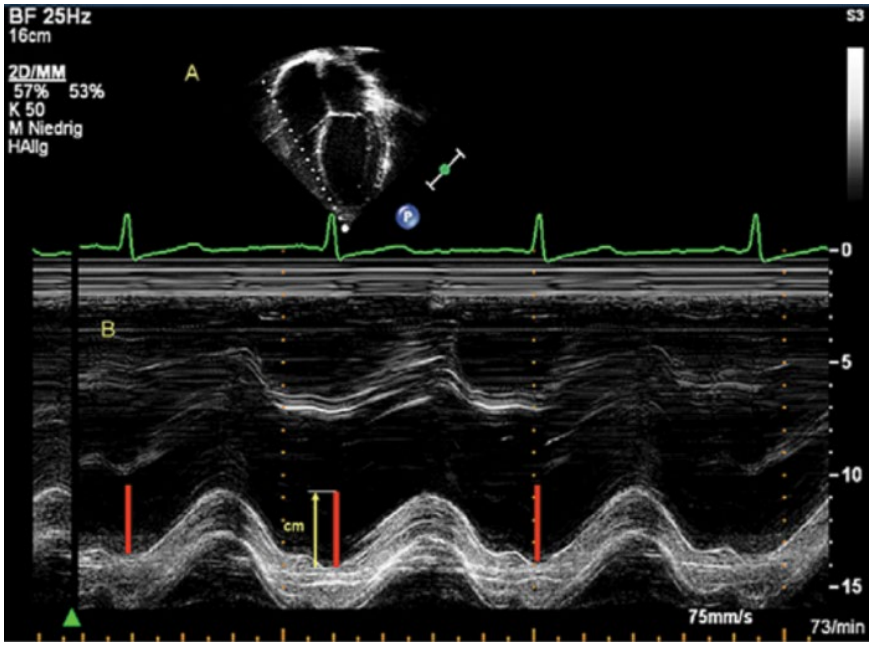


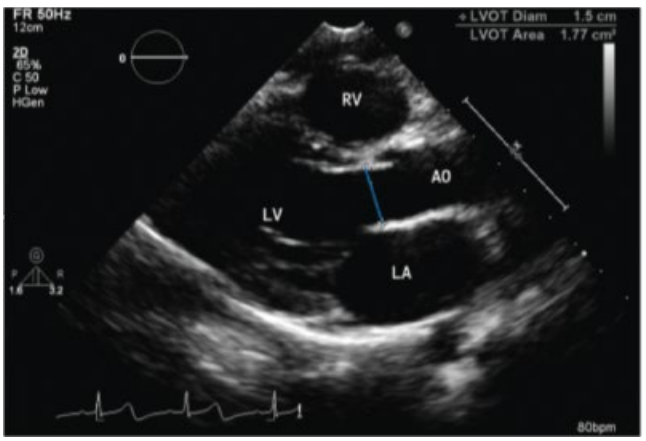
Figure 42.1 Apical four-chamber view of a transthoracic echocardiogram evaluating the right ventricle. (A) The white broken line indicates M-mode cursor placement at the tricuspid lateral annulus. (B) Representative M-mode imaging of the Tricuspid annular plane systolic excursion (TAPSE) in a patient with normal right and left ventricular function. The absolute longitudinal displacement measure (cm) is indicated by the red line. The yellow arrow marks the upper and lower measure points. *Source:* Reproduced from Koestenberger et al [57] with permission of Elsevier.

atrium). Thus, the RV pressure is the pressure difference across the tricuspid valve plus the CVP (or right atrial v-wave). For simplicity, if there is no direct catheter measurement of the CVP, it is assumed the CVP in most conditions is approximately 5–7 mmHg. Therefore, if the tricuspid jet velocity is 2.4 cm/s, the RV pressure is $4 \times (2.4)^2 + 5$ mmHg = 28 mmHg.

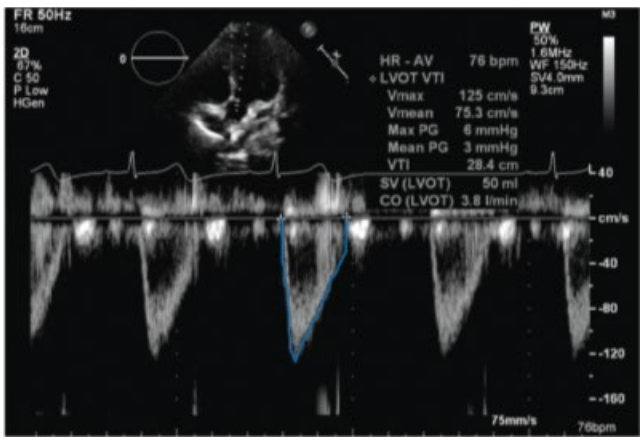
It is often important to estimate cardiac output, which can be measured by a variety of modalities. Non-invasive techniques are most commonly used and include echocardiography, magnetic resonance imaging (MRI), and non-invasive Doppler devices; however, invasive thermodilution and Fick methods may still be used in many PICUs. Echocardiography determination of cardiac output requires measuring the LV outflow tract (LVOT) diameter and the velocity time integral of the Doppler signal across the LVOT (Fig. 42.2). When the LVOT velocity time integral (LVOT VTi) is multiplied by the area of the outflow tract, a good estimation of stroke volume is obtained, using the following equation:

$$\text{Stroke volume} = \text{LVOT VTi} \times \text{LVOT cross} - \text{sectional area}$$

The cross-sectional area is calculated from the measured LVOT diameter, since area = $\pi \times (\text{diameter}/2)^2$. Cardiac output then simply becomes the calculated stroke volume multiplied by the heart rate. This Doppler-derived method assumes laminar flow across the LVOT and has been shown to be reproducible even in the context of severe heart disease [58]. LVOT



(A)



(B)

Figure 42.2 The left ventricular outflow tract (LVOT) diameter is measured in the parasternal long axis view (A) and the use of pulsed Doppler for the measurement of the velocity–time integer (VTi) is obtained in the five-chamber apical view (B). Cardiac output (CO) = SV × HR and SV = VTi × LVOT cross-sectional area. The LVOT cross-sectional area = $\pi/(\text{diameter}/2)^2$. *Source:* Reproduced from Gaspar and Morhy [334]. Gaspar, https://www.hindawi.com/journals/bmri/2015/596451/abs/. Licensed under CC BY 3.0.

VTi alone has been suggested to outperform both ejection fraction and Doppler-derived cardiac output [59]. Cardiac output by MRI can also be determined and is typically the modality of choice for measuring RV function. However, the disadvantages include transportation away from the PICU and the need for sedation in young children who cannot remain still for the time required to obtain adequate images. In 2001, the non-invasive, transcutaneous Doppler ultrasound device was introduced, and appears to be a promising adjunct in the assessment of the cardiovascular state in a variety of patients. For example, the ultrasonic cardiac output monitor (USCOM, Sydney, Australia) uses high-fidelity continuous wave Doppler to measure cardiac blood flow by placing a transducer in the left parasternal position or suprasternal notch to measure transaortic blood flow. Using a nomogram for aortic valve cross-sectional area, the cardiac output can then be continuously measured using the same principles used with Doppler echocardiography as described above. Given the continuous information this device can provide, the operator can measure response and effectiveness to medical therapy. The accuracy of such devices depends on obtaining accurate LVOT VTi, therefore continuous monitoring assumes that the ultrasound beam from the transducer remains in the same plane as the blood flow and does not move. As with Doppler echocardiography to measure cardiac output, the presence of aortic regurgitation, ascending aortic aneurysm, and arrhythmias may be sources of error. Further validation of such devices is ongoing, with recent studies showing some promise [60–62].

Cardiac output at the bedside can also be measured by the Fick method, where oxygen consumption (VO_2) is estimated, or with thermodilution using a pulmonary artery (PA) catheter. Both methods require invasive monitoring with central venous access. Furthermore, placement of a PA catheter requires a sheath to access the vein, which may present undue harm. As a result, such methods are infrequently used in children. The Fick method states that the amount of a substance taken up by the body per unit of time is equal to the arterial amount of oxygen minus the venous amount of oxygen multiplied by the cardiac output. Thus, cardiac output can then be calculated by the following formula:

$$\text{Cardiac output} = VO_2 / (C_aO_2 - C_VO_2)$$

where C_aO_2 is the arterial oxygen content and C_VO_2 is the mixed venous oxygen content (mL of O_2/dL). Oxygen consumption is difficult to measure and is therefore estimated, hence the accuracy of the Fick method relies on the correct estimation of oxygen consumption (VO_2), making it prone to error. Normal resting VO_2 is 125 mL O_2/min per m^2 body surface area (BSA). For the average adult whose BSA is 2 m^2 this is 250 mL O_2/min. Ideally with the patient breathing air, C_aO_2 and C_VO_2 can then be measured from arterial and mixed venous blood samples, respectively. Oxygen content of blood is the amount of oxygen bound to hemoglobin plus the amount of oxygen dissolved in blood, as shown by the equation:

$$O_2 \text{ content}\,(\text{mL } O_2 / \text{L}) = (1.34 \times \text{Hb} \times O_2 \text{ saturation} \times 10) + (0.003 \times PO_2)$$

where Hb is the hemoglobin (g/dL), PO_2 is the partial pressure of oxygen in blood (mmHg), 1.34 represents the amount of oxygen bound per gram of hemoglobin (mL O_2/g of Hb), and 10 represents the conversion for dL to liter. As an example, for a child with a BSA of 1.5 m^2 and Hb concentration of 14 g/dL, a blood gas drawn from a peripheral arterial line (P_aO_2 of 90 mmHg and S_aO_2 of 100%) and a blood gas drawn from a central line in the internal jugular vein ($P_{mv}O_2$ 35 mmHg and $S_{mv}O_2$ 70%), using the equation above the C_aO_2 is 187.87 mL O_2/L and the C_VO_2 is 131.43 mL O_2/L. Assuming a VO_2 of 125 mL/min/m^2, the cardiac output = (125 mL O_2/min × 1.5 m^2)/(187.87 mL O_2/L – 131.43 mL O_2/L) = 187.5/56.44 = 3.32 L/min.

The thermodilution method to calculate cardiac output uses a PA catheter and involves injecting a known quantity of an indicator (room temperature or iced sterile crystalloid) into the right atrium and then measuring the change in temperature downstream at the PA. Using software, this change in temperature measured at the thermistor of the PA catheter is graphed over time (Fig. 42.3). A curve is generated, with the area under the curve (AUC) representing the cardiac output. Cardiac output is inversely proportional to the AUC, thus the smaller the AUC the higher the cardiac output because there is less time for the thermistor to record a temperature change due to the higher cardiac output. Conversely, when blood flows slowly across the thermistor (low cardiac output), there is a greater change in temperature and the AUC is higher. Accuracy of thermodilution relies on proper temperature and volume of injectate, absence of concomitant intravenous solutions that can interfere with accurate temperature measurement, absence of respiratory cycle interference (injection is best when done at the end of expiration), proper PA catheter position, and the absence of an intracardiac shunt and right heart valvular regurgitation. With the inherent risk of

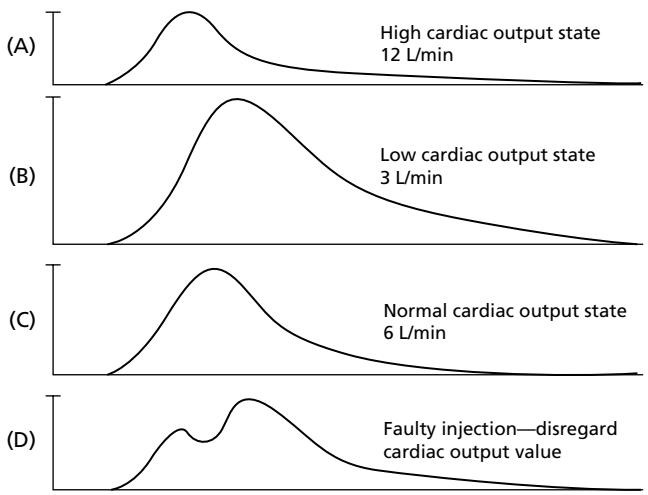


Figure 42.3 Various cardiac output thermodilution curves. The amount of temperature change is plotted along the *y*-axis and time is plotted along the *x*-axis. Administration of the cold injectate occurs just before the slope of the line starts to rise. Normal cardiac output (curve C) shows a smooth upstroke with a gradual downslope back to the baseline. When CO is high (curve A) the rise will be less than normal because the blood flow is higher past the thermistor tip of the pulmonary artery catheter, subsequently causing a smaller change in temperature. Conversely, with low CO (curve B) the rise will be greater because the blood flow past the thermistor will be slower, allowing a greater change in temperature to occur. Faulty injections (curve D) will often have uneven upstrokes on the curve, mandating a repeat injection. *Source:* Reproduced from Cruz and Franklin [335] with permission of Elsevier.

insertion and maintenance of PA catheters, and the emergence of newer non-invasive modalities, the use of PA catheters has decreased in PICUs over time. See Chapter 19 for further discussion of cardiovascular monitoring.

KEY POINTS: ASSESSMENT OF CARDIOVASCULAR FUNCTION

- Physical exam, ECG, arterial and central venous pressure; and peripheral, mixed venous, cerebral, and somatic oximetry, are all used to assess cardiac and circulatory function
- Echocardiography, including point of care bedside echo, can be extremely useful in assessment of cardiac function, filling, abnormal anatomy, and pericardial effusion
- Pulmonary artery catheterization and cardiac output measurement, pulmonary capillary wedge pressure, and oxygen delivery measurement and calculations are possible in selected PICU patients but are infrequently used

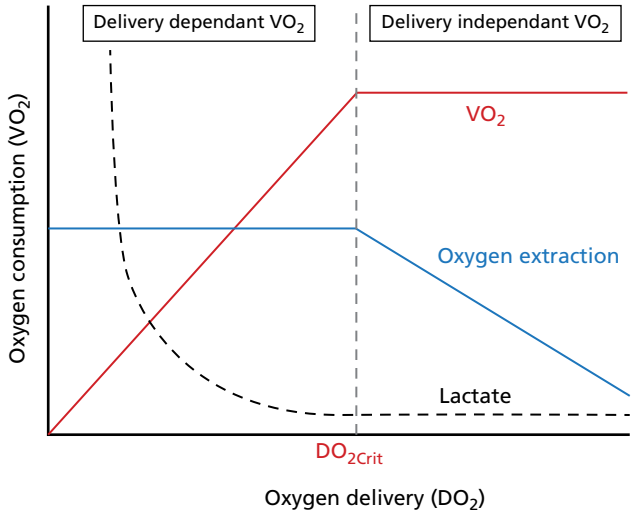


Figure 42.4 Oxygen delivery (DO_2) and consumption (VO_2) curves. As DO_2 decreases, VO_2 remains constant due to increasing oxygen extraction – during this time DO_2 is independent of VO_2. Once a critical point of DO_2 is reached, oxygen extraction cannot increase any further. Thus any further decrease in DO_2 will result in decreased VO_2. This leads to a shift to anaerobic metabolism with lactate production. Eventual circulatory collapse occurs if interventions fail to raise DO_2 back to, or above, the critical point.

Definition of shock

Shock is an unstable condition characterized by the inability to deliver adequate tissue perfusion to meet cellular needs, which can result in abnormal tissue function. Cellular hypoperfusion results in tissue hypoxia, disruption of intracellular milieu, intracellular acidosis, and abnormal cellular function. Although the initial effects can be reversed, prolonged deficiency can lead to irreversible organ injury and death. It must be recognized that shock can also occur in situations where adequate tissue perfusion exists, but there is still abnormal cellular function. In such conditions, the problem is impaired cellular uptake and/or utilization of oxygen, resulting in end-organ failure and death if not reversed. Therefore, early recognition and intervention has been the staple for the treatment of shock.

Effective management of shock requires an understanding of oxygen delivery (DO_2) and VO_2. Oxygen delivery includes the oxygen content of arterial blood (C_aO_2) and cardiac output (CO), as seen by the following equation:

$$DO_2\,(\text{mL of } O_2/\text{min}) = CO \times C_aO_2 \times 10\,\text{dL/L}$$

where cardiac output (L/min) is dependent on heart rate and stroke volume, and C_aO_2 (mL O_2/dL) encompasses the oxygen saturation and hemoglobin level, as described earlier. Tissue oxygen demand dictates VO_2. VO_2 is equal to DO_2 multiplied by oxygen extraction: $VO_2 = DO_2 \times$ oxygen extraction. As seen from the equation, when tissues are initially deprived of DO_2 in early shock, oxygen extraction increases to maintain VO_2 in an attempt to maintain aerobic metabolism. This increase in oxygen extraction is effective in most situations to maintain aerobic metabolism. Furthermore, redistribution of blood to organs that have little oxygen reserve, such as the brain and heart, occurs by sympathetic stimulation. But as shock continues, there comes a critical point (DO_{2crit}) where the ability to further increase oxygen extraction stops (Fig. 42.4). Beyond this, any further decrease in DO_2 results in a decrease in VO_2, exhausting the body's oxygen reserve and shifting to anaerobic metabolism, causing a rise in serum lactate. If interventions are not successful in raising DO_2 to at least the critical point, circulatory collapse ensues.

The effective management of shock requires interventions to improve DO_2 and reduce VO_2. VO_2 can be reduced by sedation and paralysis. DO_2 can be increased by interventions to improve both CO and C_aO_2. It is most easily done by increasing inspired oxygen concentration, maintaining appropriate hemoglobin level, and ensuring adequate heart rate and preload. The initial stage of resuscitation includes achieving adequate circulating intravascular volume by rapid intravenous fluid administration. Although crystalloids have no oxygen-carrying capacity, with intact cardiac function they can improve CO and microcirculatory perfusion, and subsequent DO_2. Improvement in CO from fluid resuscitation occurs because of an increase in fluid in the central venous system that allows more blood to flow down the pressure gradient between the central veins and the right atrium (RA). As a result, the RA pressure rises and improves both ventricular filling (preload) and myocardial stretch, leading to optimal contractility according to the Frank–Starling principle. Eventually there comes a point where further increases in RA pressure with fluid administration does not lead to improved CO, indicating the patient is no longer "fluid responsive." Thus, interventions to improve CO with the administration of adrenergic drugs may be necessary. Adrenergic agonists affect inotropy (force of contraction), chronotropy (heart rate), and systemic vascular resistance via stimulation of α- and β-adrenergic receptors (Table 42.2).

Several different classifications of shock exist. One of the most recognized classifications includes hypovolemic, distributive, cardiogenic, and obstructive shock. Each category is not mutually exclusive; a disease state can include more than one shock state.

Hypovolemic shock occurs due to loss of intravascular blood volume from either hemorrhage (e.g. trauma, surgical, or

Table 42.2 Continuous vasoactive medications

Drug	Dose	α-receptor	β1-receptor	β2-receptor	Effect	Comment(s)
Dopamine (DA)	1–10 μg/kg/min	0	++	++	Primary β effect at lower doses will increase HR, improve inotropy, and decrease systemic vascular resistance (SVR)	Because it improves CO and decreases SVR it is useful in cold shock, where the CO is low and SVR is high
	10–20 μg/kg/min	+++	++	0	Better vasoconstrictor (α > β) effect at higher doses	Greater potential of arrhythmias with higher doses. Inhalational agents may enhance arrythmogenic effects of DA
Dobutamine	1–20 μg/kg/min	+	+++	++	Primary β effects increases HR and cardiac contractility, while decreasing SVR	Useful for cardiogenic shock (low CO with preseved BP due to normal or high SVR). It can also be used with NE to improve inotropy and counteract the intense vasoconstriction of NE
Epinephrine	0.05–0.1 μg/kg/min	++	++	++	Has some β_2 effect at lower doses	First-line choice for cold hypodynamic shock. Lower doses may decrease SVR and redirect blood flow away from the splanchnic circulation, even though BP and CO increase
	0.1–0.3 μg/kg/min	++++	++++	++	More vasoconstriction (α) and inotropic (β_1) effects at higher doses	Epinephrine can cause an increase in lactate that is independent of lactate changes due to organ hypoperfusion
Norepinephrine	0.05–0.5 μg/kg/min	++++	++	0	Increases SVR (α) far more than it increases HR and contractility (β)	Some advocate its use as a first-line agent in fluid refactory, hypotensive, hyperdynamic shock (i.e. low SVR states characterized by wide pulse pressure with a DBP that is less than half the SBP)
Phenylephrine	0.1–2 μg/kg/min	++++	0	0	Direct α agonism produces intense venous and arterial vasoconstriction, with a reflexive decrease in HR	Especially useful in neurotrauma to improve MAP (and hence cerebral perfusion) without increasing cerebral metabolism and blood glucose
Milrinone	0.25–1 μg/kg/min	N/A	N/A	N/A	Selective phosphodiesterase III inhibitor that blocks cAMP hydrolysis	Altrenative to dobutamine in cardiogenic shock. Has synergistic effects with β-adrenergic agonists (which increase cAMP production) to improve inotropy. Should be used with caution as it can reduce SVR, which then leads to hypotension
Vasopressin	0.1–2 mU/kg/min	N/A	N/A	N/A	Its actions are independent of catecholamine receptor stimulation	Increases MAP by increasing SVR, without any significant increase in PVR. Can be considered in catecholamine-resistant vasodilatory shock

BP, blood pressure; cAMP, cyclic adenosine monophosphate; CO, cardiac output; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; NE, norepinephrine; PVR, pulmonary vascular resistance; SBP, systolic blood pressure; SVR, systemic vascular resistance.

gastrointestinal blood loss) or non-hemorrhagic causes. Non-hemorrhagic causes include intravascular volume loss (e.g. from gastroenteritis, diabetes insipidus, diabetes mellitus, heat stroke, burns, or decreased fluid intake) or fluid redistribution to the interstitial space (e.g. from sepsis, surgery, burns, intestinal obstruction, nephrotic syndrome, anaphylaxis, or trauma).

Distributive shock occurs as a result of inappropriate loss of peripheral vascular tone, leading to vasodilation and low systemic vascular resistance (SVR). This results in a relative hypovolemia due to an inadequate effective blood volume with a maldistribution of blood flow to organs. Blood pressure is low and CO can either be increased, unchanged, or decreased. Common causes include sepsis, anaphylaxis, neurological injury, and drug-related causes. Sepsis is perhaps the best studied and occurs from a dysregulated systemic inflammatory state in response to an infection.

Cardiogenic shock is characterized by impairment in myocardial contraction. In children without congenital heart disease (CHD), shock is most often secondary to myocarditis or cardiomyopathy, whereas shock from dysrhythmias and myocardial infarction are less common than in adults. Children with CHD who undergo repair on cardiopulmonary bypass can have postoperative low cardiac output syndrome. Some children with CHD, especially those who undergo palliative surgical procedures (e.g. Fontan), can develop ventricular failure from chronic valvular insufficiency or obstruction, as well as chronic volume overload from residual or unrepaired shunts.

Obstructive shock occurs when forward flow of blood through the heart is impaired, either from a congenital or acquired lesion. Common causes include cardiac tamponade, increased intrathoracic pressure from a tension pneumothorax, massive pulmonary embolism, pulmonary hypertension, hypertrophic obstructive cardiomyopathy, aortic valve stenosis, aortic dissection, and mediastinal masses.

The presentation of shock in children differs with age. Adults and older adolescents typically exhibit a warm shock state – decreased perfusion with brisk capillary refill and bounding peripheral pulses secondary to low SVR and normal to increased CO. Infants and young children more commonly have a cold shock state – decreased perfusion with delayed capillary refill, diminished peripheral pulses, and cool or mottled extremities secondary to increased SVR and low CO. This difference reflects the inability of infants and young children to significantly increase heart rate and SVR to the same extent as adults [63]. Consequently, vasoconstriction resulting in cold shock is the predominant response to a decrease in CO in pediatric septic shock, with hypotension manifesting as a relatively late finding in young children [64].

Treatment of shock

Guidelines for treatment of pediatric shock include treating the underlying cause, restoration of appropriate DO_2 to all tissues of the body, and removal of metabolic products produced during anaerobic metabolism. In general, established resuscitation guidelines for pediatric septic shock serve as the best example for other types of shock. The management of pediatric sepsis has been addressed at length in the Surviving Sepsis Campaign Guidelines (SSCG) in 2008 and 2012, but the most recent guidelines in 2016 did not include any additional specific recommendations in the management of pediatric sepsis. Much of what has been suggested, however, is based on expert consensus and adult evidence.

For a patient with suspected sepsis, the SSCG in 2012 suggested a protocolized approach [65]. Many recommendations were made, but emphasis was clearly on early initial resuscitation, obtaining blood cultures prior to antibiotic initiation, prompt imaging to identify potential sources for infection, early administration of empirical broad-spectrum antibiotics within 1 h of recognition of severe sepsis, and early and aggressive source control. The initial evaluation of a child begins with assessment of the state of perfusion and, if impaired, rapid intravenous access and administration of parenteral fluids should begin, with the goal to restore tissue DO_2 within the first 6 h. At the same time, laboratory tests should be obtained, and include: complete blood count, C-reactive protein, comprehensive metabolic chemistry panel (including liver and renal function tests), coagulation panel, fibrinogen, lactate, and blood or other fluid bacterial and fungal cultures. The implementation of a bundled approach to resuscitation can improve adherence to guidelines, decrease time to therapy, and improve outcomes in septic shock [66,67]. For example, implementation of a sepsis resuscitation protocol improved the median time to antibiotic administration from 130 to 30 min ($p < 0.001$) in children with severe sepsis or septic shock when they arrived at the emergency department [66].

Initial resuscitation of pediatric sepsis begins with infusion of up to 20 mL/kg of isotonic crystalloids over 5–10 min, titrated to reversal of hypotension, increased urine output, and achievement of normal capillary refill, peripheral pulses, and improved level of consciousness without inducting hepatomegaly or rales. If intravenous access cannot be obtained quickly within 5 min, it is recommended to place an intraosseous (IO) needle to prevent further delays in resuscitative measures, as it is considered to be as good as a peripheral IV for administration of fluid and medications. This is important since a higher mortality rate in children can occur when administration of 40 mL/kg is not achieved within the first hour or treatment is not initiated within the first 30 min after diagnosis (Fig. 42.5) [68].

The choice of initial fluid for resuscitation has been the subject of much recent debate. Crystalloids are typically the preferred initial choice for volume resuscitation in children because of their near-universal availability, low cost, and perceived safety. However, it must be recognized that crystalloids can quickly redistribute between the plasma and the extracellular fluid within 30 min of administration and have little oncotic properties, requiring ongoing administration. Recent concern about the use of 0.9% saline (a non-buffered/non-balanced salt solution) has emerged due to supraphysiological chloride content promoting renal injury and exacerbating systemic inflammation when compared with balanced solutions (lactated Ringer's or Plasma-Lyte®) in adults [69,70]. Although no large, randomized prospective study exists, the clinical relevance of this should be recognized and the use of a balanced salt solution should receive consideration. Nonetheless, using a large pediatric administrative database, Weiss et al showed that resuscitation in pediatric sepsis with lactated Ringer's was not associated with improved outcomes compared with 0.9% saline [71]. More studies on 0.9% saline are needed before its use is discouraged, therefore any readily available crystalloid for initial resuscitation should suffice, but consideration to switch to a balanced salt solution should occur if arterial pH falls below 7.20 or serum chloride rises to more than 110 mEq/L [63]. The use of colloids is an appealing alternative to crystalloid fluid – on the one hand they can improve plasma oncotic pressure and better restore intravascular volume, but in the presence of capillary leak they may exacerbate interstitial edema. The literature on colloid versus crystalloid for initial resuscitation is mixed, and until definitive data exist guidelines continue to recommend crystalloid for initial resuscitation but acknowledge that the addition of colloids such as 5% albumin represent a reasonable option for children with persistent shock and hypoalbuminemia (serum albumin <3 g/dL) despite 60 mL/kg of 0.9% saline or lactated Ringer's [65].

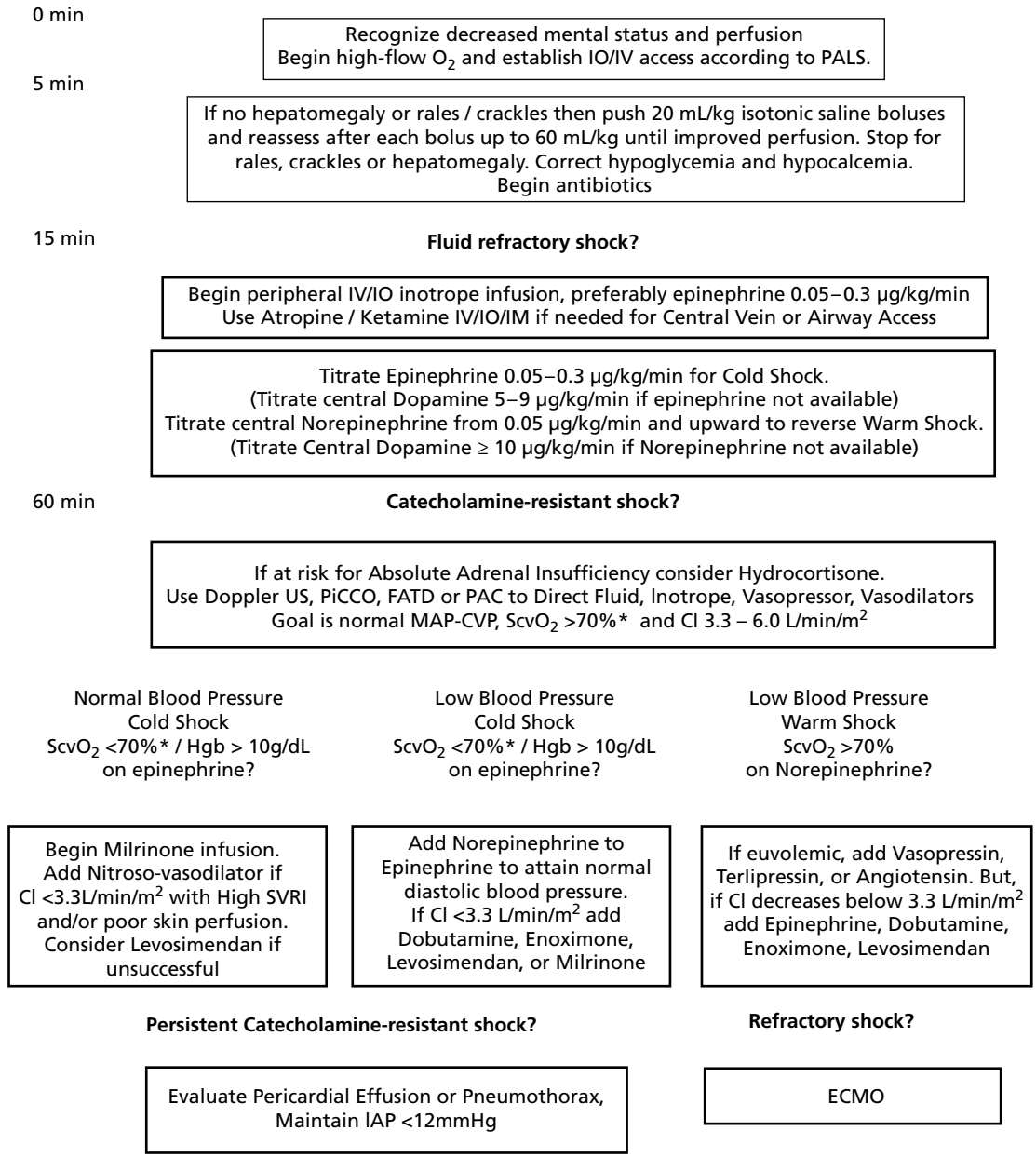


Figure 42.5 The American College of Critical Care Medicine algorithm for time-sensitive, goal-directed management of hemodynamic support in infants and children. Proceed to the next step if shock persists. (1) First-hour goals – restore and maintain heart rate thresholds, capillary refill ≤2 s, and normal blood pressure in the first hour or in the emergency department. (2) Subsequent intensive care unit (ICU) goals – if shock is not reversed proceed to restore and maintain normal perfusion pressure (MAP – CVP) for age, $ScvO_2$ >70% (* except congenital heart patients with mixing lesions), and cardiac index (CI) >3.3 to <6.0 L/min/m^2 in the PICU. CVP, central venous pressure; ECMO, extracorporeal membrane oxygenation; FATD, femoral arterial thermodilution; Hgb, hemoglobin; IAP, intra-abdominal pressure; IM, intramuscular; IO, intraosseous; IV, intravenous; MAP, mean arterial pressure; PAC, pulmonary artery catheter; PALS, pediatric advanced life support; PiCCO, pulse contour cardiac output; SVRI, systemic vascular resistance index; US, ultrasound. *Source:* Reproduced from Davis et al [82] with permission of Wolters Kluwer.

Early goal-directed therapy (EGDT) in adults was first shown to significantly reduce mortality in adults with septic shock (30.5% versus 46.5%, p = 0.009) in 2001 [72]; since that time, aggressive fluid resuscitation followed by initiation of inotropic and/or vasoactive medications for pediatric patients with fluid-refractory shock has been advocated. EGDT helps guide resuscitative efforts toward improvement in physiological parameters. A variety of clinical parameters, hemodynamic monitoring, and laboratory data can be used to asses a patient's response to fluid therapy, including heart rate, blood pressure, capillary refill time, quality of central/peripheral pulses, mental status, urine output (goal ≥0.5 mL/kg/h), CVP, central venous oxygen saturation ($S_{CV}O_2$), and serum lactate [63]. In the landmark adult study of EGDT, a continuous target $S_{CV}O_2$ >70% with red blood cell (RBC) transfusion was implemented [72]. A reduction in mortality was also seen in pediatric sepsis when continuous $S_{CV}O_2$ monitoring (39.2% versus 11.8%, p = 0.002) [73] or intermittent $S_{CV}O_2$ monitoring (33% versus 55%, p = 0.02) [74] was performed. Implementing EGDT in children therefore requires invasive central venous access, which may not be easy to obtain and may potentially distract providers from resuscitative efforts. Moreover, recent

larger studies in adults that compared EGDT with continuous $S_{CV}O_2$ monitoring with usual care showed them to be equally effective [75–78]. This change likely exists because the early sepsis trials that demonstrated significant mortality benefit with EGDT were limited by small sample size, non-randomization, and incomplete adherence to protocols [79]. Patients enrolled in more recent studies may have benefited from improved identification of sepsis, early antibiotic administration, and aggressive fluid resuscitation which have been established as standards of care since the original EGDT articles were published. Monitoring of $S_{CV}O_2$ is therefore recommended only if central venous access is established for other reasons.

An alternative to $S_{CV}O_2$ is monitoring blood lactate levels, as it is a surrogate for tissue hypoxia and anaerobic metabolism. In adults, initial level correlates with increased mortality [80], and in children whose serum lactate normalized to <2 mmol/L within 4 h of the onset of management had decreased organ dysfunction at 48 h [81]. It should be noted that the absence of elevated serum lactate does not equate to absence of severe sepsis, as not all septic patients have an elevated serum lactate. Therefore, resuscitation should not be delayed in the absence of elevated lactate.

Inotropic and vasoactive agents are frequently necessary to restore tissue perfusion in septic shock. They should be instituted if shock persists after 60 mL/kg of isotonic fluid have been administered in 15 min (fluid-refractory shock). Ideally, with each 20 mL/kg administration the patient should be evaluated for changes in clinical parameters, and if signs of fluid overload (i.e. hepatomegaly, rales, hypoxemia, tachypnea) are present, resuscitation should continue with the administration of inotropic agents. Furthermore, in patients with suspected or known components of cardiogenic shock, volume resuscitation should proceed judiciously with fluid boluses (5–10 mL/kg at a time), and, if necessary, should proceed with inotropic support using dopamine or norepinephrine.

Choosing the appropriate vasoactive mediation in children depends on the underlying clinical features. Either dopamine or epinephrine should be used if low CO and high SVR are present (cold shock) [82], but norepinephrine used if high CO and low SVR are present (warm shock) [65]. Children may have shifts between shock states, and therefore changes in vasoactive medications may be needed.

Alternative vasoactive agents in pediatric septic shock include milrinone and vasopressin. Milrinone is a phosphodiesterase-3 inhibitor most commonly used in cardiogenic shock because it improves inotropy and lusitropy (myocardial relaxation), and decreases SVR. In one randomized control trial in pediatric septic shock, when milrinone was administered together with catecholamines to volume-resuscitated patients, it improved cardiovascular function (cardiac index, stroke volume index, and DO_2) while significantly decreasing the SVR index [83]. In adults with catecholamine-resistant vasodilatory (warm) shock, vasopressin is suggested as an alternative to restore optimal tissue perfusion [65]. However, in a 2017 systematic review of children receiving vasopressin or terlipressin, there was no observed benefit on mortality and length of PICU stay, only a trend towards increased risk for tissue ischemia [84]. This difference in efficacy has been suggested to be due to variable levels of vasopressin and its precursor copeptin in children with septic shock, compared to the relative deficiency among adults [85].

The use of corticosteroids in shock is controversial. In the 2012 SSCG the use of steroids was only recommended for children with (1) fluid-refractory, catecholamine-resistant shock, and (2) suspected or proven adrenal insufficiency [65]. A single stress dose of hydrocortisone (50–100 mg/m^2/day) should be given as early as possible. A serum cortisol level should be drawn prior to administration of the first dose, because if it is low it suggests that ongoing replacement may be beneficial. It is reasonable to continue replacement steroids until the patient becomes hemodynamically stable and no longer requires vasoactive infusions; however, there is insufficient evidence to support a particular duration of time over which to wean the steroids. On the other hand, there is no proven benefit of steroids in patients with a relative adrenal insufficiency from a critical illness [86,87].

The administration of RBCs is recommended to maintain a hemoglobin goal of 10 g/dL during the initial management of septic shock, however lower hemoglobin levels could be tolerated if there is no cardiovascular instability or decreased DO_2. In one study, critically ill children who were randomized to a restrictive strategy group (Hb <7 g/dL) received 44% fewer transfusions and had no significant difference in new or progressive multiple organ dysfunction, compared with the liberal strategy group (Hb <9.5 g/dL) [45].

Intravenous immunoglobulin is an adjuvant that has been suggested for certain patients with sepsis, but pediatric studies are mixed regarding its benefit, unless there is concern for toxic shock syndrome [88,89]. Other therapies such as plasma exchange and immunomodulation therapies exist for certain subsets of shock, but general use is discouraged.

KEY POINTS: DEFINITION AND TREATMENT OF SHOCK

- Shock is characterized by the inability to deliver adequate tissue perfusion and oxygenation to meet cellular needs, which can result in abnormal tissue function
- Shock may be hypovolemic, distributive, cardiogenic, or obstructive
- Treatment of shock depends on the cause but involves increasing oxygen delivery and maintaining or decreasing oxygen consumption

Disorders of cardiac rhythm

Arrhythmias in children occur more frequently in children with underlying CHD than in those with a structurally normal heart [90]. Children with CHD have a lifelong risk for the development of arrhythmias. Arrhythmias can occur secondary to electrolyte abnormalities, myocardial hypoxemia, elevated catecholamine states (e.g. pain, anxiety, fever), or due to iatrogenic causes (e.g. central venous catheters, drug-induced). Arrhythmias most commonly affect hemodynamics when ventricular function is compromised. Thankfully emergencies due to unstable arrhythmias are rare in children [90].

Arrhythmias originate above the ventricles (atrial or supraventricular) or from the ventricles. Premature atrial

contractions are usually benign, even if they occur frequently. Premature ventricular contractions have a wider QRS complex followed by a pause, and if frequent require investigation because they may contribute to LV dysfunction. Correction of electrolyte abnormalities and screening for underlying cardiac disease is necessary.

Arrhythmias can also be classified as either tachyarrhythmias or bradyarrhythmias. Tachyarrhythmias decrease diastolic time, which can result in myocardial ischemia from increased demand and decreased supply. This is most problematic in children with underlying heart disease. Bradyarrhythmias, however, are more concerning in young infants and children because the stroke volume does not increase with lower heart rates to maintain CO [91].

Supraventricular tachycardia (SVT) describes any narrow complex (QRS <120 ms) tachyarrhythmias that originate above the bundle of His. SVT is due to re-entry pathways or increased automaticity. Tachycardia from re-entry originates from circuits within an accessory pathway (atrioventricular (AV) re-entry tachycardia), within the AV node (AV nodal re-entry tachycardia), or within the atrium (atrial flutter or fibrillation). Tachyarrhythmias from increased automaticity occur from foci within the atrium (ectopic atrial tachycardia, multifocal atrial tachycardia) or from ectopic junctional foci.

Atrioventricular re-entry tachycardia is the most common type of SVT in children, and more commonly occurs in infants [90]. It classically involves antegrade conduction down the AV node with retrograde conduction back up to the atrium through the accessory pathway which lies outside the AV node. However, during sinus rhythm antegrade conduction across both the AV node and accessory pathway results in the characteristic pre-excitation of the QRS wave ("delta wave"). This ECG finding is known as the Wolf–Parkinson–White pattern, and for those who develop SVT it is known as the Wolf–Parkinson–White syndrome. AV nodal re-entry tachycardia is the most common SVT in older children and adolescents [90]. It occurs when there are two pathways within the AV node itself, each having different conduction and refractory periods. Management of both AV re-entry tachycardia and AV nodal re-entry tachycardia is similar. If hemodynamically stable, termination of the rhythm can be attempted with vagal maneuvers (bag of ice to the face) or pharmacological block of AV node conduction with adenosine (initial dose of 100 μg/kg with subsequent increases of 100 μg/kg to a maximum of 400 μg/kg/dose). If adenosine is unsuccessful or the child is hemodynamically unstable, synchronized direct current (DC) cardioversion (0.5 J/kg) should be administered. If re-entry recurs, sotalol, flecainide, or amiodarone may be necessary [90]. Verapamil is a calcium channel blocker that blocks the AV node for a longer period of time than adenosine, but due to its risk of hemodynamic collapse in infants <6 weeks of age its use is contraindicated in infants less than 2 years old [92].

Atrial flutter and atrial fibrillation are tachyarrhythmias that are rarely seen in children. Atrial flutter usually occurs in the newborn period, except in patients who have had CHD surgery (tetralogy of Fallot, atrial septal defect, or Fontan operations). It is due to a re-entry circuit around the tricuspid valve. Adenosine does not convert atrial flutter or fibrillation to a sinus rhythm and can lead to serious rhythm degeneration and even death. Acute atrial flutter or fibrillation can be terminated with pharmacological (IV amiodarone) or electrical DC cardioversion. Evaluation of an atrial thrombus should be considered prior to cardioversion if long-standing. Alternatively, rate control without conversion can be achieved with β-blockers or calcium channel blockers.

Ectopic atrial tachycardia (EAT) and multifocal atrial tachycardia (MAT) occur from increased automaticity. When present, EAT can be difficult to control with medication and cardioversion. Treatment requires amiodarone, sotalol, flecainide, digoxin, or catheter ablation [90]. Early recognition and treatment are important since long-standing EAT can lead to tachycardia-induced cardiomyopathy. MAT is usually due to underlying CHD or metabolic abnormality [91]. Treatment of MAT involves treating the underlying condition, or achieving rate control with β-blockers and calcium channel blockers. Cardioversion of MAT can also occur with amiodarone or flecainide administration [90].

Junctional arrhythmias are supraventricular rhythms that originate above the bundle of His near the AV junction. They are characterized by a narrow QRS complex with a regular R-R interval, with absent or non-conducted P waves, unlike when the rhythm originates from the sinus node. Junctional rhythms can be slow (junctional bradycardia) or fast (junctional tachycardia). In children, the most common junctional rhythm is junctional ectopic tachycardia. It is seen following repair of CHD (e.g. ventricular septal defect, tetralogy of Fallot, AV canal) and can result in hemodynamic compromise. It occurs from AV dissociation with a ventricular rate that exceeds the atrial rate (e.g. if QRS rate >170 bpm, then the P wave rate <170 bpm). Treatment involves decreasing the ventricular rate by correcting fever and cooling to 32–34°C, correcting electrolytes, treating hypovolemia and anemia, discontinuing or reducing inotropes, optimizing sedation (i.e. dexmedetomidine) and neuromuscular blockade, IV amiodarone, and/or over-ride pacing.

Ventricular tachyarrhythmias have a widened QRS (≥120 ms) and can originate above the ventricles (i.e. SVT with aberrant conduction across an accessory pathway or associated bundle branch block) or from the ventricles (i.e. ventricular tachycardia). Regardless, it is important to initially evaluate and treat all ventricular tachyarrhythmias as if they are ventricular tachycardia (VT), which could be potentially life threatening [91]. Ventricular tachycardia (≥3 consecutive beats) originates below the bundle of His. If it lasts longer than 30 s, it is considered sustained VT. Monomorphic VT has the same QRS morphology whereas polymorphic VT has changing QRS complexes. The mechanisms by which VT occurs is similar to SVT, either by re-entry pathways or increased automaticity [90]. It can be seen in structural heart disease, myocardial ischemia, cardiomyopathy, myocarditis, drug toxicity, electrolyte derangements, and genetic channelopathies [90]. If the patient is hemodynamically stable, IV amiodarone (5 mg/kg over 30–60 min, maximum 300 mg/dose) or procainamide (15 mg/kg over 30–60 min) should be administered, with close hemodynamic monitoring [90]. Synchronized cardioversion (0.5-1 J/kg) is necessary if hemodynamic instability occurs at any point in time, and immediate defibrillation (2–4 J/kg) if the patient is pulseless. In torsades de pointes (wide QRS complexes "twisting" around the ECG axis) treatment is with IV magnesium sulfate (25–50 mg/kg).

Conditions that increase the risk of sudden cardiac death include structural abnormalities such as hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy, as well as diseases without structural heart disease that include inherited channelopathies (Brugada syndrome, Lev–Lenègre syndrome, long QT syndrome, short QT syndrome, and catecholaminergic polymorphic VT) [93,94]. Such patients should have close cardiology care and those at high risk for degeneration to ventricular tachyarrhythmias may benefit from ICU placement.

Bradyarrhythmias can occur from a reduction in impulse generation at the sinus node or disruption of its propagation across the AV node. They are usually benign and rarely need acute treatment; however, they can represent life-threatening conditions that need prompt intervention, such as increased intracranial pressure (ICP), medication effects/overdose, myocardial ischemia, severe hypothermia, and acute systemic hypoxemia [90]. They can also occur in children following cardiac surgery due to injury to the sinus node, necessitating temporary pacing. Second- and third-degree heart block occurs due to intermittent failure or complete absence of conduction across the AV node, respectively. In infants, symptomatic patients may appear severely ill at presentation. Furthermore, in sick sinus syndrome an alternation between bradycardia and tachycardia can occur, known as tachy-brady syndrome. In such conditions, temporary or permanent pacemaker implantation may be necessary [90].

KEY POINTS: DISORDERS OF CARDIAC RHYTHM

- Arrythmias are more common in children with CHD and most commonly affect hemodynamics when underlying ventricular function is compromised
- Arrhythmias can be supraventricular or ventricular, or tachy- or bradyarrythmias
- Early rapid treatment of hemodynamically unstable tachydysrhythmias with drugs or cardioversion, and bradydysrhythmias with drugs or pacing, is essential to prevent further deterioration

Congenital heart disease

Care of the child with CHD begins at birth when the transition from fetal circulation occurs. If the underlying diagnosis was diagnosed prenatally, pre-emptive preparations and plans are typically in place prior to delivery of the infant. However, if there was no prenatal diagnosis, prompt recognition followed by stabilization and transport to an appropriate monitored location is needed. Children with CHD require a collaborative effort from many different subspecialties, which can be best accomplished in a children's hospital. Extracardiac malformations are also best addressed in such facilities.

Care for the newborn with suspected CHD is initially performed in a neonatal ICU or PICU. Recognition of newborns with CHD first begins by determining if the disease is ductal dependent. Ductal-dependent lesions require a patent ductus arteriosus to either provide adequate pulmonary blood flow or adequate systemic blood flow (Fig. 42.6). When the ductus arteriosus begins to close, newborns with ductal-dependent pulmonary blood flow will become profoundly cyanotic, whereas those with ductal-dependent systemic blood flow develop systemic hypoperfusion with shock. Quickly re-establishing ductal patency can restore stable physiology. A continuous infusion of prostaglandin E1 is started, and is best administered through reliable intravenous access, such as a central umbilical venous catheter. In extremis, IV or IO placement should not be delayed by attempts to place a central catheter.

Delineation of the underlying cardiac anatomy often only requires a transthoracic echocardiogram. Then, depending on the underlying lesion, a surgical or interventional procedure is necessary. Newborn surgical or interventional procedures (definitive or palliative) are performed to provide a more reliable source of blood flow. While awaiting intervention, frequent monitoring of oxygenation and systemic perfusion is required. In mixing lesions, where shunting can occur, an equal balance of pulmonary and systemic blood flow is targeted. Not infrequently this requires controlled ventilation with intubation and mechanical ventilator support or inotropic support with vasoactive medications. In cases of life-threatening cyanosis or pulmonary hypertension, a bedside balloon atrial septostomy under ultrasound guidance is performed. This allows increased amount of mixing at the atrial level (i.e. for transposition of great arteries) or relief of elevated right heart pressure in newborns with pulmonary hypertension. When such interventions fail, mechanical circulatory support (i.e. extracorporeal membrane oxygenation (ECMO)) may be necessary. Until a surgical or interventional procedure can be performed, the goal is to provide adequate end-organ perfusion. This is best monitored by observing the level of alertness/consciousness, myocardial function (i.e. correlate of adequate coronary perfusion), urine output, cerebral and somatic oximetry using near-infrared spectroscopy, capillary refill time, and serum laboratory values (lactate, renal, and liver function tests).

Postoperative surgical care almost exclusively occurs in specialized PICUs. Care has dramatically improved over the years and is thought to be attributable, at least in part, to improvements in diagnostic modalities, surgical techniques, cardiopulmonary bypass support, anesthetic management, postoperative care, and the use of ECMO to manage postoperative cardiac dysfunction [95]. A systematic and comprehensive hand-off between surgeon and anesthesiologist and the ICU team is mandatory when transitioning care. Standard of care universally involves continuous intra-arterial and CVP monitoring for children undergoing repair on cardiopulmonary bypass. While early extubation is safe in many cases, many children still require postoperative mechanical ventilation. The influence of cardiopulmonary interactions help dictate ventilator strategies and settings. Frequent assessment for postoperative bleeding is required, and in small children blood product replenishment is often necessary. Finally, postoperative cardiac function is of utmost importance. Low cardiac output syndrome is commonly observed 6–12 h after bypass, with an incidence of 25%, and requires inotropic support [95]. In addition, temporary cardiac pacing can be used to augment cardiac output or when conduction abnormalities occur (e.g. junctional rhythms, AV conduction block). As myocardial function improves, inotropic support and temporary

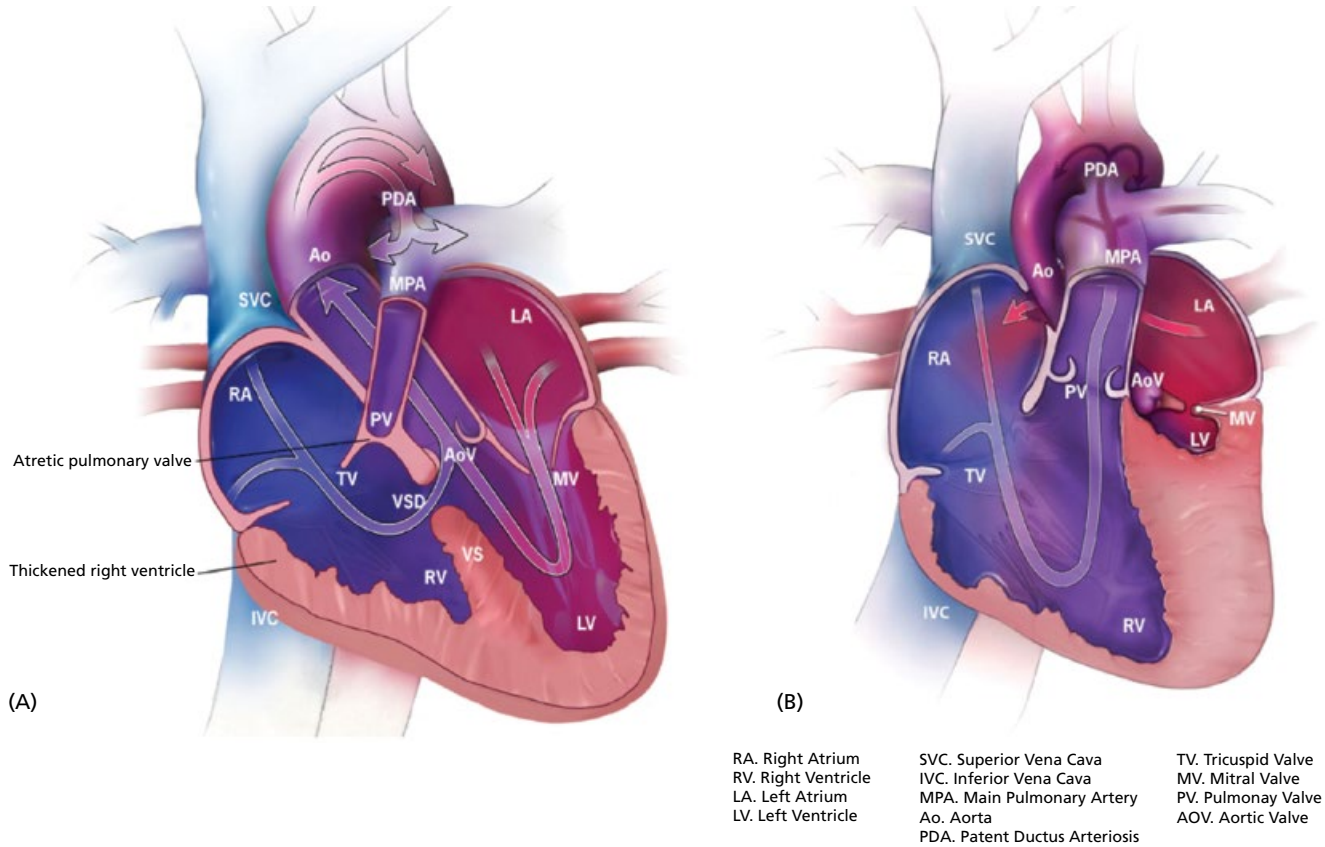


Figure 42.6 Many congenital heart disease lesions are ductal dependent with varying direction of blood flow across the ductus arteriosis. (A) Severe tetralogy of Fallot/pulmonary atresia: left-to-right flow, from the aorta to the pulmonary arteries (ductal-dependent pulmonary blood flow). (B) Hypoplastic left heart syndrome: right-to-left flow, from the pulmonary artery to the aorta (ductal-dependent systemic blood flow). Examples of ductal-dependent pulmonary blood flow include pulmonary atresia, critical pulmonary stenosis, tricuspid atresia, severe tetralogy of Fallot, and severe Ebstein anomaly. Examples of ductal-dependent systemic blood flow include critical aortic stenosis, interruption of the aortic arch, and hypoplastic left heart syndrome. *Source:* Courtesy of the Centers for Disease Control and Prevention, Division of Birth Defects and Developmental Disabilities.

pacing can be discontinued. If conduction abnormalities remain, permanent pacemaker implantation may be needed.

Although most surgical patients recover adequate ventricular function to separate from cardiopulmonary bypass, some do not. In such situations mechanical circulatory support with ECMO is needed. ECMO can also be initiated in the ICU should patients fail to recover adequate cardiac function. Should this situation arise, prompt evaluation of cardiac function and laboratory markers is needed. When cardiac function improves, ECMO can be discontinued. If it does not, further investigation with cardiac catheterization or surgical reintervention is indicated. However, despite all efforts, if recovery does not occur, either bridge to transplant or terminal discontinuation support may be necessary.

Medical cardiac disease

Heart failure in children can occur in both those with structurally normal hearts and in children with CHD. Cardiac dysfunction in non-surgical, structurally normal hearts can occur from a variety of factors: infection, autoimmune disease, chromosomal abnormalities, chronic arrhythmias, pulmonary hypertension, metabolic diseases, and toxin exposure, to name a few. This section will focus on two of the more common medical causes of heart failure resulting in admission to the PICU: myocarditis and cardiomyopathy.

Myocarditis

Myocarditis is an inflammatory disease that results in myocardial injury. It can present with a broad spectrum of clinical manifestations, ranging from generalized malaise to non-specific symptoms that rapidly progress to cardiac arrest. In the developed world, viruses are the most common etiology (adenovirus, coxsackie virus, parvovirus B19, Ebstein–Barr virus, human herpesvirus 6, cytomegalovirus, influenza virus) [96]. Myocardial injury is thought to be from both direct viral invasion and the host immune system response [96,97]. Delayed gadolinium enhancement of the myocardium on MRI is increasingly being used to evaluate children with suspected myocarditis, but endomyocardial biopsy or serum viral polymerase chain reaction studies are needed to identify the causative organism [96]. Outcomes for children are substantially better than in adults, with an overall mortality of 7.2% in one multi-institutional pediatric database [98]. Treatment depends on the severity of dysfunction. Acute management may include intravenous immunoglobulin, corticosteroids, inotropic agents, and even mechanical circulatory support as a bridge to recovery or transplantation (i.e. ECMO or ventricular assist device) [96]. Subacute and chronic management may also include diuretics, vasodilators, angiotensin-converting enzyme inhibitors, β-blockers, aldosterone antagonists, and aspirin. Functional echocardiographic recovery in children with myocarditis has been reported to be as high as 70%, with a cardiac transplantation requirement as high as 23% [99].

Cardiomyopathy

Pediatric cardiomyopathies are a group of diseases that affect the ventricular myocardium and is not due to abnormal loading conditions or CHD [100]. According to the International Society for Heart and Lung Transplant, cardiomyopathy is the most common cause of heart transplantation in children older than 1 year, with nearly 40% of children with a symptomatic cardiomyopathy either undergoing heart transplant or dying within 2 years [101]. The major cardiomyopathies encountered in childhood are dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy (RCM), LV noncompaction cardiomyopathy, and one with a mixed phenotype (Fig. 42.7). Pediatric cardiomyopathies are genetically heterogeneous with many different causative genes and multiple mutations in each gene [100]. Furthermore, environmental and infectious factors either causing or contributing to cardiomyopathy may be present, particularly in children with dilated cardiomyopathy where evidence of viral myocarditis is common [100].

The evaluation of a child with suspected cardiomyopathy may require an extensive work-up, including genetic and metabolic testing, due to the multifactorial etiology. Echocardiography and cardiac MRI can establish the diagnosis and provide risk stratification. Although treatment is disease specific based on the underlying pathophysiology, goals of therapy are the same: improving symptoms and reversing the ventricular remodeling process that is linked to the progressive heart failure that occurs [102]. These children can go on to require implantable cardioverter defibrillator, mechanical circulatory support, or cardiac transplantation.

Ventricular assist devices

The emergence of mechanical circulatory support (MCS) of the failing heart has helped advance the treatment of heart failure. MCS can be used in the short term (e.g. acute postsurgical cardiac failure or acute graft rejection) when the expected recovery is within days or weeks, or in the long term when the underlying disease state is unlikely to recover.

Options for MCS include ECMO, intra-aortic balloon pumps, and left ventricular assist devices (LVADs). ECMO provides short term cardiopulmonary support and can be emergently initiated via percutaneous insertion; however, the lack of mobility, higher risk of complications, and inability to provide prolonged support are limitations. Similar to ECMO, intra-aortic balloon pumps can quickly be inserted percutaneously, but are unable to provide long-term support. Furthermore, decreased familiarity among pediatric providers and the higher heart rates and incidence of arrhythmias interfering with coordinated inflation and deflation of the balloon frequently preclude the use of intra-aortic balloon pumps in children [103]. LVADs can be used both for short- and

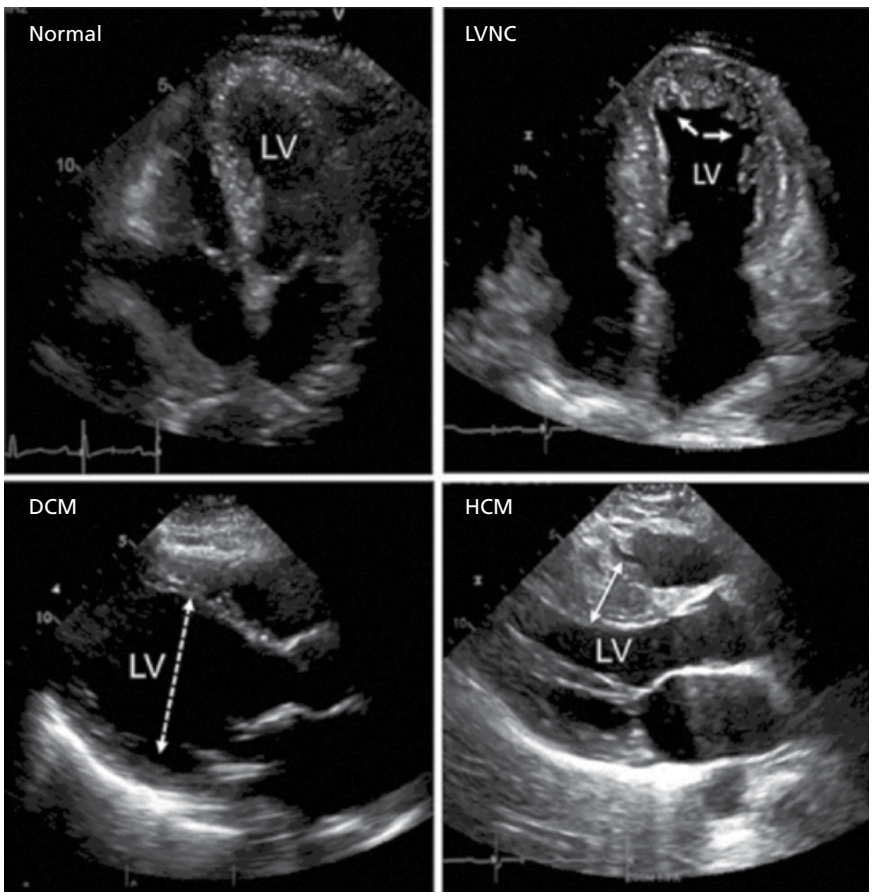


Figure 42.7 Echocardiography of the three more common forms of cardiomyopathy. Left ventricular non-compaction (LVNC) is shown in the upper right (arrows indicate deep trabeculations in the left ventricle (LV)). Dilated cardiomyopathy (DCM) is defined by enlarged LV diameters (dashed double-sided arrow). Hypertrophic cardiomyopathy (HCM) is defined with a thickened LV, including the septum (marked with double-sided arrow). *Source:* Reproduced from McNally and Mestroni [336] with permission of Wolters Kluwer.

long-term therapy, have a lower risk of infection and inflammatory response, allow for early extubation, facilitate mobility and rehabilitation, and allow for hospital discharge [104]. Subsequently, the use of LVADs has become common in bridging to cardiac transplant for patients with advanced heart failure not responding to medical therapy.

LVADs work by decompressing the failing LV and pumping blood into the systemic circulation to restore end-organ function. The first LVADs developed mimicked the pulsatile flow of the native heart; however, they have been largely replaced by continuous flow devices that are smaller, more durable, and almost completely internalized [104]. Infants and children with BSA <0.7 m^2 are still supported with pulsatile ventricular assist devices. Pulsatile LVADs preserve arterial pulses because a predetermined volume is ejected into the arterial circulation with each discharge. The Berlin Heart EXCOR® (Berlin Heart AG) ventricular assist device consists of a pneumatically operated diaphragm using a large external compressor (Fig. 42.8). The large external system precludes discharge from the hospital, and its higher incidence of side-effects have given way to the use of continuous flow devices when able.

The most common continuous flow LVADs available in the United States are the HeartMate II™ axial flow LVAD (Abbott Laboratories) and the HeartWare™ centrifugal flow HVAD (Medtronic). The new HeartMate 3™ centrifugal flow LVAD (Abbott Laboratories) is currently available only to adults participating in clinical trials (Fig. 42.9) [105]. The HeartMate II

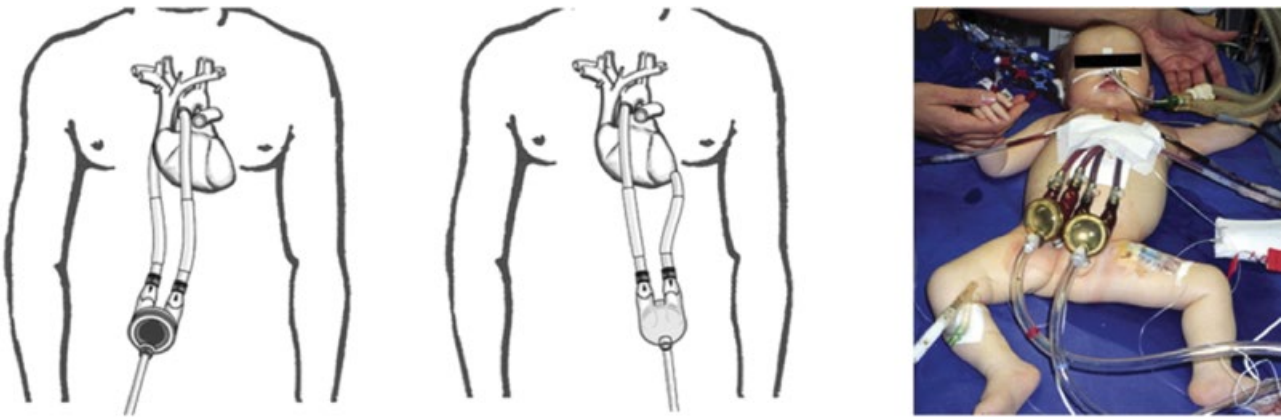


Figure 42.8 Implantation of a Berlin Heart EXCOR® Pediatric ventricular assist device in left (A, B) and biventricular (C) modes. This device is a paracorporeal, pneumatic, compressor-operated diaphragm pump. It can provide cardiac outputs of 0.4 to >5 L/min, depending on pump chamber size and pump rates. Pump chamber sizes are available in stroke volumes of 10–80 mL. The inflow cannula to the device is implanted either in the left atrium (A) or the apex of the left ventricle (B). Left apical implantation is preferred because it provides better unloading of the left ventricle. (C) Implantation is also possible for biventricular support. *Source:* Reproduced from Hetzer et al [337] with permission of Elsevier.

Figure 42.9 Continuous flow LVADs currently available in the United States. (A) The HeartMate II™ system has an axial flow pump design with the pump residing within the intraperitoneal space. (B, C) The HeartWare™ and HeartMate 3™ systems have a centrifugal pump design with the pump residing within the pericardial space. All devices can provide up to 10 L/min of flow. *Source:* Courtesy of Thoratec and Medtronic websites.

can be used in children >45 kg or with a BSA >1.3 m^2; its use has been supplanted by the smaller HeartWare HVAD system which can be used for patients with BSA >0.7 m^2. Constant drainage of the LV by continuous flow LVADs can result in a dampened arterial pulse or eliminate it altogether. Contractility of the LV with aortic valve opening are required to generate a palpable pulse. To measure blood pressure, a Doppler ultrasound is placed over the brachial artery and an upper extremity blood pressure cuff is slowly deflated. The first audible sound heard is the mean arterial pressure (MAP). Alternatively, an intra-arterial catheter can be used to continuously monitor the MAP, and it is preferred when major intravascular fluid shifts or volume loss are anticipated (e.g. major surgical cases). Effective blood pressure control and intravascular volume allows for optimal LVAD performance. LVADs, especially continuous flow LVADs, are "preload dependent" and "afterload sensitive." Unobstructed flow into the LVAD inflow cannula within the LV is dependent on adequate ventricular filling (preload). LVAD outflow into the aorta is affected by afterload. In situations with high afterload (high blood pressure), the LVAD will perform a greater amount of work to meet systemic needs. This higher work may require higher LVAD speed and produces higher power (watts), which can lead to greater fluid requirements and increased RBC hemolysis. This in turn can increase strain on the right heart.

Patients with LVADs require anticoagulation and antiplatelet therapy to prevent thrombosis within the device and decreased risk for arterial embolic stroke. As a result, bleeding is the most frequent adverse event in adults with LVADs and accounts for 9% of the total mortality associated with LVADs [106]. It is not uncommon to have gastrointestinal bleeding from the development of AV malformations with friable vessels that are prone to bleeding [107]. Therefore, management requires a thoughtful approach to making adjustments to anticoagulation and antiplatelet therapy. The right balance between the risk of bleeding and thrombosis needs to be found for each individual, especially if invasive procedures are required. Chapters 27 and 28 present additional information about congenital and acquired heart disease.

KEY POINTS: CONGENITAL HEART DISEASE, MEDICAL CARDIAC DISEASE, AND VENTRICULAR ASSIST DEVICES

- Routine early surgery on neonates with CHD and an understanding of the effects of cardiopulmonary bypass on cardiac, respiratory, and neurological systems are cornerstones of cardiac surgery care in the ICU
- Heart failure from myocarditis and cardiomyopathy are common; aggressive treatment to provide diuresis, hemodynamic and respiratory support, and increase oxygen delivery are essential to prevent multiorgan failure and cardiac arrest
- ECMO and ventricular assist device support are increasingly used in heart failure and should be applied early before cardiac arrest or severe deterioration

Respiratory disease

Respiratory monitoring

Clinical examination of the critically ill child remains the cornerstone of respiratory assessment and monitoring, and should include visual inspection (e.g. skin color and perfusion, respiratory rate and pattern, nasal flaring, retractions, use of accessory muscles) and auscultation to evaluate the presence of abnormal respiratory sounds (e.g. stridor wheezing, rales, rhonchi). A child in impending respiratory arrest may display respiratory pauses, cyanosis or pallor, bradycardia, and a decreased level of consciousness associated with severe hypoxemia and/or hypercarbia.

The respiratory rate of PICU patients is continuously monitored using impedance pneumography. The percent oxygen saturation of arterial hemoglobin (SpO_2) is also continuously monitored using pulse oximetry. Modern pulse oximetry has become more reliable than in the past with devices that protect against artifacts due to external light sources (e.g. surgical lights) or motion. Pulse oximetry provides inaccurate readings in states of low cardiac output, increased venous pulsations, presence of fetal hemoglobin, carboxyhemoglobin (e.g. smoke inhalation), methemoglobin (e.g. during therapy with inhaled nitric oxide), or during treatment with methylene blue. Pulse oximetry also loses accuracy once saturations drop below 60%. Pulse oximetry is primarily utilized for the detection of hypoxemia, which is generally defined as SpO_2 <90% or a decline of >10% below baseline SpO_2. Pulse oximetry is also used to help guide FiO_2 delivery and thus minimize blood draws for repeated blood gases. The FiO_2 delivered varies by type of non-invasive delivery method (Table 42.3).

Non-invasive monitoring of ventilation in the critically ill child is conducted with capnography and transcutaneous CO_2 monitoring devices. Capnography has become routine in the modern PICU. It measures and graphically displays changes in CO_2 concentrations during the respiratory cycle as a function of time. Practitioners are familiar primarily with $ETCO_2$ monitoring or time-based capnography. In addition to $ETCO_2$ monitoring, volume-based capnography can be used to measure anatomic dead space and pulmonary capillary perfusion. $ETCO_2$ represents the partial pressure of CO_2 at the end of expiration and is normally <5 mmHg lower than $PaCO_2$ in healthy children. This difference increases in states of decreased cardiac output, right-to-left intracardiac shunting, pulmonary vascular abnormalities, and pulmonary overdistention leading to increased dead space. Volume-based capnography allows for measurement of alveolar minute ventilation and the

Table 42.3 Oxygen delivery by non-invasive means

Device	FiO_2	Flow
Nasal cannula	Up to 40%	<5 L/min
Simple facemask	Up to 60%	6–10 L/min
High-flow humidified nasal cannula	Close to 100%	1–30 L/min
Non-rebreather mask with reservoir	Close to 100%	6–15 L/min
CPAP or BiPAP therapy	100%	As needed to deliver pressure

BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure.

ratio of relative dead space (Vd) to tidal volume (Vt): Vd/Vt = ($PaCO_2$ – ECO_2)/$PaCO_2$; where ECO_2 is the mean expired CO_2.

Capnography can be initiated in the non-intubated, spontaneously breathing child, using sidestream monitoring devices via a nasal cannula. In mechanically ventilated patients, $ETCO_2$ monitoring is conducted with sidestream, or, more commonly, low-volume mainstream monitoring devices. The capnography waveform presence and shape, and $ETCO_2$ value, provide valuable information in a variety of clinical scenarios: confirmation of endotracheal tube placement, prompt alert for ventilator malfunction or disconnected circuits, information on respiratory rate and pattern, dead space estimates, variations in cardiac output, and presence of obstructive airway disease.

Mechanical causes for a sudden drop or absent $ETCO_2$ include a displaced or obstructed endotracheal tube, or a dysfunctional ventilator or ventilator circuit that is disconnected or defective (e.g. leaking). Pathological causes for decreasing $ETCO_2$ include hyperventilation, decreased cardiac output, or decreased pulmonary capillary blood flow due to pulmonary artery embolism or pulmonary hypertension. A high $ETCO_2$ indicates hypoventilation, improved cardiac output, or increased pulmonary capillary blood flow.

Transcutaneous CO_2 monitoring is used primarily in neonatal ages in an effort to decrease repeated blood sampling [108], and tends to lose accuracy at older ages. In the PICU, transcutaneous CO_2 monitoring is used to observe trends in patients where capnography cannot be used (e.g. high-frequency oscillatory ventilation, non-invasive positive pressure ventilation without ability to use sidestream $ETCO_2$).

Esophageal manometry is used to measure changes in pleural or transpulmonary pressures during the respiratory cycle. Esophageal pressure monitoring can complement extubation readiness tests, but has limitations related to its invasive nature (i.e. placement of a balloon catheter into the lower third of the esophagus) and artifacts, as well as inadequate accuracy of measurements in the pediatric age [109,110].

Continuous monitoring and display of airway graphics is a routine feature of modern mechanical ventilators. Besides measures of Vt, gas flow, and airway pressures, displays of flow–volume, pressure–volume, flow–time, pressure–time and volume–time loops guide clinicians in selecting the optimal amount of support for each individual patient, with the goal of minimizing the work of breathing and optimizing patient–ventilator synchrony. Normal values for measurements of respiratory mechanics are presented in Table 42.4. See Chapter 19 for additional discussion of respiratory monitoring.

Finally, imaging is an important component of respiratory monitoring, with the chest radiograph the mainstay of assessment, often performed daily for intubated PICU patients, or whenever a major change or event occurs. Recently, point of care ultrasound (POCUS) of the lungs and airway has been increasingly used at the bedside, and can be used to quickly determine causes of respiratory deterioration, including lung consolidation, pneumonia, pneumothorax, pleural effusion, pulmonary edema, and endotracheal tube position [111]. As more intensivists are trained in POCUS techniques they are likely to see more daily use, and may even potentially replace the chest radiograph in some settings [112,113]. See Chapter 19 for further discussion of POCUS.

Table 42.4 Respiratory mechanics

	Infant	Adult
Respiratory frequency (breaths/min)	30–40	12–16
Inspiratory time (s)	0.4–0.5	1.2–1.4
I:E ratio	1:1.5–1:2	1:2–1:3
Inspiratory flow (L/min)	2–3	24
Tidal volume		
mL	18–24	500
mL/kg	6–8	6–8
Functional residual capacity (FRC)		
mL	100	2200
mL/kg	30	34
Vital capacity		
mL	120	3500
mL/kg	33–40	52
Total lung capacity		
mL	200	6000
mL/kg	63	86
Total respiratory compliance		
mL/cmH_2O	2.6–4.9	100
mL/cmH_2O/mL FRC	0.04–0.06	0.04–0.07
Lung compliance		
mL/cmH_2O	4.8–6.2	170–200
mL/cmH_2O/mL FRC	0.04–0.07	0.04–0.07
Specific airway conductance (mL/s/cmH_2O/mL FRC)	0.24	0.28
Respiratory insensible water loss (mL/24 h)	45–55	300

Status asthmaticus

Epidemiology

Asthma is an important public health problem around the world. In the USA, the prevalence of asthma has been estimated at 8.4% in children aged 0–17 years, and this has increased over time [114,115]. Asthma is the leading cause of chronic illness in children, with exacerbations resulting in emergency department asthma visit rates of 10.7 and asthma hospitalization rates of 2.1 per 100 children with asthma [115]. Asthma death rates are estimated at 0.03 per 1000 children with asthma [115]. Risk factors for mortality include a history of prior PICU admission or respiratory arrest requiring intubation.

Pathophysiology

Asthma is a multifactorial disease with polygenetic and environmental influences. It is a chronic inflammatory disorder characterized by bronchoconstriction, airway hyper-responsiveness, and airway edema, with hypersecretion of mucus and mucus plugging [116]. In time, patients with asthma develop remodeling of the airways, with sub-basement fibrosis, injury to epithelial cells, smooth muscle hypertrophy, and angiogenesis [116]. Typical asthma symptoms include cough, wheezing, chest tightness, and breathlessness [116]. Status asthmaticus presents with exacerbation of these symptoms and respiratory distress that can vary in intensity. Common triggers for status asthmaticus are exposure to allergens and viral infections. Severe airway obstruction leads to air trapping with increased dead space, reflected in flattening of the diaphragm on chest imaging. A prolonged expiratory phase ensues, due to active, rather than passive, expiration against increased airway resistance.

Hypoxia develops early during status asthmaticus due to ventilation/perfusion mismatch. The initial compensatory tachypnea is manifested by hypocarbia on blood gases. In time, patients develop respiratory muscle fatigue leading to hypercarbia and respiratory failure if unaddressed.

Hemodynamics can be affected during status asthmaticus by several factors. Lung hyperinflation leads to stretching of the pulmonary vasculature, increased pulmonary vascular resistance, and subsequent right ventricular strain. In addition, large fluctuations in intrathoracic pressure lead to increased left ventricular afterload and decreased venous return to the right atrium, with development of pulsus paradoxus, an exaggerated decline in systolic blood pressure during inspiration that can be diagnosed by pulse palpation or examination of pulse oximetry or arterial waveform tracings.

Therapy

Children presenting with status asthmaticus require immediate medical attention to avoid respiratory failure and arrest. Hypoxia is addressed with supplemental oxygen via a nasal cannula or facemask. Inhaled bronchodilators and systemic corticosteroids should be initiated early. Patients who do not show signs of improvement should be considered candidates for transfer to the PICU for advanced therapies, including additional inhalational bronchodilators, systemic bronchodilators, heliox, non-invasive and invasive ventilation, inhaled anesthetics, and ECMO. Table 42.5 summarizes the dose, physiological action, potential benefits, and adverse events and risks for therapies used for status asthmaticus [117].

Presentation of a child with wheezing, cough, and respiratory distress does not equate to asthma exacerbation. The differential diagnosis of a first time episode of wheezing includes new-onset asthma, as well as foreign body aspiration, congestive heart failure, and pneumonia. However, in severe status asthmaticus, diagnostic testing should not delay initiation of therapy and/or transfer to the PICU. When time allows, an arterial or venous blood gas to determine the degree of gas exchange abnormalities, complete cell blood count to evaluate for infection, basic metabolic panel and lactate to evaluate for electrolyte abnormalities, degree of dehydration, and anaerobic metabolism, and a chest radiograph should be obtained. In most instances, chest radiographs in children with status asthmaticus will reveal hyperinflation. A chest radiograph should be obtained in all severe cases to rule out other diagnoses as noted above and diagnose complications related to status asthmaticus (e.g. pneumothorax). See Chapter 7 for further discussion of the etiology, pathophysiology, and treatment of asthma.

Pediatric acute respiratory distress syndrome

Consensus definition

Differences in pathophysiology, co-morbidities, clinical practice, and outcomes of acute respiratory distress syndrome (ARDS) in children compared with adults [118,119] have motivated the development of a pediatric-specific ARDS definition, published in 2015 following the conclusion of the Pediatric Acute Lung Injury Consensus Conference (PALICC) (Table 42.6) [120]. A definition for children at risk for pediatric ARDS was also developed to raise the alert for patients at risk for respiratory deterioration (Table 42.7) [121]. The PALICC definition of ARDS accounts for the increasing utilization of non-invasive mechanical ventilation in children, for the decrease in invasive monitoring (including arterial catheters) in children, and for special pediatric populations cared for in the ICU (i.e. cyanotic heart disease, chronic lung disease, left ventricular dysfunction) [121]. Pediatric ARDS is the development of respiratory failure not fully explained by cardiac failure or fluid overload, within 7 days of a known clinical insult, associated with chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease, and hypoxia requiring non-invasive or invasive mechanical ventilation [121]. Hypoxia is defined using the oxygenation index for ventilated patients (OI = mean airway pressure divided by the PaO_2/FiO_2 ratio) as mild (OI 4 to <8), moderate (OI 8 to <16), and severe (OI ≥16), and as PaO_2/FiO_2 ≤300 or SpO_2/FiO_2 ≤264 while on full facemask bi-level ventilation or continuous positive airway pressure (CPAP) ≥5 cmH_2O [121]. While pediatric ARDS does not have age limits, it excludes patients with perinatal-related lung disease [121].

Pathophysiology

ARDS is characterized by the loss of the epithelial and endothelial permeability barrier integrity and the presence of protein-rich edema fluid in the alveoli, immune activation and severe inflammation, activation of coagulation with suppression of fibrinolysis, and surfactant depletion and degradation – a combination of pathophysiological processes that lead to injury of the lung epithelium and vascular endothelium [119]. The clinical consequences of these pathophysiological changes are hypoxemia, decreased functional residual capacity, increased physiological deadspace, decreased lung compliance, and radiographic opacities [119]. Resolution of ARDS starts early in the ARDS course, and entails resolution of the inflammatory process, repair of the lung epithelium and endothelium, and fluid removal [119].

Therapy

Treatment recommendations for pediatric ARDS were published by PALICC in 2015 [120], along with supporting arguments [122–126]. The goals of pediatric ARDS management in the PICU are to support oxygenation, ventilation, and work of breathing while minimizing barotrauma, atelectrauma, and volutrauma, to treat the underlying cause, and to provide general ICU supportive care while minimizing complications. Pediatric ARDS is treated with multimodal therapies including non-invasive support and ventilation using high-flow nasal cannula, CPAP, or bi-level positive airway pressure (BiPAP), and mechanical ventilatory support. Pulmonary pharmacological therapies such as inhaled nitric oxide (iNO), exogenous surfactant, or anti-inflamatory agents (e.g. corticosteroids) are not recommended for routine use in pediatric ARDS [120]. iNO use may be considered in cases of severe pediatric ARDS or documented pulmonary hypertension or severe right heart dysfunction [120]. Other pulmonary ancillary therapies include cautious suctioning to minimize the risk of derecruitment, and prone positioning attempting to improve oxygenation in severe pediatric ARDS [120]. Non-pulmonary therapies include: (1) provision of minimal yet effective sedation to facilitate tolerance of mechanical ventilation, to optimize oxygen delivery and

Table 42.5 Adjunct therapies for status asthmaticus

Therapy	Suggested dose	Physiological action	Potential benefits	Adverse effects and risks	Risk potential (frequency)
Ipratropium	250 μg every 6 h	Bronchodilation and decreased mucous production	Prevents hospital admissions when given early in emergency department setting; no clear benefit to continuing after admission to hospital	No reported adverse events	Mild (rare)
B-agonists (intravenous)	Terbutaline intravenously: 10 μg/kg bolus, then 0.2 μg/kg/min; may titrate 0.2–1 μg/kg/min	Bronchodilation/smooth muscle relaxation via β-receptors	Intravenous route may improve delivery to distal airways; no clear additive benefit to inhaled β-agonists	Tachycardia, dysrhythmias, diastolic hypotension	Moderate (common)
Methylxanthines	Aminophylline intravenously: 6 mg/kg bolus, then 1 mg/kg/h; titrate to goal serum level 5–15 μg/mL	Bronchodilation/smooth muscle relaxation; phosphodiesterase inhibitor	Similar effectiveness of intravenous β-agonists; no reduction in ICU or hospital length of stay	Tachycardia, nausea	Moderate (common)
Magnesium (intravenous)	25–75 mg/kg intravenous bolus (maximum 2.5 mg)	Bronchodilation/smooth muscle relaxation by altering calcium flow into sarcoplasmic reticulum	Prevents hospital admissions when given early in emergency department setting	Malaise, nausea	Mild (rare)
Magnesium (nebulized)	150 mg of inhaled insulin (2.5 mL of 250 mmol/L solution)		May improve lung function in patients with severe asthma when added to inhaled β-agonist; probably not additive or superior to intravenous magnesium	No reported adverse events	Mild (rare)
Antibiotics	Azithromycin 10 mg/kg every 24 h per oral or intravenously	Treatment of concomitant bacterial infections; anti-inflammatory effect of macrolides	Potential improvements in lung function with chronic use of macrolides but no clear benefit to routine antibiotic administration during asthma exacerbations	No reported adverse events	Mild (rare)
Ketamine	1 mg/kg bolus followed by 0.75 mg/kg/h intravenous infusion	Bronchodilation through catecholamine release in peripheral nervous system	Immediate decrease in airway resistance and improved lung function; no data on patient outcomes	Tachycardia, bronchorrhea, hallucinations, laryngospasm	Moderate (common) to severe (rare)
Heliox	Goal ≥50% inhaled helium (i.e. FiO_2 <50%)	Promotes laminar flow by reducing gas density	Immediate decreases in work of breathing and $PaCO_2$	No reported adverse events	Mild (rare)
Non-invasive ventilation (NIV)	N/A	Positive pressure supports respiratory muscles and may stent open small airways; HFNC may assist with CO_2 wash-out	NIV leads to decreases in work of breathing and improvements in oxygenation; no data regarding other outcomes or benefits with HFNC	Intolerance of mask interface, air leak syndrome	Mild (rare)
Inhaled anesthetics	Sevoflurane: 0.5–3% concentration in inhaled gas	Bronchodilation/smooth muscle relaxation	Immediate decreases in $PaCO_2$ and airway resistance	Hypotension, apnea, malignant hyperthermia	Moderate (common) to severe (rare)
Extracorporeal membrane oxygenation	N/A	Gas exchange through artificial membrane	Allows surrogate oxygenation and ventilation while reducing mechanical ventilatory support	Bleeding, stroke, vessel injury, mechanical failure	Moderate (common) to severe (rare)

ICU, intensive care unit; HFNC, high-flow nasal cannula.
Source: Reproduced from Rehder [117] with permission of Daedalus Enterprises Inc.

Table 42.6 Pediatric acute respiratory distress syndrome (PARDS) definition

Age	Exclude patients with perinatal related lung disease			
Timing	Within 7 days of known clinical insult			
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload			
Chest Imaging	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease			
Oxygenation	**Non-invasive mechanical ventilation**	**Invasive mechanical ventilation**		
	PARDS (No severity stratification)	Mild	Moderate	Severe
	Full facemask bi-level ventilation or CPAP ≥5 cm H_2O†	4 ≤ OI < 8	8 ≤ OI < 16	OI ≥ 16
	PF ratio ≤ 300	5 ≤ OSI < 7.5*	7.5 ≤ OSI < 12.3*	OSI ≥ 12.3*
	SF ration ≤ 264*			
	Special Populations			
Cyanotic Heart Disease	Standard Criteria above for age, timing, origin of edema and chest imaging with an acute deterioration in oxygenation not explained by underlying cardiac disease.‡			
Chronic Lung Disease	Standard Criteria above for age, timing, and origin of edema with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline which meet oxygenation criteria above.‡			
Left Ventricular dysfunction	Standard Criteria for age, timing and origin of edema with chest imaging changes consistent with new infiltrate and acute deterioration in oxygenation which meet criteria above not explained by left ventricular dysfunction.			

* Use PaO_2-based metric when available. If PaO_2 is not available, wean FiO_2 to maintain SpO_2 (2 × [mean airway pressure × 100]/SpO_2) or SpO_2:FiO_2 (SF) ratio.
† For non-intubated patients treated with supplemental oxygen or nasal modes of non-invasive ventilation, see Table 41.7 for "at-risk" criteria.
‡ ARDS severity groups stratified by OI (FiO_2 × mean airway pressure × 100]/PaO_2) or OSI should not be applied to children with chronic lung disease who normally receive invasive mechanical ventilation or children with cyanotic congenital heart disease.
CPAP, continuous positive airway pressure; OI, oxygenation index; OSI, oxygen saturation index.
Source: Reproduced from Khemani et al [121] with permission of Wolters Kluwer.

Table 42.7 At risk of pediatric acute respiratory distress syndrome (PARDS) definition

Age	Exclude patients with perinatal related lung disease		
Timing	Within 7 days of known clinical insult		
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload		
Chest Imaging	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease		
Oxygenation	**Non-invasive mechanical ventilation**		**Invasive mechanical Ventilation**
	Nasal mask CPAP or BiPAP	Oxygen via mask, nasal cannula or High Flow	Oxygen supplementation to maintain SpO_2 ≥ 88% but OI < 4 or OSI < 5*
	FiO_2 ≥ 40% to attain SpO_2 88-97%	SpO_2 88-97% with oxygen supplementation at minimum flow†: < 1 year: 2 L/min 1–5 years: 4 L/min 5–10 years: 6 L/min >10 years: 8 L/min	

* If PaO_2 is not available, wean FiO_2 to maintain SpO_2.
† Given lack of available data, for patients on an oxygen blender, flow for at-risk calculation = FiO_2 × flow rate (L/min) (e.g. 6 L/min flow at 0.35 FiO_2 = 2.1 L/min).
BiPAP, bi-level positive airway pressure; CPAP, continuous positive airway pressure; OI, oxygenation index; OSI, oxygen saturation index.
Source: Reproduced from Khemani et al [121] with permission of Wolters Kluwer.

consumption, and work of breathing; (2) addition of neuromuscular blockade when sedation is not adequate to achieve effective mechanical ventilation; (3) nutrition aimed at meeting metabolic needs, and to maintain growth and facilitate recovery; (4) goal-directed fluid management aimed at maintaining adequate intravascular volume while preventing positive fluid balance, end-organ perfusion, and optimal delivery of oxygen; and (5) transfusion at a threshold hemoglobin of 7 g/dL in clinically stable children with adequate oxygen delivery, excluding cyanotic heart disease, bleeding, and severe hypoxemia [120].

Outcomes

Mortality following pediatric ARDS has decreased over time, with current rates estimated between 21% and 45% [127,128]. Children requiring ICU-level care for ARDS are at risk for pulmonary function abnormalities after hospital discharge, representing both obstructive and restrictive disease [128]. Current recommendations include screening with respiratory symptom questionnaires and pulse oximetry, spirometry when developmentally appropriate, and referral to a pediatric pulmonologist for any patients with identified deficits in pulmonary function [120]. Pediatric ARDS follow-up should also include physical, neurocognitive, emotional, family, and social function evaluation within 3 months of hospital discharge, as well as prior to entering school, for young patients [128,129], with mounting evidence indicating long-term deficits in functional status, health-related quality of life, and risk for post-traumatic stress disorder in mechanically ventilated pediatric patients [130].

KEY POINTS: RESPIRATORY DISEASE

- Monitoring, including physical exam, capnography, flow–volume and pressure loops, chest radiography, and lung ultrasound are important assessment tools
- Severe status asthmaticus requires immediate transfer to the PICU for advanced therapy including inhaled and IV bronchodilators, non-invasive and invasive ventilation, heliox, inhaled anesthetics, and ECMO
- ARDS is the development of respiratory failure not fully explained by cardiac failure or fluid overload, and treatment is supportive with non-invasive and invasive ventilation, iNO, pulmonary toilet, nutrition, and hemodynamic support to maximize oxygen delivery

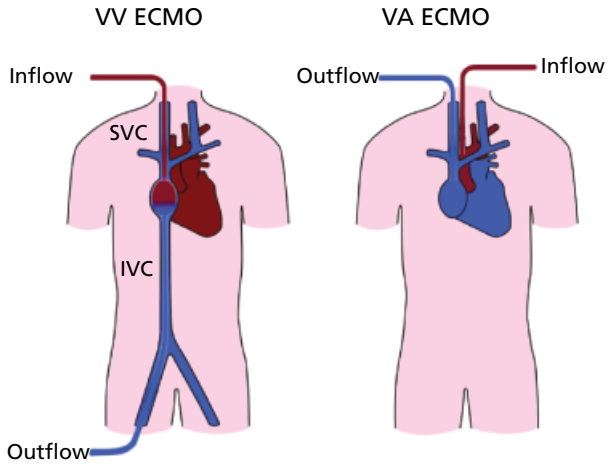


Figure 42.10 Venovenous (VV) and venoarterial (VA) extracorporeal membrane oxygenation (ECMO). IVC, inferior vena cava; SVC, superior vena cava. *Source:* Reproduced from Thiagarajan [338] with permission of Wolters Kluwer.

Extracorporeal life support

Modes of support and circuit configurations

Extracorporeal life support (ECLS) in children is primarily provided in the form of ECMO. ECMO is deployed in children with severe refractory cardiopulmonary failure or cardiac arrest who do not respond to conventional modes of therapy and support. It entails cannulation of one or more large vessels. The two most common circuit configurations are venovenous, with blood draining from and returning to the venous system, and venoarterial, with blood draining from the venous system and returning directly into the systemic arterial system. Venovenous ECMO is used primarily for respiratory failure, while venoarterial ECMO is used primarily for cardiac failure and extracorporeal cardiopulmonary resuscitation (ECPR). Venovenous ECMO operates in series with the heart and lungs, while venoarterial ECMO operates in parallel with the heart and lung, thus providing partial bypass of the two organs.

In infants, the vessels used for ECMO cannulation are the right internal jugular vein for venovenous ECMO support using a double-lumen cannula, or the right internal jugular vein and right common carotid artery for venoarterial ECMO support using two single-lumen cannulas. Older children and adolescents can be cannulated through the femoral vessels for both venovenous as well as venoarterial ECMO support. Children of all ages can be cannulated through a central approach (i.e. direct cannulation of the heart or major vessels) through a thoracic incision, typically a median sternotomy. Deoxygenated blood drains from the patient through a drainage cannula, to a plastic circuit, a pump, a membrane lung, and heat exchanger. Oxygenated blood is then returned to the patient, directly in the arterial circulation via the aorta or to the venous circulation where it is circulated through the lungs prior to reaching the systemic circulation (Fig. 42.10). An optional venous reservoir can be inserted between the drainage cannula and the pump to serve as a compliance chamber and to allow non-invasive pressure measurements.

Two types of pumps are used for ECLS: roller and centrifugal pumps (Fig. 42.11). Roller pumps are occlusive pumps that function by positively displacing blood as a function of

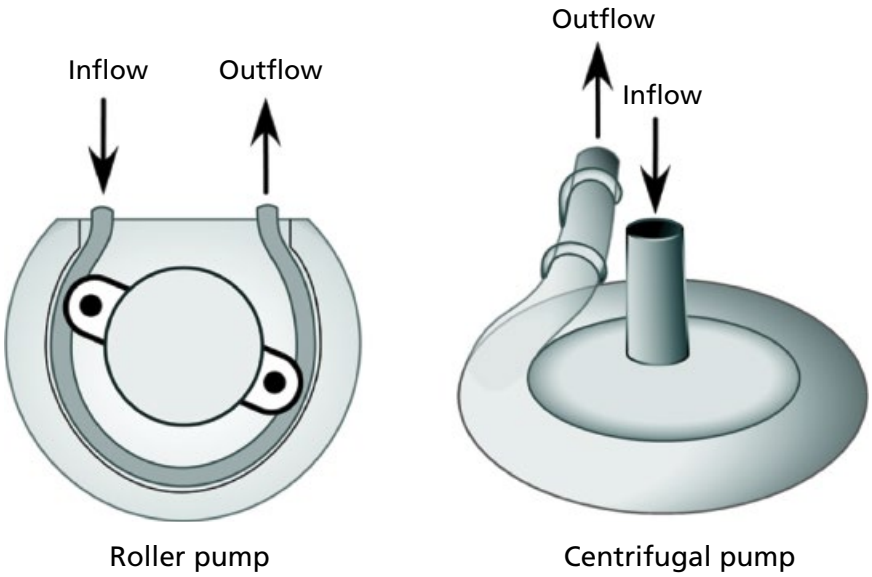


Figure 42.11 Roller and centrifugal pumps. *Source:* Reproduced from Thiagarajan [338] with permission of Wolters Kluwer.

pump speed. Centrifugal pumps are non-occlusive pumps that use an impeller assembly to produce a hydrodynamic gradient through rotational kinetic energy. Both types of pumps have been successfully used in children, although in recent years centrifugal pumps have been increasingly replacing roller pumps [131]. The Extracorporeal Life Support Organization reported that, from 2009 to 2015, centrifugal pumps were used in 55–60% of pediatric ECLS and neonatal cardiac and ECPR cases reported to the registry, while roller pumps were used in 54% of neonatal respiratory cases [131].

The membrane lung transfers O_2 and CO_2 by diffusion across a membrane between a blood phase and a gas phase. Most contemporary membrane lungs use hollow fibers, with extracapillary blood flow and intracapillary gas flow. The two most common membrane materials are polymethylpentene and polypropylene. The sweep gas is the gas applied to the gas phase of the membrane lung, typically a blend of O_2 and nitrogen, occasionally with added CO_2 or nitric oxide. The sweep gas inlet O_2 fraction (FsO_2) is controlled by a gas blender and ranges from 0.21 to 1.0.

The heat exchanger transfers heat between the blood phase and a water phase, separated fully by a heat exchanging material. The temperature of the blood returning to the patient can be fully controlled at a preset level. Modern membrane lungs may have integrated heat exchangers. A bridge is an optional tubing connection between the drainage and the reinfusion lines of the circuit, close to the patient. For venoarterial ECMO, clamping of the drainage and infusion limbs with opening of the bridge allows blood to circulate in the circuit while the patient undergoes a weaning trial. Access ports for medication and blood product administration, blood draws, and connections to renal replacement therapy (RRT) or plasmapheresis devices, can be added to ECMO circuits, and may be essential in small infants and children with inadequate vascular access. ECMO circuits are also equipped with safety devices, including bubble sensors placed on the reinfusion limb of the circuit to detect and avoid air embolization, and alarms for pressure changes. Pressure is usually monitored at the pump inlet and preoxygenator, and postoxygenator sites. An increasing pressure gradient between pre- versus postoxygenator sites usually indicates clot formation in the oxygenator. Lastly, contemporary ECMO circuits contain non-invasive devices for monitoring and display of blood flow rate, hemoglobin, hematocrit, PO_2, PCO_2, mixed venous saturation, etc., as well as surface coating or modification with materials that improve biocompatibility and reduce thrombogenesis [132].

General indications and contraindications

Indications for ECMO have evolved since the technique was first used in an intensive care unit in 1972 [133]. While initially ECMO was primarily used in the neonatal age primarily for respiratory indications, the last years have seen a plateau in neonatal ECMO utilization, accompanied by an increase in pediatric ECMO for primary respiratory, cardiac, and ECPR indications [131].

Respiratory indications for neonatal ECMO support include primary pulmonary hypertension of the newborn, meconium aspiration syndrome, congenital diaphragmatic hernia, and other, more rare, pulmonary diseases. Of these, congenital diaphragmatic hernia has the lowest survival to hospital discharge (50%), while meconium aspiration syndrome has the highest survival (93%) [131]. Respiratory indications for pediatric ECMO support are diverse and include ARDS, infections (e.g. bronchiolitis, pertussis, bacterial, viral, or fungal pneumonia), foreign body aspiration, and asthma. Venovenous ECMO as a bridge to lung transplantation has also been increasingly reported in the literature [134]. Overall survival in children with respiratory failure requiring ECMO support is 60% [131].

Cardiac indications for ECMO support include perioperative support and support for non-surgical conditions. Perioperative pediatric cardiac support may be required for preoperative stabilization (e.g. profound cyanosis, cardiogenic shock, or severe pulmonary hypertension), inability to wean patients from cardiopulmonary bypass, postoperative low cardiac output syndrome, and postoperative cardiac arrest. Non-surgical cardiac conditions that may require ECMO support include myocarditis and cardiomyopathy, pulmonary hypertension, arrhythmias with hemodynamic compromise (including from toxic ingestion), septic shock, cardiac trauma, and rejection of transplanted heart. Overall survival to hospital discharge is 45% following neonatal cardiac ECMO and 57% following pediatric cardiac ECMO [131].

ECPR represents rapid deployment of ECMO to support children with cardiac arrest failing to respond to conventional cardiopulmonary resuscitation. Specialized multidisciplinary teams and hospital-wide systems are required for the development and sustainability of an ECPR program. The overall survival following ECPR in neonates and children is 43% [131].

Contraindications for ECMO support have also evolved over time. General relative contraindications include prematurity <34 weeks' gestation, small size (<2 kg), poor prognosis of primary diagnosis, severe brain injury, uncontrolled hemorrhage, irreversible organ failure, and limitations in care [135]. Risks and benefits of ECMO support should be discussed with the patient's family in the context of each individual patient's disease and wishes.

Management of the neonatal and pediatric ECMO patient

The vascular site of cannulation and appropriate cannula selection based on expected size of the vessels and amount of flow needed are typically discussed by a multidisciplinary team prior to deployment of the ECMO team. In the pediatric age group, cannulation is typically performed by a general pediatric surgeon or a cardiac surgeon. A dose of 75–100 units/kg of unfractionated heparin is administered prior to cannula insertion. Correct cannula placement can be confirmed by x-ray, fluoroscopy, and/or echocardiography. The ECMO circuit can be primed with crystalloid (typically for children >20 kg) or blood, especially in infants and young children at risk for hemodilution. Adequate critical care personnel, equipment, and medications should be available at the bedside for ongoing support of the critically ill child undergoing ECMO cannulation, including the ability to perform exquisite cardiopulmonary resuscitation should the need arise.

Neurological monitoring. Neurological injury is frequent in children supported on ECMO due to risk factors associated with their critical illness as well as ECMO-related risk factors. Neurological injury in the form of intracranial hemorrhage, thromboembolic stroke, or anoxic brain injury has been described in up to one-third of pediatric ECMO patients [131,136,137]. Ideally, sedation and the use of neuromuscular blockade should be minimized in ECMO patients. When unsafe to do so (e.g. in severe pulmonary hypertensive crises), neurological monitoring is typically conducted using modalities such as cerebral oximetry, electroencephalography, and serial transfontanellar cranial ultrasounds [138].

Respiratory support. The goals of respiratory support during ECMO are to avoid atelectasis while limiting ventilator-induced lung injury, to mobilize secretions, and the resolution of pulmonary edema. When possible, sedation is decreased or interrupted to allow for spontaneous ventilation with pressure support, or extubation. Otherwise, mechanical ventilation is usually via pressure control ventilation with a positive end-expiratory pressure of ~10 cmH_2O, a rate of 10 breaths/min, and a peak inspiratory pressure of 18–20 cmH_2O [135].

Cardiovascular support. Cardiovascular support during venovenous ECMO is provided according to standard ICU practice, as the patient's cardiac output is fully dependent on native cardiac function. Following venovenous ECMO support, improved oxygenation through the circuit's membrane lung, decreased right ventricular strain, and decreased intrathoracic pressure due to ability to decrease ventilatory support and thus mean airway pressure all have a favorable impact on the patient's hemodynamics. If needed, vasoactive infusions can and should be used during venovenous ECMO. In patients on venoarterial ECMO support, total cardiac output is the sum of the native cardiac output and the extracorporeal flow [135]. Usually, vasoactive infusions required immediately prior to venoarterial ECMO initiation can be quickly decreased and/or discontinued once ECMO flow is established. Vasopressors may need to be maintained during the ECMO course in patients with vasoplegia (e.g. septic shock, toxic ingestions).

Renal supportive therapy. Sixty to 74% of children on ECMO meet criteria for acute kidney injury (AKI) at the time of ECMO initiation, with 86–93% of patients meeting the criteria for AKI by 48 h on ECMO [139]. Diuretics and RRT in the form of continuous venovenous hemofiltration or hemodialysis are frequently used in ECMO patients. While fluid overload has been shown to be associated with unfavorable outcomes in ECMO patients [140] and should be avoided, controversy remains regarding the optimal timing of RRT initiation and rate of fluid removal during ECMO.

Nutrition. Children on ECMO are usually managed following nutrition recommendations for other critically ill children. Early introduction of enteral nutrition can be beneficial, with no evidence that it is associated with adverse events [141,142].

Infection surveillance. The prevalence of hospital-acquired infections in ECMO patients is 10–12% [143,144]. Temperature is controlled through the circuit's heat exchanger, therefore the ECMO team relies on other signs and symptoms of infection and laboratory data suggesting a new infection. There are no data to support routine blood prelevation for culture or the use of prophylactic antibiotics during the ECMO course, although both have been reported as relatively common practices [145].

Anticoagulation and blood product administration. Exposure of blood to the artificial ECMO circuit is accompanied by a systemic inflammatory response with capillary leak, multiple organ dysfunction, and activation of the coagulation pathway and cellular blood elements (leukocytes, platelets) [132]. The result is a hypercoagulable state in the circuit that requires initiation of anticoagulation therapy, with a precarious balance of maintaining circuit patency, avoiding thrombus formation in the circuit and thus risk for embolization, while at the same time avoiding hemorrhage in the anticoagulated patient [132]. Although newer generations of ECMO circuits, pumps, and oxygenators are more biocompatible and less thrombogenic, thrombosis and bleeding remain important complications during ECMO [131,146] and require close monitoring and management of anticoagulation. Typically, unfractionated heparin infusion is initiated upon ECMO cannulation, at rates ranging from 10 to 40 units/kg/h. Activated clotting time remains the main point-of-care test for anticoagulation monitoring during pediatric ECMO, with general goals of 180 to 220 s. Other tests of coagulation, including antifactor Xa, activated partial thromboplastin time, prothrombin time, INR, antithrombin III, thromboelastography, or rotational thromboelastometry are used at different frequencies and combinations by most ECMO programs [147]. Antithrombin administration in the form of pooled plasma antithrombin or recombinant antithrombin has become common practice in many ECMO centers, but data on pharmacokinetics, pharmacodynamics, and safety are still subject to controversy and will require further study [148–151].

ECMO patients receive large amounts of blood products required in face of bleeding, disseminated intravascular coagulation, or hemolytic anemia and thrombocytopenia secondary to shear injury. It is estimated that children on ECMO receive as much as 40–105 mL RBCs/kg/day [152,153]. Generally, ECMO centers use a hemoglobin goal of 10 g/dL in an effort to optimize oxygen delivery. Platelet count goals vary based on risk of bleeding and underlying pathology, but generally range between 50,000 and 100,000 cells/mm^3 [147]. Plasma and cryoprecipitate are administered for goal fibrinogen concentrations of 100 or 150 mg/dL prior to surgical procedures. Administration of activated factor VII may be required in cases of severe intractable hemorrhage [154,155].

Procedures on ECMO

The heparin infusion rate is usually decreased in anticipation of on-ECMO procedures such as chest tube placement, vascular catheter placement, or complex surgery (e.g. congenital diaphragmatic hernia repair). If the patient is supported on a circuit with antithrombotic surface modification, the heparin infusion can also be discontinued temporarily, with close and frequent inspection to monitor for clot formation and/or coagulopathy. Antifibrinolytic agents (e.g. Ɛ-aminocaproic acid, tranexamic acid) may be required, as well as administration of platelets, plasma, or cryoprecipitate to optimize platelet count and fibrinogen prior to the procedure.

Weaning from ECMO

Signs of improvement in respiratory and cardiac function should be assessed daily during the ECMO course. Improved oxygenation and ventilation and indicators of improved

cardiac function (e.g. increasing pulse pressure, $ETCO_2$, mixed venous saturations) are indicators for respiratory and cardiac recovery. Weaning from venovenous ECMO entails decreasing FsO_2 (sweep gas inlet oxygen fraction) and eventually interrupting gas flow through the oxygenator. Weaning from venoarterial ECMO in neonates and children usually entails gradual decrease in extracorporeal flow, along with optimization of ventilatory support, and the addition of inodilators, inotropes, or pulmonary vasodilators, as needed. A weaning trial is then performed by discontinuing flow from and to the patient by clamping the drainage and return limbs of the circuit close to the cannulas and opening the bridge to maintain flow through the circuit. The amount of hemodynamic support that the patient may still require off ECMO is assessed clinically and using echocardiography data. After a period of ~30 min, a decision can be made on whether the patient can be safely decannulated or if continued extracorporeal support is needed.

KEY POINTS: EXTRACORPOREAL LIFE SUPPORT

- ECMO can be venoarterial for severe cardiac with or without respiratory failure, or venovenous for primary respiratory failure without severe cardiac failure
- Respiratory indications for ECMO include ARDS, infections, sepsis, asthma, and as a bridge to lung transplant
- Cardiac indications for ECMO include postcardiac surgery, myocarditis, cardiomyopathy, pulmonary hypertension, and arrhythmias

Neurological diseases

Neurological examination

The purpose of the neurological examination is to assess and monitor the integrity of the central and peripheral nervous systems. This can be challenging in an infant who, developmentally, may not be able to speak or follow basic commands at baseline. A thorough history that chronologically identifies the onset and setting of symptoms including frequency, duration, and effects on the child is essential to an accurate diagnosis. Typically, the history is given by a parent, guardian, or caretaker who has the child's best interests in mind, but in the case of abusive head trauma, the individual may also be the child's assailant. It is essential to determine if a child is developmentally appropriate by asking about prematurity, prior illnesses, accidents, surgeries, hospitalizations, medications, parental consanguinity, and how their performance is in daycare or school when compared to their peers as part of the neurological exam [156]. Most developmentally normal children 4 years and older can accurately contribute to their medical history [157].

It is important to ask questions about whether, and to what extent, the neurological disorder has impacted cognition, behavior, and language, and the degree to which daily living activities have been compromised. A skilled clinician develops a focused differential diagnosis during history taking and uses the physical examination to further narrow and confirm the exact diagnosis and determine the extent of impairment. Given the critical instability of children in the PICU, the neurological exam is often limited by sedative agents, neuromuscular blockade, severity of illness, or recent trauma. Upon admission to the PICU, all children will have a neurological exam, and those with new neurological deficits or altered mental status will most likely have the neurological exam repeated every 1–3 h. At minimum, all children should be evaluated for their level of consciousness, comfort, cranial nerve function including pupillary light reflex, respiratory effort, motor function, sensory function, tone, and reflexes.

Assessing consciousness

When infants and children have severely altered level of consciousness, the GCS is used to establish and trend their level of consciousness. Developed over 40 years ago, the GCS is an easily reproducible scale that allows multiple caregivers to consistently assess and monitor the level of consciousness over a period of time [158]. The GCS, now a core part of most traumatic brain injury (TBI) clinical guidelines, influences initial decision making, surgical management, and alerts intensivists to the neurologically deteriorating patient in their unit. New research from the large multicenter Approaches and Decisions in Acute Pediatric TBI (ADAPT) trial suggests that early GCS scores are strongly associated with mortality in pediatric TBI patients [159,160]. The same GCS developed for adults is used for children; however, a modified scale is used for infants who are developmentally unable to speak (Table 42.8). Both the adult and pediatric GCS overall scores range from 3 to 15 and are calculated from the patient's motor, verbal, and eye-opening response to audible and physical stimulation. Many neurointensivists have opined that inclusion of pupil reactivity would improve the performance of the GCS at lower total scores in both adults and children [161].

Assessing comfort

Often, critically ill babies and children cannot self-report their level of pain because of their baseline inability, changes in cognition, the use of sedatives, or the presence of an endotracheal tube. As a result, the PICU utilizes many validated, standardized pain assessment tools. For example, the Wong–Baker FACES® pain rating scale is a visual scale for interactive patients, aged 3 years and older, that uses a series of cartoon faces ranging from happy at 0 to a devastated, crying face at 10. The patient chooses the face that best describes their current pain level (Fig. 42.12) [162]. The face, legs, activity, cry, and consolability scale (FLACC scale) is a validated measurement used to assess pain in infants and children 2 months to 7 years or in any non-verbal, developmentally delayed patient. The FLACC scale is based on five criteria, each assigned a score between 0 and 2, with an overall score range of 0–10 [163]. The state behavioral scale (SBS) is a validated, sedation assessment instrument that provides a systematic description of the sedation–agitation continuum for infants and young children supported on mechanical ventilation. The SBS is a 6-point scale ranging from –3 to +2 that is typically monitored at the same frequency as vital signs (Fig. 42.13) [164]. The neonatal infant pain scale (NIPS) is a validated, standard pain assessment tool for neonates that contains five behavioral measurement and one physiological measurement with an overall score range of 0–7 (Table 42.9) [165]. The routine use of simple, yet valid and reliable, observational tools to assess

Table 42.8 Adult and pediatric Glasgow coma scales

Activity	Adult/child response	Infant response	Score
Eye opening (E)	Spontaneous	Spontaneous	4
	To verbal stimuli	To verbal stimuli	3
	To pain	To pain	2
	None	None	1
Best verbal response (V)	Oriented, appropriate	Coos and babbles	5
	Confused conversation	Irritable cries	4
	Inappropriate words	Cries to pain	3
	Incomprehensible sounds	Moans to pain	2
	No response	None	1
Best motor response (M)	Obeys verbal command	Normal spontaneous movement	6
	Localizes stimulus	Withdraws to touch	5
	Withdraws from noxious stimulus	Withdraws to pain	4
	Decorticate flexion	Decorticate flexion	3
	Decerebrate extension	Decerebrate extension	2
	No response (flaccid)	No response (flaccid)	1

Total score is sum of E + V + M
Minimum score is 1E + 1V + 1M = 3
Maximum score is 4E + 5V + 6M = 15

Figure 42.12 Wong–Baker FACES® pain rating scale. *Source:* Reproduced from Jacob [162] with permission of Elsevier.

pain in the PICU is necessary to ensure adequate pain management in critically ill patients.

Cranial nerves

A basic cranial nerve exam should be performed upon admission to the PICU and followed daily to hourly if any deficits are identified. If deficits are identified or the patient is at high risk for developing deficits, the pediatric neurology team is often consulted for a more complete cranial nerve examination. *Cranial nerve I* is rarely evaluated by intensivists. In the awake and cooperative patient, *cranial nerve II*, the optic nerve, is evaluated by testing visual acuity with a Snellen chart. In patients with depressed mental status, funduscopic examination with an ophthalmoscope looking for papilledema or optic disk pallor can quickly assess for intracranial hypertension or optic neuritis. It is essential to evaluate for retinal hemorrhages with an ophthalmoscope in babies less than 3 years of age presenting with head trauma, looking for retinal pathology associated with abusive head trauma [152]. If retinal pathology is identified, consultation to pediatric ophthalmology for further investigation, documentation, and monitoring is needed [152]. Determining and monitoring the optic nerve sheath diameter with bedside ultrasound has a good level of diagnostic accuracy for detecting intracranial hypertension in children [166].

Cranial nerves III, IV, and VI. The extraocular muscles are controlled by cranial nerves III, IV, and VI. Extraocular movements can be quickly evaluated by having the child visually follow the movement of your finger in six cardinal directions without moving their head. Paralysis of cranial nerve III will lead to ptosis, dilation of the pupil, and displacement of the eye downward and outward. Dysfunction of cranial nerve IV will cause the eye to deviate up and outwards, often causing a compensatory head tilt by the child to correct diplopia. Injury to the cranial nerve VI causes medial deviation of the eye and inability to abduct the eye beyond the midline. Nystagmus is involuntary and unsurpassable eye movements that may be vertical, horizontal, rotatory, or mixed. Horizontal nystagmus is often a side-effect of drugs like phenytoin or can be due to injury to the cerebellum or vestibular system in the brainstem. Structural abnormalities or brainstem dysfunction cause vertical nystagmus. The pupils should be examined for size, equality, and response to light. Unreactive pupils are an ominous sign, while small reactive pupils may indicate the presence of opioids or barbiturates but may also be caused by damage to the pons. Large reactive pupils may be caused by atropine, tricyclic antidepressants, or pharmacological withdrawal. In a comatose child where evaluation of extraocular eye movements is impossible, the pupillary exam can and should be performed frequently.

Cranial nerves V, VII, VIII, IV, X, and XII. The sensory component of cranial nerve V innervates the ophthalmic, maxillary, and mandibular regions of the face, which can be stimulated by either light touch or pain. In an unconscious

Dimensions	Levels
Respiratory drive	1. No spontaneous respiratory effort 2. Spontaneous but ineffective exhaled tidal volume (Patient specific: <4mL/kg) 3. Spontaneous and effective exhaled tidal volume (Patient specific: > 4mL/kg)
Response to ventilation	1. No spontaneous breathing 2. Easy spontaneous breathing (fully synchronized with mechanical ventilation) 3. Having difficulty synchronizing with ventilator 4. Unsynchronized with mechanical ventilation, compromising oxygenation/ventilation
Coughing	1. No cough with suction 2. Coughs only when suctioned 3. Coughs when repositioned 4. Occasional spontaneous cough 5. Frequent spontaneous coughing that does not resolve with suctioning 6. Bronchospastic or choking
Best response to stimulaiton	1. No resonse to noxious stimuli 2. Responds to noxious stimulis 3. Responds to touch 4. Responds to voice 5. No external stimulus is required to elicit response
Attentiveness to care provider	1. Unable to pay attention to care provider 2. Able to pay attention to care provider but drifts off after stimulation 3. Spontaneously pays attention to care provider (Infant – fixes and follows) 4. Vigilant of care provider/Eyes follow care provider – watchful 5. Hyper-vigilant to care provider/Panicky when care providers approch patient
Tolerance to care	1. Does not distress with any procedure including noxious 2. Will distress with noxious procedures 3. Distresses with procedures (i.e., repositioning) 4. Distressed (e.g., picking at tubes, pulling at restraints, etc.) 5. Patient intermittently unsafe (e.g., biting ETT) 6. Patient unsafe (e.g., attempting to pull at ETT/catheters, cannot be left alone)
Consolability	1. Self-regulates/modulates own behavior 2. Able to calm with comforting touch or voice when stimulus removed; distractible 3. Does not consistently calm despite a 5-minute attempt to console 4. Unable to console
Movement after consoled	1. Does not move 2. Occasional movement of extremities or shifting of position in bed 3. Increased movement (restless, squirming) 4. Excessive movement (thrashing side to side, kicking legs, arched, rigid) 5. Combative

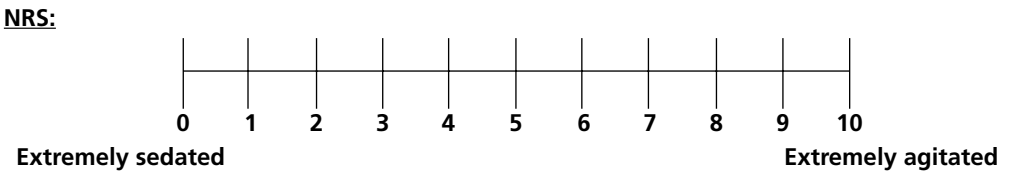


Figure 42.13 State behavioral scale: a sedation assessment instrument for infants and young children supported on mechanical ventilation. ETT, endotracheal tube; NRS, numeric rating scale. *Source:* Reproduced from Curley et al [164] with permission of Wolters Kluwer.

patient, the corneal response is elicited by lightly touching the cornea with cotton and observing for eye closure. Mastication and jaw movements (horizontal and lateral) are the motor functions of cranial nerve V. Cranial nerve VII controls taste, volume of hearing, and facial strength. Facial asymmetry is the most obvious manifestation of cranial nerve VII dysfunction. Cranial nerve VIII, the auditory nerve, is rarely tested in critically ill children while acutely ill. Common risk factors for cranial nerve VIII malfunction are prematurity, asphyxia, hyperbilirubinemia, ototoxic drug exposure, congenital rubella, herpes, or cytomegalovirus infections. In the unconscious patient, the vestibular function of cranial nerve VIII can be assessed with the cold caloric test. Cranial nerve IX is tested by the presence of a gag reflex, and vocal cord paralysis is reflective of injury to cranial nerve X. Cranial nerve XI is tested by voluntary, forceful rotation of the child's head and neck against the examiner's hand; however, cranial nerves XI and XII are rarely evaluated by the intensivist. Cranial nerve XII innervates the tongue.

Table 42.9 Neonatal infant pain scale (NIPS)

Variable	Finding	Points
Facial expression	Relaxed (restful face, neutral expression)	0
	Grimace (tight facial muscles, furrowed brow, chin, jaw)	1
Cry	No cry (quiet, not crying)	0
	Whimper (mild moaning, intermittent)	1
	Vigorous crying (loud scream, shrill, continuous). If infant is intubated, score silent cry based on facial movement.	2
Breathing pattern	Relaxed (usual pattern for this infant)	0
	Change in breathing (irregular, faster than usual, gagging, breath holding)	1
Arms	Relaxed (no muscular rigidity, occasional random movements of arms)	0
	Flexed/extended (tense, straight arms, rigid and/or rapid extension, flexion)	1
Legs	Relaxed (no muscular rigidity, occasional random movements)	0
	Flexed/extended (tense, straight legs, rigid and/or rapid extension, flexion)	1
State of arousal	Sleeping/awake (quiet, peaceful, sleeping or alert and settled)	0
	Fussy (alert, restless and thrashing)	1
Hear rate	Within 10% of baseline	0
	11–20% of baseline	1
	>20% of baseline	2
O_2 saturation	No additional O_2 needed to maintain O_2 saturation	0
	Additional O_2 required to maintain O_2 saturation	1

Limitations: a falsely low score may be seen in an infant who is too ill to respond or who is receiving a paralyzing agent. A score greater than 3 indicates pain.

Source: Reproduced from Witt et al [163]. Witt2016, https://link.springer.com/article/10.1007/s40138-016-0089-y. Licensed under CC BY 4.0.

Assessing motor function, sensory function, tone, and reflexes

Muscle strength is graded on a five-point scale: 0 (no contraction), 1 (flicker or trace contraction), 2 (active movement with gravity eliminated), 3 (active movement against gravity), 4 (active movement against gravity and resistance), and 5 (normal strength). A sensory exam is tested with either pain sensation or light stimulation running up the infant, beginning at the toes and ending with the cranium. Sensory deficits often identify a spinal cord level of injury resulting from trauma, infection, or a spinal cord mass.

Tone is evaluated by assessing the resistance to passive motion at an individual joint. A spastic extremity is associated with decreased spontaneous movements, atrophy, hyperactive deep tendon reflexes, and plantar extensor reflexes. While flexing and extending an extremity, initially the movement is restricted followed by a "clasp-knife"-like release of the increased tone in a spastic limb. The deep tendon reflexes are graded on a scale of 0 (absent) to 4 (markedly increased). Upper motor lesions cause increased deep tendon reflexes; asymmetrical reflexes suggest lateralizing lesions. Reduced or absent reflexes are associated with neuropathies, myopathies, and cerebellar disease. Rigidity refers to constant resistance to both flexion and extension of passive movements and commonly results from lesions in the basal ganglia. Hypotonia is common with injury to the cerebral cortex, cerebellum, spinal cord, or peripheral nerves.

Neuroimaging

In a child with altered mental status, the rapid and accurate recognition of injury clinically guides the medical and surgical strategies, and any delay could result in significant morbidity and mortality. Head trauma can be separated into two categories: primary brain injury, which occurs at the time of trauma, and secondary brain injury, occurring after the initial insult. Examples of primary brain injury are skull fractures, subdural and epidural hematomas, hemorrhagic contusion, and diffuse axonal injury. Secondary brain injury is often due to anoxia, ischemia, metabolic derangements, inflammation, and cerebral edema. Primary brain insults are most commonly identified with rapid head computed tomography (CT) scans, while secondary insults are often better identified with brain MRI.

Diagnosing skull fractures in infants is complicated by normal sutural anatomy, which can be mistaken for fractures (Fig. 42.14A). True fractures generally show a linear course without well-defined sclerotic borders and often cross rather than merge with adjacent sutures [167]. Extra-axial hemorrhage is classified by the space in which it occurs – epidural, subdural, and subarachnoid. Epidural hemorrhage has a lentiform shape and does not cross sutural boundaries but may cross the midline (Fig. 42.14B). Epidural hemorrhage results from injury of the epidural arteries or veins and is often associated with an overlying calvarial fracture [168]. Subdural hematoma is characterized by its crescentic shape and ability to cross sutures (Fig. 42.14C). Subdural hemorrhage is bounded by the midline falx and results from tearing of bridging cortical veins [168]. Subarachnoid hemorrhage appears as increased attenuation in the cerebral sulci and cerebrospinal fluid cisterns on CT (Fig. 42.14D). The presence of subarachnoid hemorrhage in the setting of trauma is common; however, in non-traumatic scenarios it is often associated with ruptured aneurysm or arterial venous malformation.

Cortical contusions are best identified with brain MRI and tend to be multiple, bilateral, and occur along the inferior frontal lobes and anterior temporal lobes, where the brain has a greater chance of direct impact against rigid bone. It is important to look at the soft tissues of the scalp because intraparenchymal contusions are classically coup or contrecoup in location. Cortical contusions occur in the gray matter and tend to spare the adjacent subcortical white matter unless the hemorrhage is large [169]. Diffuse cerebral edema in the pediatric brain will appear symmetrical with loss of gray–white matter differentiation and effacement of the ventricles, cisterns, and sulci. The midbrain and cerebellum are the least vulnerable to hypoxic injury and diffuse cerebral edema, often resulting in the ominous "white cerebellum sign" [170]. Diffuse axonal injury results from shear–strain deformation of the brain due to rotational acceleration and deceleration. Diffuse axonal injury often does not appear on head CT; instead it is typically identified with brain MRI susceptibility-weighted and diffusion-weighted images [171].

Abusive head trauma or "shaken baby syndrome" includes any non-accidental, inflicted injury to a child's head and body often characterized, but not limited to, the repetitive acceleration–deceleration forces with or without blunt head impact. The constellation of subdural hematoma, diffuse axonal injury, and retinal hemorrhage in an infant or child carries a 91% probability of abusive head trauma [172]. All concerns for abusive head trauma should be thoroughly investigated with head imaging – preferably brain MRI, retinal exam,

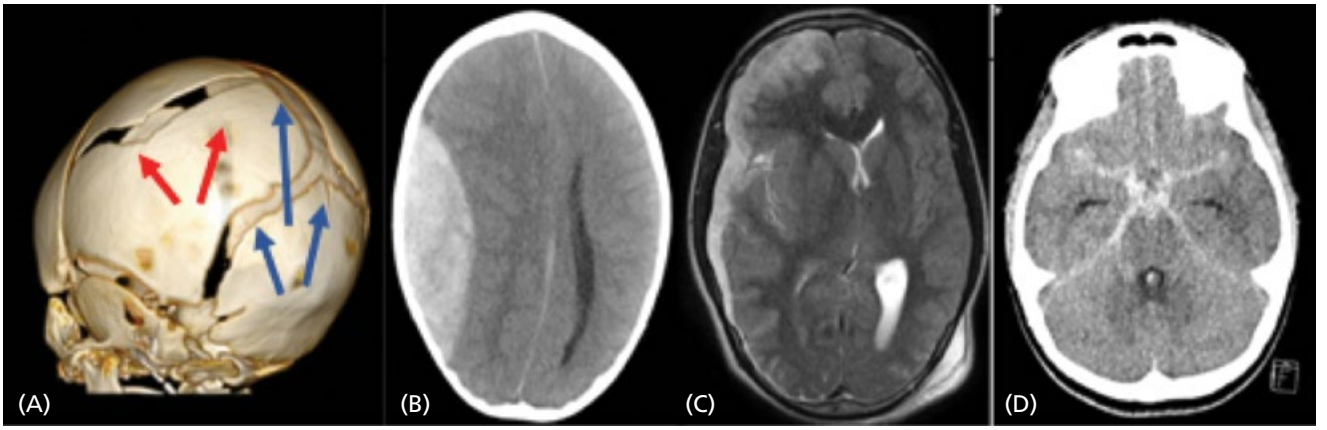


Figure 42.14 (A) Three-dimensional reconstruction of a head CT with red arrows showing a large left parietal bone fracture and blue arrows showing widening of cranial sutures. (B) Head CT without contrast showing right epidural hematoma with mass effect and midline shift. (C) T_2-weighted brain MRI showing right-sided subdural hemorrhage with mass effect and midline shift. (D) Head CT without contrast showing subarachnoid hemorrhage.

skeletal survey, coagulation work-up, and referrals to child protective services and local law enforcement. Prompt identification of the site and severity of brain injury can prove to be life saving for the critically ill pediatric patient.

Near-infrared cerebral oximetry and continuous EEG monitoring

Near-infrared cerebral oximetery can be used to monitor oxygenation in a sample volume of the frontal cerebral cortex; newer monitors with multiple wavelengths and spatially resolved algorhithms are more likely to represent absolute brain tissue oxygen saturation. These monitors are now in wide use in cardiovascular ICUs, with 65% of 42 pediatric cardiovascular ICUs in Europe responding that near-infrared spectroscopy was in regular use in their units [173]. Additional information is presented in Chapter 19.

Continuous electroencephalography (EEG) monitoring can be utilized in the PICU for monitoring and treatment of status epilepticus, and for other patients at high risk for seizures such as those with TBI, postcardiac arrest, ECLS, or postcardiac surgery [174]. In addition, in comatose patients this modality can be useful to monitor for new slowing, laterality of findings, or burst suppression. The increasing availability of this monitoring technology and outcome data associating early seizure recognition and treatment with improved outcomes will likely translate into more widespread use of this approach. Drawbacks include expense and complexity, and the need for trained personnel, or automated computer algorithms, to monitor the EEG and notify clinicians.

KEY POINTS: NEUROLOGICAL EXAMINATION AND NEUROIMAGING

- Early Glasgow coma scale scores are strongly associated with neurological morbidity and death after traumatic brain injury
- Comfort, pain, and sedation scales are a crucially important component of neurological assessment
- CT scans, MRI, transfontanelle ultrasound, near-infrared spectroscopy, and continuous EEG are important neuromonitoring modalities

Traumatic brain injury

Evidence-based guidelines for children suffering from severe traumatic brain injury were first published in 2003 [175] and revised in 2012 [176] (Figs 42.15 and 42.16). The ADAPT trial is a large, multicenter, observational cohort study that intends to develop new evidence-based recommendations that will evolve into universal standards of care for treating pediatric TBI [177]. An infant and pediatric GCS should be utilized to accurately determine the child's GCS score. Current guidelines support a stat head CT to rule out a neurosurgical emergency in all TBI patients with a GCS score ≤8. An ICP monitor should be placed if the GCS score remains ≤8, the child requires prolonged surgical intervention regardless of GCS score, or the child's neurological exam cannot be monitored due to neuromuscular blockade or long-acting sedatives. Criteria for tracheal intubation of children with TBI and other forms of acute brain injury include hypoxemia unresponsive to supplemental oxygen, apnea, hypercarbia ($PaCO_2$ >45 mmHg), GCS score ≤8, any rapid decrease in GCS score of >3 points, anisocoria >1 mm, spinal injury compromising ventilation, inability to protect airway, or any clinical signs of herniation syndrome [178].

Neuroprotective intubation and sedation

Approximately half of all children with cervical spinal injury also have a simultaneous TBI [179]. Pediatric Advanced Life Support Guidelines advise that oral intubation should be performed while maintaining spine immobilization using a cuffed endotracheal tube in children with TBI [180]. A multicenter, randomized control trial demonstrated no increase in postextubation stridor or long-term complications when using cuffed tubes [181]. Always assume a full stomach and use a cerebral-protective rapid-sequence induction with cricoid pressure and preoxygenation. Because the apnea tolerance of an infant less than 6 months old is less than 100 s with optimal bag–mask ventilation using 100% oxygen [182], many pediatric anesthesiologists use a modified rapid-sequence induction with gentle pressure-limited mask ventilation (10–12 cmH_2O) with 100% oxygen after induction of anesthesia to avoid hypoxemia [183].

Pretreat all children [184] with lidocaine (1.5 mg/kg IV with maximum dose 100 mg), and in children ≤1 year old [185] pretreat with atropine (0.02 mg/kg IV with minimum dose

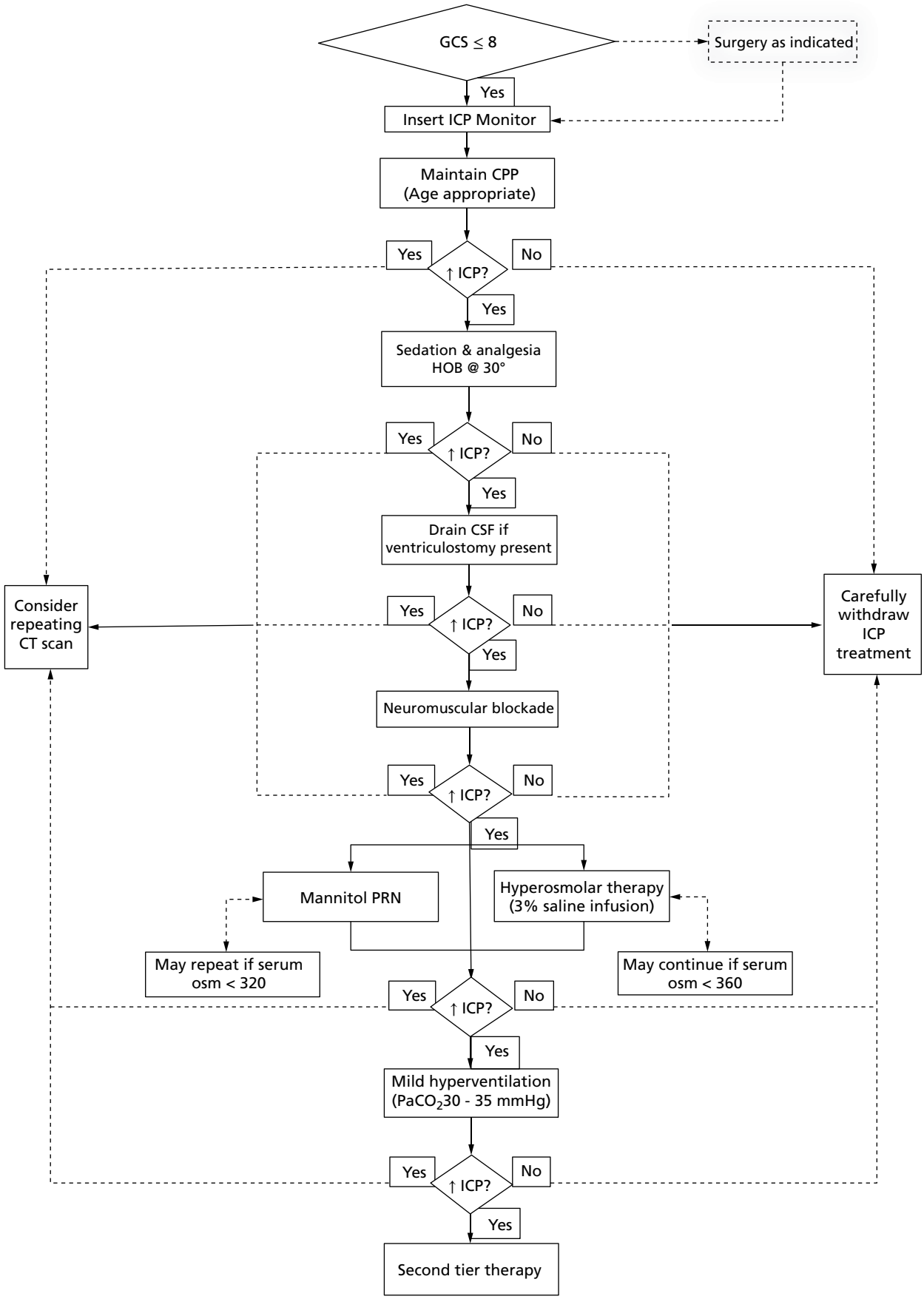


Figure 42.15 Critical pathway for the treatment of established intracranial hypertension in pediatric traumatic brain injury: first tier. CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; CT, computed tomography; GCS, Glasgow coma scale; HOB, head of bed; ICP, intracranial pressure; PRN, as needed.
Source: Reproduced from Adelson et al [175] with permission of Wolters Kluwer.

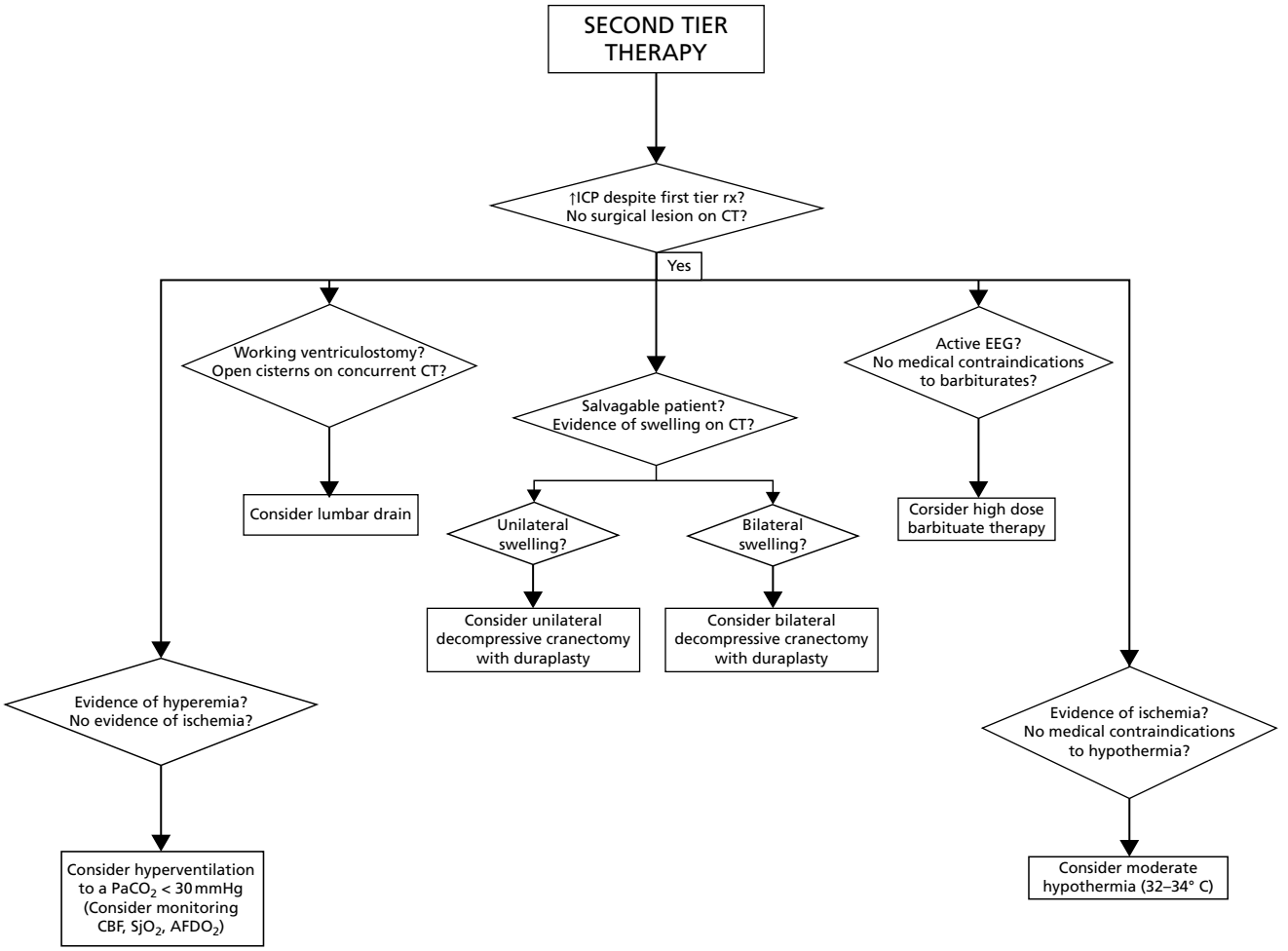


Figure 42.16 Critical pathway for the treatment of established intracranial hypertension in pediatric traumatic brain injury: second tier. $AJDO_2$, arterial-jugular venous difference in oxygen content; CBF, cerebral blood flow; CT, computed tomography; EEG, electroencephalogram; ICP, intracranial pressure; SjO_2, jugular venous oxygen saturation. *Source:* Reproduced from Adelson et al [175] with permission of Wolters Kluwer.

0.1 mg and maximum single dose 0.5 mg). For hemodynamically unstable children, the combination of etomidate (0.2–0.6 mg/kg) and neuromuscular blockade with rocuronium (1 mg/kg) or vecuronium (0.3 mg/kg) IV is often used. Succinylcholine is avoided because of the risk of malignant hyperthermia, possible ICP elevation [186], hyperkalemia, and life-threatening complications associated with unknown occult metabolic or neuromuscular disease [187,188]. Fentanyl (2-4 μg/kg) or ketamine (1–2 mg/kg) IV are alternative sedatives, and recent pediatric studies show that ketamine does not increase ICP and may be neuroprotective [189–191]. If hemodynamically stable, midazolam (0.1–0.2 mg/kg) can be added to any of the above combinations. After successful intubation, oxygen saturation of 100% and normocarbia (35–39 mmHg) should be confirmed by arterial blood gas. Unless the child has signs of herniation, prophylactic hyperventilation ($PaCO_2$ <35 mmHg) should be avoided [192].

Hemodynamic status must be maintained when administering sedatives to assure adequate cerebral perfusion pressure (CPP). An age-based CPP between 45 and 65 mmHg has been recommended for infants and children [193,194]. Overall, there is limited research or evidence-based recommendations regarding the use of sedatives, analgesics, and neuromuscular blocking agents in pediatric patients with acute brain injury. Continuous infusions of propofol, especially over a 24 h period have been associated with lethal cases of propofol infusion syndrome (metabolic acidosis and death); therefore, a continuous infusion of propofol is not recommended for pediatric TBI treatment or for continuous sedation in pediatric patients with acute brain injury [195,196]. The ideal continuous sedative for intubated children with TBI is remifentanil (0.05–1 μg/kg/min), because its rapid onset and short duration of action allow for frequent reliable neurological checks with only brief infusion pauses. If remifentanil is unavailable, a continuous infusion of fentanyl (0.5–5 μg/kg/h) is used for sedation of intubated children with TBI. More frequently, aggressive hyperventilation is being replaced with the use of barbiturates to treat refractory intracranial hypertension. All endotracheal tube suctioning should be pretreated with lidocaine (1 mg/kg IV) and additional sedation if needed to blunt rises in ICP.

Intracranial pressure and cerebral perfusion pressure

A continuous ICP monitor is essential when utilizing medical therapies to normalize ICP and assure an adequate CPP. The calculation for determining cerebral perfusion pressure is CPP = mean arterial pressure – intracranial pressure (CPP = MAP – ICP). Ideally, the ICP should be maintained <20 mmHg, and the CPP should be within the following age-based ranges:

0–1 year ≥45–50, 1–12 years ≥50–60, and >12 years ≥65 [193,197]. To assure adequate CPP, the MAP can be increased with rapid fluid resuscitation assuring a CVP of 5–10 mmHg, vasopressors/inotropes, or blood transfusion to maintain the hemoglobin >8 g/dL [198]. The ideal vasopressor infusion in pediatric TBI is phenylephrine (0.1–0.5 μg/kg/min) providing pure α-adrenergic stimulation; however, if myocardial depression from either polytrauma or sedative agents is present, dopamine (3–20 μg/kg/min) or epinephrine (0.05–0.2 μg/kg/min) infusions are commonly utilized.

The ICP should be maintained <20 mmHg. If the ICP is >20 mmHg, ensure that the patient's head of bed is at 30° and their neck is in a neutral position to facilitate blood flow through the internal jugular arteries. Next, optimize sedation and analgesia while supporting hemodynamics to assure an adequate CPP. If the ICP does not normalize with these measures, give hyperosmolar therapies while considering the need for repeat head CT to rule out new intracranial pathology or EEG to detect seizure activity. Hypertonic saline is available in 2%, 3%, 7%, 9%, and 23% formulations [199,200]. In pediatrics, the use of 2% or 3% hypertonic saline is preferred. Give a rescue bolus of 3% hypertonic saline (5 mL/kg with maximum dose of 500 mL) or 2% hypertonic saline (10 mL/kg) and consider starting a continuous infusion of 3% (0.1–2 mL/kg/h) titrating to the minimum dose needed to maintain a serum sodium goal of 150–160 and an ICP <20. Hypertonic saline should not be utilized if serum osmolarity is >360 mOsm/L. Alternatively, if hypertonic saline does not lower the ICP below 20 mmHg, consider administering a bolus of mannitol (0.25–1 g/kg) over 20 min [199] To minimize cerebral metabolic demands, avoid hyperthermia with a goal core temperature of 35.5–37°C, provide seizure prophylaxis, maintain normoglycemia (80–180), avoid hypoxia or hyperoxia (goal PaO_2 75–125), and avoid hypercarbia (goal $PaCO_2$ 35–45 mmHg) [176]. If the ICP remains consistently >20 mmHg remove cerebral spinal fluid if ventriculostomy is present, obtain continuous EEG readings, and treat for seizures if suspected clinically or electrographically.

Post-traumatic seizure management

Current evidence-based guidelines for the management of post-traumatic seizures in children contain no level I or level II recommendations; however, reports from the ADAPT trial show that most pediatric trauma centers provide seizure prophylaxis and aggressive seizure treatment in children with TBI [201]. The two most utilized prophylactic medications for post-traumatic seizures are levetiracetam (20–60 mg/kg/day divided bid) and fosphenytoin (4–8 mg phenytoin sodium equivalents per kg/day divided bid) [201]. First-line treatment for active, post-traumatic seizures is with benzodiazepines, typically either lorazepam (0.1 mg/kg, maximum 2 mg for babies and 4 mg for children) or midazolam (0.15 mg/kg, maximum 3 mg for babies or 6 mg for children). If the seizure persists, the following are second-line agents: Phenytoin (20 mg/kg load with a maximum infusion rate of 1 mg/kg/min), fosphenytoin (20 mg/kg load with a maximum dose of 1500 mg and a maximum infusion rate of 3 mg/kg/min), phenobarbital (20 mg/kg), or levetiracetam (60 mg/kg, maximum dose 4500 mg) [202]. If seizures persist after administering 2–3 adequate doses of these anticonvulsants, refractory status epilepticus has developed, and the initiation of either a high-dose midazolam or pentobarbital infusion should be started. Continuous EEG must be in place with the goal of either midazolam or pentobarbital infusions to stop the seizures by achieving burst suppression detected on EEG. If utilizing midazolam, give a loading dose of 0.2 mg/kg IV followed by an infusion of 0.1 mg/kg/h, increasing the infusion by 0.1 mg/kg/h every 5–15 min until seizures resolve or until a maximum of 2 mg/kg/h is reached [203]. If utilizing pentobarbital, give an initial loading dose of 1–5 mg/kg followed by an infusion of 1 mg/kg/h, titrating up every 15–30 min to a maximum dose of 3 mg/kg/h [203]. Often the limitations of either of these high-dose infusions is hemodynamic instability refractory to fluid and vasoactive support.

Refractory intracranial hypertension

Decompressive craniectomy is a controversial, emergency procedure for the treatment of refractory intracranial hypertension following severe TBI. Large decompressive craniectomy with duraplasty, leaving the bone flap out, may be considered for pediatric patients with TBI showing early signs of herniation or who have refractory intracranial hypertension during the early stages of their treatment. While decompressive craniectomy can be acutely life saving, there is a high incidence of complications, with over 70% of patients requiring multiple additional surgeries, with long-term sequela from neurological devastation, hydrocephalus, infection, epilepsy, and often no improvement in overall GCS than similar patients not decompressed [204]. Studies have shown a favorable outcome after decompressive craniectomy in children with severe TBI [205–207]; however, others have shown poor outcomes [208–211].

High-dose barbiturate therapy, accompanied with continuous EEG monitoring, may be considered in hemodynamically stable patients with refractory intracranial hypertension despite maximal medical and surgical management. Potentially toxic cardiorespiratory side-effects are common – decreased cardiac output, hypotension, lower systemic vascular resistance, decreased left ventricular stroke volume, and increased intrapulmonary shunt resulting in lower CPP and hypoxia. Continuous arterial blood pressure monitoring and cardiovascular support are required to assure adequate CPP when high-dose barbiturate therapy is used to treat refractory intracranial hypertension [175]. High-dose barbiturates lower ICP through metabolic suppression and alteration of the vascular tone resulting in higher brain oxygenation with lower cerebral blood flow and decreased ICP from decreased cerebral blood volume [212]. Barbiturate levels are poorly correlated with electrical activity; hence, monitoring electrographic patterns to achieve burst suppression is more reflective of therapeutic effect than drug levels [176]. Begin pentobarbital therapy with a loading dose of 1–5 mg/kg slow IV push followed by initiation of an infusion (0.5–1 mg/kg/h). Every 30–60 min give an additional 1–5 mg/kg slow push IV bolus followed by an increase in the pentobarbital infusion to a maximum infusion of 3 mg/kg/h. Due to the high precipitation risk, the infusion should be given through a dedicated peripheral IV rather than a central line [175]. Near maximum reduction in cerebral metabolism and cerebral blood flow occurs when burst suppression is induced. Clinicians typically wait for at least a 24 h period of ICP control without

sustained elevations with stimulation before beginning to taper the barbiturate infusion [176].

Although not evidence based, hypothermia and hyperventilation can be considered in extreme cases of traumatic refractory intracranial hypertension in children. Hyperventilation reduces ICP by unpredictably increasing cerebral vasoconstriction, resulting in decreased cerebral blood volume that may also decrease cerebral oxygenation and induce brain ischemia. If utilized, advanced neuromonitoring evaluation of cerebral ischemia must also be considered [213]. Hyperventilation is also known to reduce the buffering capacity of cerebrospinal fluid and is associated with poor outcomes in children. Avoidance of hypercarbia (goal $PaCO_2$ 35–45 mmHg) is standard of care for treating children with severe TBIs; however, mild hyperventilation ($PaCO_2$ <35 mmHg) and moderate hyperventilation ($PaCO_2$ <30 mmHg) is not supported but can be acutely life saving [212]. Large, multicenter pediatric trials have shown no benefit and potential harm with therapeutic hypothermia (32–33°C) treating refractory intracranial hypertension in children with TBI [214–216]. Therapeutic hypothermia theoretically works by reducing secondary injury through decreased cerebral metabolic demands, inflammation, lipid peroxidation, excitotoxicity, cell death, and seizure activity [58]. If hypothermia is induced for any indication, rewarming at a rate of >0.5°C/h should be avoided. Avoidance of hyperthermia with a targeted core body temperature goal of 35.5–37.0°C is strongly supported by the literature and is routinely practiced [175–177,215].

Pediatric brain death

In 1987, a multi-society task force published guidelines for the determination of pediatric brain death and revised the guidelines in 2011 [217]. The timely diagnosis of brain death is important for a variety of reasons, including the allocation of medical resources, facilitating organ donation [218], and relieving family members from end-of-life decisions. Brain death is defined as the irreversible cessation of functions of the entire brain, including the brainstem [217]. In children, brain death is diagnosed following two standardized neurological exams with apnea tests that are consistent with the absence of complete neurological function in the setting of a known irreversible cause of coma [217]. Ancillary studies are only utilized to confirm brain death when the full clinical exam is unable to be adequately performed due to underlying medical conditions, findings are uncertain, concern for medication effect, or to reduce the time interval between exams [217]. Initial requirements for brain death evaluation are clinical or radiographic evidence of an acute catastrophic cerebral event, exclusion of neurological confounders such as drugs, seizures, metabolic derangements (Na^+, BUN, NH_4^+, glucose), absence of drug intoxication or poisoning, core body temperature >35°C, and mean arterial pressure at an age-appropriate level [217]. The 2011 taskforce showed strong evidence to defer the initial brain death evaluation for 24 h from the last cardiopulmonary arrest, if possible [217]. Brain death examinations should be performed by two separate attending physicians with the age-appropriate waiting period between; however, the apnea test may be performed by the same physician [217]. Brain death testing cannot be performed in a neonate less than 37 weeks' gestational age. In a neonate of 37 weeks' gestational age up to 30 days old, there must be a minimum 24 h waiting period between brain death evaluations [217]. If the child is >30 days to 18 years of age, a minimum 12 h waiting period must be observed between exams. If the child is not stable enough to perform certain parts of the exam, ancillary testing may be used to assist in the diagnosis; however, if unnecessary, ancillary testing is avoided.

The same physiological parameters required for the neurological exam are also required for the apnea test, with the addition of normalizing the pH and $PaCO_2$ as much as physiologically possible [217]. Placement of an arterial line is suggested for hemodynamic monitoring and frequent arterial blood gas sampling. Preoxygenate with 100% oxygen for 10–60 min with the ventilator prior to the apnea test, while providing 100% oxygen without ventilation (self-inflating bag) throughout the test. There must be no spontaneous respiratory efforts observed despite a final $PaCO_2$ ≥60 mmHg and a ≥20 mmHg increase above baseline [217]. Arterial blood sampling should occur in 5–10 min intervals throughout the apnea test documenting the rise in $PaCO_2$.

Abusive head trauma

Any infant less than 3 years old presenting with TBI, especially with subdural hemorrhages, should be considered for possible abusive head trauma workup and investigation. Abusive head trauma (AHT) is the leading cause of child abuse deaths in the United States, with a cost of $7.2 million dollars per AHT death [219]. At least one-third of AHT cases are not identified upon initial presentation to the emergency department [220–221]. AHT, often characterized but not limited to repetitive acceleration–deceleration forces with or without blunt head impact, has a mortality rate of 30%, and 80% of survivors suffer permanent neurological damage [221–223]. Ocular manifestations of AHT are typically identified by a dilated ophthalmic exam showing retinal hemorrhages that are too numerous to count, multilayered, and extending to the periphery [224]. Extensive retinal injury occurs when a baby is forcefully shaken. With infants who cannot speak for themselves, this retinal injury often distinguishes AHT from accidental head trauma in the early diagnostic period. The probability of AHT in a baby found with both head trauma and retinal hemorrhages is 91% with an odds ratio of 14.7 [225]. Given this high probability, the American Academy of Pediatrics recommends that ophthalmological examination should take place within the first 24–72 h of suspected AHT [226].

The common injury profile of abusive head trauma is the combination of TBI, retinal pathology, rib fractures, and metaphyseal chip fractures in an infant who has little to no visible signs of physical injury [221]. Intracranial injury most associated with abusive head trauma are subdural hemorrhage, subarachnoid hemorrhage, diffuse axonal injury, and hypoxic-ischemic injury. If abusive head trauma is suspected, the initial investigation will include brain imaging, retinal examination, a full radiographic skeletal survey, and urgent consultation to the child abuse protection team and child protective services. Further genetic, metabolic, coagulopathic, and radiological investigations may be required by the child protective services if evidence of abusive head trauma is discovered.

KEY POINTS: TRAUMATIC BRAIN INJURY

- A GCS score ≤8 indicates severe traumatic brain injury; protective intubation, neuroimaging, ICP monitoring to maintain adequate CPP, and, if needed, decompressive craniectomy are all used to salvage as much viable brain tissue as possible
- Treatment of seizures, normocarbia, or slight hypocarbia, vasopressor support, and osmotic diuresis are also utilized
- Any infant <3 years old with traumatic brain injury, especially with subdural hemorrhages, should be considered for abusive head trauma work-up

Renal diseases

Acute kidney injury

Acute kidney injury is a common occurrence in the PICU. By some estimates, close to 6% of children have some degree of AKI at the time of PICU admission, and as many as 30–70% of critically ill children develop AKI during their hospitalization [227–230]. AKI is associated with poor outcomes, including increased risk of death, use of mechanical ventilation, and RRT [229]. The pathogenesis of AKI in critically ill children is multifactorial. Multiple risk factors are implicated in the development of AKI, including prerenal (e.g. low cardiac output, low systemic vascular resistance such as seen in warm septic shock, dehydration), intrinsic (e.g. acute tubular necrosis, including aminoglycoside toxicity, acute interstitial nephritis due to drug toxicity and toxic ingestions, chronic kidney disease), and postrenal (e.g. obstructive uropathy, mechanical obstruction) factors. Cardiac surgery, solid organ transplantation, bone marrow transplantation, sepsis, shock, and multiple organ dysfunction syndrome have all been implicated in the development of AKI.

The determination of AKI in hospitalized children has been the subject of much collaborative study. A rise in serum creatinine, which was used in the past to diagnose AKI, is associated with increased mortality even if modest. Reliance on serum creatinine only hampers early AKI recognition. Three definitions of AKI have been used to define AKI in hospitalized children in the last decade, including: (1) the Pediatric Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (pRIFLE); (2) the AKI Network (AKIN); and (3) the Kidney Disease Improving Global Outcomes (KDIGO) criteria [230]. Applying the three definitions to the same cohort of hospitalized children can lead to differences in AKI incidence and severity staging [230]. The KDIGO criteria represent the most recent modification of the AKI definitions; its components include plasma creatinine, urine output, estimated glomerular filtration rate (eGFR) and initiation of RRT (Table 42.10).

The glomerular filtration rate is estimated using the Schwartz formula:

$$\text{eGFR}\left(\text{mL/min/1.73 m}^2\right) = \text{k} \times \text{height}\left(\text{cm}\right) / \text{plasma creatinine}\left(\text{mg/dL}\right)$$

where k is a constant defined as 0.45 for infants <1 year of age, 0.55 for children and for adolescent females, and 0.70 for adolescent males.

Table 42.10 Kidney Disease Improving Global Outcomes (KDIGO) criteria for acute kidney injury: definition and staging

	Plasma creatinine	Urine output
Definition	Increase by ≥0.3 mg/dL (≥26.5 µmol/L) within 48 h *OR* Increase by ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days	Urine volume <0.5 mL/kg/h for 6 h
Staging		
Stage 1	1.5–1.9 times baseline *OR* ≥0.3 mg/dL increase	<0.5 mL/kg/h for 6 -12 h
Stage 2	2.0–2.9 times baseline	<0.5 mL/kg/h for ≥12 h
Stage 3	3.0 times baseline *OR* Increase in plasma creatinine to ≥4.0 mg/dL *OR* Initiation of renal replacement therapy *OR* In patients <18 years of age, a decrease in eGFR to <35 mL/min/1.73m^2	<0.3 mL/kg/h for ≥24 h *OR* Anuria for ≥12 h

eGFR, estimated glomerular filtration rates.
Source: Reproduced from Sutherland et al [230] with permission of American Society of Nephrology.

At the bedside, the following markers should be integrated to evaluate for AKI, ideally at baseline and then serially during the PICU stay: serum creatinine, creatinine clearance to estimate glomerular filtration rate, BUN, urine output, total fluid input to output ratio, and serum electrolytes. Laboratory and imaging studies can be used to evaluate for potential causes of AKI, including urinalysis to evaluate for bacteriuria, proteinuria, hematuria, casts; renal ultrasound including Doppler to evaluate for intrinsic, vascular, or obstructive causes of AKI; and the fractional excretion of sodium (FE_{Na}). FE_{Na} is calculated as:

$$\text{FE}_{\text{Na}} = \left[\left(\text{Na}_{\text{urine}} \times \text{creatinine}_{\text{plasma}}\right) / \left(\text{Na}_{\text{plasma}} \times \text{creatinine}_{\text{urine}}\right)\right] \text{x}\,100$$

Usually, FE_{Na} <1% represents prerenal disease, and ≥2% represents intrinsic disease or postrenal obstruction. Of note, FE_{Na} cannot be interpreted during therapy with diuretic agents.

Many contemporary PICUs have systems in place for monitoring for AKI using an active surveillance process that integrates clinical and laboratory data collected in the electronic medical record. Emphasis is placed on early identification and treatment of causes for AKI, removing or replacing nephrotoxic medications, adjusting medication doses, and monitoring for adverse effects of medications whenever AKI is suspected or diagnosed. Promising new work is currently being conducted on the prediction of AKI in critically ill children, using the concept of "renal angina," a composite of early injury signs and risk of disease with incorporation of urinary biomarkers (e.g. neutrophil gelatinase-associated lipocalin, human kidney injury molecule, interleukin-18, liver-type fatty acid-binding protein) in future scoring systems [231].

Renal replacement therapy

An estimated 3–5% of children admitted to the PICU require RRT [228,232]. The main indications for RRT in critically ill children are management of severe AKI, fluid overload, acid–base imbalance, and electrolyte and/or metabolic abnormalities [232]. Occasionally, patients with chronic renal failure on intermittent hemodialysis are admitted to the PICU but are stable enough to continue intermittent therapy. More frequently, critically ill children in the PICU undergo continuous RRT (CRRT) using continuous venovenous hemofiltration, hemodialysis, or hemodiafiltration via double-lumen acute dialysis catheters, or peritoneal dialysis via a peritoneal catheter. Peritoneal dialysis in the PICU is primarily utilized in neonates and infants following cardiac surgery [232].

Nephrology and critical care services typically work in conjunction at initiation and during the course of RRT. There is no clear consensus on the timing of CRRT initiation in the PICU, although data suggest that outcomes including mortality are worse when children develop greater fluid overload prior to CRRT initiation [233]. It is generally accepted that CRRT should be initiated at a fluid overload >20%, with more studies needed to determine whether fluid overload between 10% and 20% should prompt consideration of CRRT [234].

Water removal during CRRT occurs due to a hydrostatic pressure gradient across the membrane. Solutes are removed by transmembrane movement in association with ultrafiltered plasma water (convection) or due to a concentration gradient (diffusion). Anticoagulation is typically needed to avoid circuit clotting, and is achieved using regional citrate or systemic heparin. Some data suggest that regional citrate may be superior to systemic heparin in children, but citrate can pose a safety hazard in small infants with an inability to adequate metabolize it [235]. Hypocalcemia due to citrate utilization can be avoided by using a calcium infusion postfilter (citrate is infused prefilter). Circuit clotting can lead to interruptions in therapy, blood loss, and increased cost [235]. Children on CRRT are also at risk for volume shifts (both hypovolemia and hypervolemia), electrolyte imbalance, acid–base imbalance, hypothermia, and citrate toxicity. Therefore, close monitoring of the critically ill child on CRRT with strict intake and output measurements, continuous cardiorespiratory monitoring, serial chemistries, complete blood cell counts, and coagulation profile, is needed to avoid complications.

KEY POINTS: RENAL DISEASES

- AKI is common, with up to 30–70% of children in the PICU developing this condition
- Serum BUN/creatinine, creatinine clearance, AKI definitions, fractional excretion of sodium, and biomarkers such as neutrophil gelatinase-associated lipocalinare used to monitor renal injury
- Renal replacement therapy using perioneal dialysis, continuous venovenous hemofiltration, or continuous venovenous hemofiltration with hemodialysis or hemodiafiltration is reserved for the approximately 3–5% of patients with severe renal insufficiency with electrolyte abnormalities or severe fluid overload

Hematology/oncology

Oncological disease

Among children with oncological disease, 15–40% require intensive care during their illness [236]. The mortality of children with cancer admitted to the PICU has been reported to be as high as 35% [236]. Risk factors for mortality include high pediatric risk of mortality score at admission, diagnosis of sepsis or septic shock, neutropenia, number of organ failures, use of mechanical ventilation, and inotropic support [236]. Delay in transfer of hospitalized children from the floor to the PICU has been shown to be associated with worse 1-month survival [236].

The main reasons for PICU admission in children with oncological disease are complications related to the primary disease, toxicity related to chemotherapy, and immunodeficiency stemming from the oncological disease and/or its therapy. Oncological emergencies include airway and respiratory compromise (e.g. mediastinal mass, infection, hemoptysis), neurological emergencies (e.g. spinal cord compression, increased ICP, seizures, stroke, posterior reversible encephalopathy syndrome), cardiac failure (e.g. due to chemotherapy toxicity), metabolic and electrolyte disturbances (e.g. tumor lysis syndrome, hypercalcemia, diabetes insipidus, cerebral salt-wasting syndrome), and hemorrhagic emergencies (e.g. due to profound thrombocytopenia and/or coagulopathy). As innovative therapies are being developed, new pathologies are also emerging. Recently, cytokine release syndrome has been described in 46% of children with relapse and/or refractory B-precursor acute lymphoblastic leukemia who were treated with chimeric antigen receptor-modified T-cell therapy [237]. Cytokine release syndrome can result in rapidly evolving shock and MODS that require intensive care [237].

Pediatric hematopoietic stem cell transplantation

Overall outcomes of pediatric hematopoietic stem cell transplantation (HSCT) have improved over the last decades and data published in the last years suggest that intensive care in these children is associated with encouraging outcomes. In a multicenter study published in 2013, intensive cardiopulmonary support during HSCT, including continuous positive pressure ventilation, dopamine infusion ≥10 μg/kg/min, or the use of any other vasoactive infusion, was not significantly associated with worse 1-year survival, rates of chronic graft-versus-host disease, creatinine, forced expiratory volume in 1 min, cardiac shortening fraction, or performance status, compared with non-intensive support [238]. Intensive therapies including high-frequency oscillatory ventilation and ECLS have been reported in pediatric as well as adult HSCT recipients, with mixed results [239–241].

Amongst HSCT children admitted to the PICU, as many as 73–88% have pulmonary complications [242]. PICU mortality in pediatric allogeneic HSCT recipients with acute respiratory failure requiring mechanical ventilation is 60.4% [241]. In a cohort of 222 pediatric HSCT recipients from 12 PICUs in the USA, non-invasive ventilation use prior to intubation and delayed high-frequency oscillatory ventilation in those who transitioned from conventional mechanical ventilation to the latter were associated with increased odds of death [241]. The

conclusion drawn by the investigators was that earlier and more aggressive interventions in pediatric HSCT recipients admitted to the PICU with acute respiratory failure may be warranted and potentially offer an opportunity to improve outcomes [241]. In this same cohort of pediatric HSCT patients, a secondary analysis revealed that 91.5% met the criteria for pediatric ARDS based on the PALICC definition (11% mild, 28% moderate, and 61% severe), during the first week of mechanical ventilation [242]. The degree of severity of pediatric ARDS was associated with mortality, as was the median maximum oxygenation index [242].

Sickle cell disease

The most common hemoglobinopathy treated in the PICU is sickle cell disease (Hb SS) followed by sickle cell trait (Hb SC). Historically associated with significant morbidity and mortality, sickle cell disease was once considered a pediatric disease; however, with medical advancements, children with sickle cell disease are now expected to live through young adulthood [243–245]. As mortality has decreased in these children, the primary focus has shifted to improvements in quality of life and decreases in the major causes of morbidity, particularly vaso-occlusive pain, acute chest syndrome, stroke, sepsis, priapism, sudden deafness, and acute anemia, particularly from aplastic crisis and splenic sequestration. The clinical manifestations of Hb SS range from asymptomatic to multiple potentially fatal complications, creating the need for individualized patient treatment plans based on general evidence-based guidelines [246,247].

Preventive treatments

The only proven curative treatment for sickle cell disease is hematopoietic stem cell transplant [248,249]. Preventive measures are the hallmark for the management of both acute and chronic manifestations of sickle cell disease. Due to functional asplenia, upon diagnosis, all infants are provided daily penicillin prophylaxis and when age appropriate are given meningococcal and pneumococcal vaccines, in addition to routine childhood immunizations for added protection against encapsulated bacteria. Stroke prevention with daily hydroxyurea and chronic blood transfusions monitored with transcranial Doppler changes have resulted in a significant reduction of cerebral infarcts and improved quality of life [250]. However, chronic, monthly blood transfusions are not without potential sequelae, most notably iron overload, alloimmunization, and transfusion reactions. Frequent use of incentive spirometry, optimizing pain control, and generous hydration are supportive measures used to prevent acute chest syndrome in children hospitalized with vaso-occlusive pain [251,252].

Acute treatments

Acute manifestations of sickle cell disease are managed by treating the associated symptoms. For example, pain crises are treated with hydration, warm packs, and analgesics ranging from non-steroidal anti-inflammatory drugs to opioids. In splenic sequestration, severe, acute anemia is a life-threatening symptom, and is thus treated with blood product transfusions and possible splenectomy. Acutely, a stroke is treated as it would be in any non-sickle cell disease patient, with the addition of providing urgent exchange blood transfusions rapidly decreasing the Hb S concentration to <30% for the remaining HbSS red blood cells. Serious bacterial infections are treated per standard of care, with the addition of avoiding glucocorticoids if possible, and carefully considering the increased hemorrhagic risks due to Hb SS.

Acute chest syndrome

The presentation, natural course, etiology, and mortality rate of acute chest syndrome are highly variable and differ considerably with age. Most importantly, acute chest syndrome in young children rarely results in death (<1% of episodes); whereas, in adults, about 9% of all episodes result in death [253]. Children are far more likely to present with a fever and cough, possibly a normal physical exam, and initially no distinct infiltrate on chest radiograph [254]. The most likely cause of acute chest in children is infection [253].

Treatment of acute chest syndrome typically includes supportive measures with broad-spectrum antibiotics effective against *Streptococcus pneumoniae*; a macrolide should be started for possible treatment of *Chlamydia pneumoniae* or *Mycoplasma pneumoniae* [255]. Efforts are made to increase oxygen-carrying capacity with incentive spirometry, supplemental oxygen, non-invasive (BiPAP) and invasive positive pressure (intubation), and simple and/or exchange blood transfusions. A simple transfusion will be given to raise the hemoglobin concentration up to approximately 10 g/dL if the patient's current Hb level is <9 g/dL [256]. If the current Hb is ≥9 g/dL, an exchange transfusion is given to prevent an increase concentration to higher than 10 g/dL while reducing the Hb S concentration to <30% [256]. Common risks associated with exchange transfusion in the setting of acute chest syndrome are posterior reversible encephalopathy syndrome, alloimmunization, stroke, and iatrogenic complications associated with arterial and central line placement. Other respiratory support measures such as BiPAP devices might be started, but these do not replace the use of blood transfusion therapy. If pain is associated with acute chest syndrome, analgesics are provided to remove the associated reduction in ventilation.

KEY POINTS: HEMATOLOGY/ONCOLOGY

- Children with cancer can become critically ill from sepsis, neurological emergencies, coagulopathy, chemotherapy toxicity, cytokine release syndrome, and airway/respiratory compromise
- Stem cell transplantation patients admitted to the ICU with respiratory compromise, sepsis, hemodynamic compromise, or neurological change have significantly high morbidity and mortality
- Supportive measures for acute chest syndrome in sickle cell disease include antibiotics and chest physiotherapy, oxygen including non-invasive ventilation, pain control, and simple or exchange transfusion

Transfusion therapy

Blood product transfusion is a common practice for many patients in the PICU. For RBCs, the estimated incidence rate is 304 transfusion per 1000 PICU admissions [257]. Transfusions of blood products are an essential, life-saving component of critical care. However, transfusion is an independent variable for morbidity and mortality in PICU patients, and this finding has led to significant modifications of transfusion practices over the last 10 years [257–261]. There is increasing evidence that a restrictive RBC transfusion strategy is beneficial in PICU patients [45,262–265]. Furthermore, there is limited evidence on the transfusion practices for other blood products.

The balance between the benefits and the potential for harm must be evaluated for each PICU patient. This balance is rarely static and can change from minute to minute. Further complicating this process is the wide variety of patients and physiology found in the PICU environment. Cyanotic congenital heart patients may have different needs to those with traumatic brain injury. Many PICUs care for these patients in the same location and the variability in transfusion practices can lead to confusion for both primary providers and consultants.

Red blood cell transfusion

Anemia in the pediatric critical care patient can occur for many reasons including bleeding due to trauma or surgery, frequent blood draws, hemolysis, or coagulopathy. Anemia is a common finding in the PICU and is seen in 74% of patients during their PICU stay [266]. The easiest method to treat anemia is to transfuse RBCs, but there are many risks with transfusion including infection and non-infectious serious hazards of transfusion such as hemolysis, transfusion-associated circulatory overload, transfusion-associated lung injury, and transfusion-related immune modulation among many others [267]. There has been an increase in studies, including randomized prospective trials, attempting to answer the question of the optimal threshold to transfuse in a critically ill patient.

The landmark TRIPICU study [45] evolved from the adult Transfusion Requirements in Critical Care (TRICC) trial published in 1999 [268]. The study came to the relatively simple conclusion that using a Hb threshold of 7 g/dL for RBC transfusion can decrease transfusion requirements, without increasing adverse outcomes in the hemodynamically stable critically ill child [45]. The concept of a restrictive transfusion strategy first proposed after the TRICC trial has become pervasive no matter what type of ICU the patient is in.

Cardiac surgical patients represent a unique patient population and were not included in many of the initial studies and trials on PICU transfusions. Cyanotic patients in particular were excluded from enrollment due to their physiological need for higher Hb for oxygen delivery. Many prospective trials have been published in the last few years that have addressed this concern, and have suggested that a restrictive transfusion strategy with Hb thresholds adapted to the cardiac physiology decreases the number of transfusions, donor exposures, and potential risks [264,265,269].

Plasma and cryoprecipitate

There is limited evidence on the use of plasma and pooled or recombinant coagulation factors in the pediatric critically ill population. Plasma had been used as a volume expander in many disease states, in exchange transfusions, disseminated intravascular coagulation, and to correct coagulation factor deficiencies. However, there is limited evidence to support its use in many of these conditions [270]. Evidence-based practice guidelines for plasma transfusion developed by the American Association of Blood Banks recommend that plasma be transfused for a limited number of indications: trauma patients requiring massive transfusion and warfarin anticoagulation-related intracranial hemorrhage [271].

The evidence for cryoprecipitate is even further lacking as there are no clinical studies that evaluate its use in critically ill children. Cryoprecipitate contains an enriched proportion of factor VIII, von Willebrand factor (vWF), factor XIII, and fibrinogen. Therefore, its use is limited to procedures and bleeding due to a lack of these specific factors.

Platelets

Platelets are transfused in the PICU for two general reasons, as prophylaxis or as treatment for ongoing blood loss. The data for prophylactic transfusion come primarily from patients with oncological diseases to prevent the risk of spontaneous bleeding [272]. The threshold for prophylactic platelet transfusions is now considered to be 10,000 cells/mm^3. The risk of spontaneous bleeding is thought to be higher in children compared with adults [272]. Generally recommended goals for platelet counts are >50,000 cells/mm^3 for certain surgical procedures and bleeding, and between 75,000 and 100,000 cells/mm^3 for neurological surgery and ECMO [273–275].

Current transfusion practices in the PICU

General dosing recommendations for blood products are presented in Table 42.11. Recently, there has been a push for goal directed transfusion practice given the lack of evidence for indications for blood product administration in the PICU. This transition is more than just the use of laboratory numbers but functional studies using thromboelastography (TEG) and thomboelastometry. Both of these methods use measurements of clot strength and formation to evaluate the potential causes of bleeding. A recent study showed a change in treatment plan in 47% of the cases in which TEG was used [276]. These tests have become routine for surgical cases that have

Table 42.11 Blood component therapy

Product	Dose	Comments
Red blood cells	10 mL/kg	Raises hemoglobin 2–3 g/dL
Random donor platelets	1 unit/10 kg or 5–10 mL/kg	Pooled units from multiple donors
Apheresis platelets	10 mL/kg	Donation from a single individual
Fresh frozen plasma	10–15 mL/kg	Will provide 20–30% of coagulation factors, often resulting in normal clotting
Cryoprecipitate	1 unit/10 kg	Contains a significant amount of fibrinogen (60–80 mg/dL)

significant bleeding risks (e.g. neonatal cardiac surgery, liver transplants) and there may be an increase in utilization in the future in the PICU too.

Use of massive transfusion protocols is another concept that has moved from the operating room to the PICU. Generally those treated under these protocols are trauma patients but they can also be patients who have massive amounts of bleeding from surgical procedures. Many of these patients transition to and from the emergency room, operating room, and PICU. The current studies on massive transfusion protocols are primarily about implementation and policies and more studies will have to be conducted before such protocols become widely implemented [277–279]. It is generally accepted that platelets, plasma, and RBCs should be administered in 1:1:1 or 1:1:2 ratios [280], but prospective, randomized controlled trials in children do not exist at this time.

Coagulopathy in the critically ill child

Coagulopathy is defined as an impairment in the ability of blood to form clots. While many children admitted to the PICU may have an impairment based on laboratory findings, few actually have any active bleeding because of it. There are many reasons for a child to have bleeding in the PICU, but there are only a few where the primary cause is a true coagulopathy.

Disseminated intravascular coagulation

The human body is in a perpetual state of balance between the systems of coagulation and fibrinolysis. Disseminated intravascular coagulation (DIC) occurs when this homeostasis becomes unbalanced and thrombin formation occurs in multiple areas along the microvascular bed. Consumption of clotting factors and platelets ensues, leading to a coagulopathic state with a high likelihood of bleeding [281]. The most common inciting causes of DIC in children are sepsis, liver disease, and trauma [282,283]. Regardless of the cause, DIC is associated with mortality as high as 56%, and as high as 66% when combined with MODS [284].

There is no single test that has high specificity and sensitivity for DIC. Therefore multiple laboratory tests are used in an attempt to make a diagnosis, including platelet count, fibrinogen, prothrombin time, fibrin degradation products, and D dimer (Table 42.12) [282]. DIC is managed by treating the underlying cause and providing supportive care for bleeding and coagulopathy via blood products, although there are no established goal values for coagulation studies. Transfusion amounts and goals are usually based on the clinical status of the patient and can vary depending on the underlying cause of the DIC.

Table 42.12 Laboratory tests for the diagnosis of disseminated intravascular coagulation

Test	Discriminator value
Platelet count	<80,000–100,000 or a decrease of >50% from baseline
Fibrinogen	<100 mg/dL or a decrease of >50% from baseline
Prothrombin time	>3 s prolongation more than upper limit of normal
Fibrin degradation products	>80 mg/dL
D dimer	Moderate increase

Source: Reproduced from Parker [333] with permission of Elsevier.

Liver disease

The liver is an integral organ system for the clotting cascade. The liver is the organ of synthesis for factors II, V, VII, IX, and X and fibrinogen. Acute and chronic liver disease can cause these derangements and can lead to elevated prothrombin time, partial thromboplastin time, and INR. Derangements and likelihood of bleeding are two separate components, and there is no evidence that supports the administration of blood products for patients with liver dysfunction and associated coagulation laboratory derangement in the absence of active bleeding. When bleeding, some investigators have suggested using functional studies (e.g. TEG) as a means of assessing each component of the coagulation cascade because of the liver's unique role in clotting homeostasis [285].

Acquired factor deficiencies

Acquired coagulation factor deficiency is a relatively rare but potentially unique finding in the critical care environment. The most common of these deficiencies is vWF – a large glycoprotein that promotes platelet adhesion to each other and to vessel walls at sites of injury. Acquired vWF deficiency in the PICU population is caused by shear stress usually due to ventricular assist or ECMO devices. However, vWF deficiency can also be seen in pediatric patients with valvular abnormalities [286]. Some studies have suggested the majority of patients on ventricular assist device or ECMO support have some component of vWF deficiency [287]. Typical coagulation tests including functional studies do not diagnose this disorder; diagnosis requires multimer analysis. Administration of vWF concentrate requires further studies of safety and efficacy.

Thrombosis

Thrombosis has become an increasing concern in the PICU and is associated with increased morbidity and cost [288–290]. There is little consistency in the use and type of thromboprophylaxis, which may be complicated by the difficulty in creating a valid risk assessment tool [288,291]. The most common pharmacological agents used are aspirin, clopidogrel, unfractionated heparin, low molecular weight heparin (LMWH), and warfarin. These drugs have different targets along the coagulation cascade and different therapies for reversal, potentially impacting patients who have long ICU stays and require multiple trips to and from the operating room.

Despite the increasing attention to thrombosis, a larger number of pediatric patients are being placed on long-term anticoagulation primarily due to catheter-related thrombi [292]. Generally, a risk–benefit analysis should be done before discontinuing long-term anticoagulation prior to surgery. Although not evidence based in pediatric patients, many practitioners suggest maintaining long-term anticoagulation

only if the bleeding risk of the surgery or procedure is high. Many would bridge the patient with LMWH or unfractionated heparin until the day of surgery, but practices vary from institution to institution. There also are no data on the timing of reinitiation of anticoagulation postoperatively, with a high degree of variability even in adult practice where the data are generally more robust [293].

KEY POINTS: TRANSFUSION THERAPY AND COAGULOPATHY IN THE CRITICALLY ILL CHILD

- Blood transfusion is common and life saving, but also an independent variable for morbidity and mortality in the PICU
- A restrictive RBC transfusion protocol targeting 7 g/dL for hemodynamically stable PICU patients can decrease transfusion requirements without adverse outcomes
- Plasma, cryoprecipitate, and platelet transfusions are reserved for specific deficiencies in coagulation components, postsurgical bleeding, and to maintain hemostasis in ECMO patients

Endocrine disease

Glycemic control

Both hypoglycemia and hyperglycemia are relatively common occurrences in the PICU and have been associated with unfavorable outcomes in critically ill children [294–296]. A randomized controlled trial of postoperative tight glycemic control versus standard care conducted in 980 children 0–26 months of age undergoing cardiac surgery at two centers, showed that glycemic control (with the use of an insulin-dosing algorithm targeting a blood glucose level of 80–110 mg/dL (4.4–6.1 mmol/L)) did not significantly change the infection rate, mortality, length of stay, or measures of organ failure compared with standard care [297]. A secondary analysis of this trial showed that tight glycemic control did not impact neurodevelopmental outcomes compared with standard care, but suggested a possible association between moderate to severe hypoglycemia and poorer neurodevelopmental outcomes at 1 year [298]. A more recent randomized controlled trial involving 35 PICUs randomized 713 critically ill children who had not undergone cardiac surgery and who had confirmed hyperglycemia to a lower target glycemic control group (80–110 mg/dL or 4.4–6.1 mmol/L) or a higher target group (150–180 mg/dL or 8.3–10.0 mmol/L) [299]. There were no differences in the primary outcome of ICU-free days between the two arms, and increased rates of healthcare-associated infections and severe hypoglycemia, defined as a blood glucose level below 40 mg/dL (2.2 mmol/L), were observed in the lower target group [299]. The trial was stopped early due to a low likelihood of benefit and possibility of harm [299]. With these results in mind, clinicians should avoid hypoglycemia and treat hyperglycemia in critically ill children. As a cautionary note, data are currently lacking on the optimal blood glucose, duration of glucose control, and methodology (e.g. continuous glucose monitoring) to avoid harm due to hypoglycemia when insulin infusions are used in children.

Diabetic ketoacidosis

Type 1 diabetes mellitus affects approximately 200,000 children in the USA [300]. Children with diabetes remain at high risk for life-threatening complications including hypoglycemia and diabetic ketoacidosis (DKA), although mortality has declined significantly over the last four decades [300]. Multipronged interventions have been credited with this decline in mortality, including increased awareness and education on diabetes symptoms, early treatment, and management of DKA [300]. Increased utilization and advances in insulin pump technology may have also contributed to the decline in rates of acute diabetes complications [301]. In a population-based multi-country cohort study conducted in 30,579 children from 2011 to 2015, insulin pump therapy, compared with insulin injection therapy, was associated with lower risks of severe hypoglycemia and DKA, and with better glycemic control [301].

DKA diagnosis is based on clinical and biochemical criteria. Clinical signs of DKA include dehydration, tachycardia, tachypnea, Kussmaul respirations, nausea, vomiting, abdominal pain, confusion, drowsiness, and eventually loss of consciousness [302]. Biochemical criteria include hyperglycemia (blood glucose >11 mmol/L (~200 mg/dL)), venous pH <7.3 or bicarbonate <15 mmol/L, ketonemia, and ketonuria [302].

DKA is the result of absolute insulin deficiency or stress, infection, or insufficient insulin intake, with high circulatory levels of counter-regulatory hormones such as glucagon, cortisol, cathecolamines, and growth hormone, which in turn lead to increased lipolysis, decreased glucose utilization and increased glycogenolysis, increased proteolysis and decreased protein synthesis, with a cascade of consequences as displayed in Figure 42.17 [302].

Management of DKA needs to be prompt yet deliberate. The goals of therapy are to provide initial stabilization based on pediatric advanced life support guidelines, to treat dehydration, correct acidosis, and reverse ketosis, to slowly restore osmolarity and blood glucose to near normal, to monitor for complications of DKA and its treatment, and to diagnose and treat the inciting cause [302]. Laboratory evaluation includes blood glucose, blood gases, blood or urine ketones, serum electrolytes, and complete blood count. These are repeated serially to guide therapy. Dehydration is corrected with volume expansion using isotonic fluids, if peripheral circulation is compromised, followed by continuous fluid replacement at a rate calculated to correct the fluid deficit evenly over 48 h [302]. Dextrose is generally added to intravenous fluids when blood glucose declines to 250–280 mg/dL. Insulin therapy via continuous intravenous infusion should be initiated after fluid replacement therapy has begun, at a rate of 0.05–0.1 U/kg/h. Potassium supplementation is deferred in patients who present with hyperkalemia, otherwise potassium is added to the intravenous fluids at a concentration of 20 or 40 mmol/L in patients receiving fluids at rates >10 mL/kg/h [302] and after urine output is documented. Phosphate correction may be needed in case of hypophosphatemia. Bicarbonate is not recommended outside of acute therapy for hyperkalemia.

Providers should pay utmost attention to signs and symptoms of cerebral edema, a severe, multifactorial complication of DKA and its therapy. Clinically apparent cerebral edema occurs in 0.5–0.9% of children with diabetes and has a mortality rate of 21–24% [302]. Cerebral edema manifests by

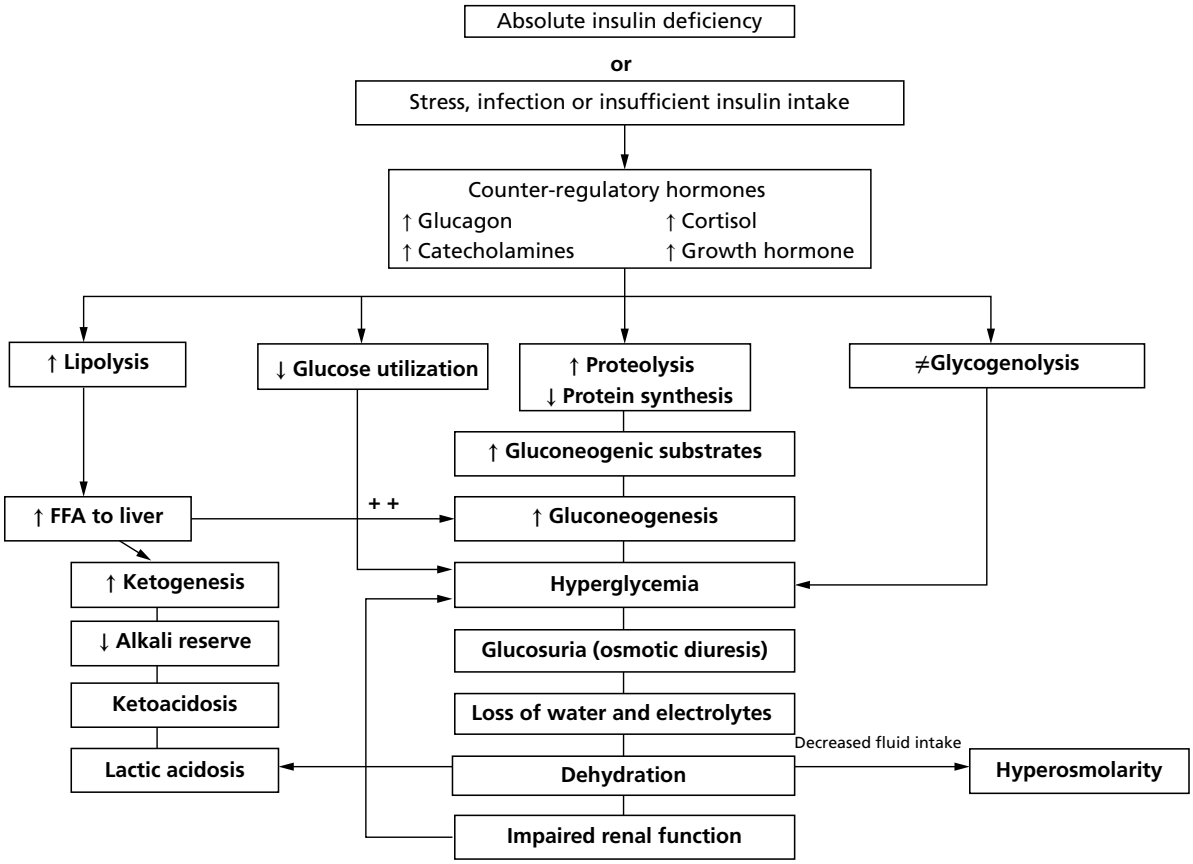


Figure 42.17 Pathophysiology of diabetic ketoacidosis. FFA, free fatty acids. *Source*: Reproduced from Wolfsdorf et al [339] with permission of American Diabetes Association.

headache, decline in mental status (restlessness, irritability, drowsiness, incontinence) and changes in neurological exam (cranial nerve palsies), bradycardia, hypertension, and respiratory depression [302,303]. Prompt intervention with mannitol or hypertonic saline is recommended for acute deterioration in neurological status [214]. Impending uncal herniation should be treated with standard measures (hyperosmolar therapy, head of bed elevated at 30°, endotracheal intubation, and mechanical ventilation). A brain CT may be obtained, only after acute stabilization [302,304], to determine degree of edema and to investigate if other acute intracranial pathology is present (e.g. intracranial hemorrhage, stroke, venous sinus thrombosis). The pathogenesis and risk factors for cerebral edema are still subject to debate, and include disruption of the blood–brain barrier, regional differences in cerebral perfusion with hyperemia in some brain regions coexisting with hypoperfusion of others (specifically the brainstem), as well as a rapid decrease in osmolarity leading to fluid shifts, as a side-effect of DKA treatment [302,303].

Inciting events for DKA, including viral and bacterial infections, should be investigated (e.g. respiratory viral testing, blood, urine, or throat cultures) and treated (e.g. antibiotics if bacterial infection is suspected).

Adrenal dysfunction

During critical illness, dysregulation of the hypothalamic–pituitary–adrenal axis, altered cortisol metabolism, and tissue resistance to glucocorticoids contribute to the development of critical illness-related corticosteroid insufficiency (CIRCI) [305]. Pathophysiological mechanisms of CIRCI are presented in Table 42.13 [305].

CIRCI has been described in a variety of disease entities, including sepsis, ARDS, trauma, burns, and major surgery [306]. CIRCI can develop at any point during critical illness, and therefore clinicians are encouraged to remain vigilant throughout a patient's hospitalization in recognizing its signs and symptoms (Table 42.14) [307]. There is no consensus on the optimal diagnostic test for CIRCI [307]. A random plasma cortisol concentration of <10 μg/dL can be used to diagnose CIRCI, as can a total cortisol level response of <9 μg/L from baseline to 60 min after administration of 250 μg of adrenocorticotropic hormone.

In adults, current evidence-based recommendations are to use corticosteroids in patients with septic shock that is not responsive to fluid and moderate- to high-dose vasopressor therapy, and in early moderate to severe ARDS, and to not use corticosteroids in hospitalized adult patients with major trauma and sepsis without shock [307]. Studies of corticosteroid therapy in critically ill children are not conclusive, and some observational studies have suggested no benefit or potential harm [308]. For children, guidelines for corticosteroid therapy have been developed only for septic shock: "if a child is at risk of absolute adrenal insufficiency or adrenal pituitary axis failure (e.g. purpura fulminans, congenital adrenal hyperplasia, prior steroid exposure, hypothalamic/pituitary abnormality, intubation with etomidate induction) and remains in shock despite epinephrine or norepinephrine

Table 42.13 Main pathophysiological mechanisms of critical illness-related corticosteroid insufficiency (CIRCI)

General defect	Main mechanisms	Key factors
Decrease in cortisol production		
Altered adrenal synthesis of cortisol	Necrosis/hemorrhage	Acute kidney failure
		Hypocoagulation
		Disseminated intravascular coagulation
		Cardiovascular collapse
		Tyrosine kinase inhibitors
	Decreased availability of esterified cholesterol	Depletion in adrenal storage regulated by annexin A1-formyl peptide receptors
		Downregulated scavenger receptor B1
	Inhibition of steroidogenesis	Immune cells/Toll-like receptors/cytokines
		Drugs (e.g. sedatives, corticosteroids)
		ACTH-like molecules (e.g. corticostatins)
Altered synthesis of CRH/ACTH	Necrosis/hemorrhage	Cardiovascular collapse
		Disseminated intravascular coagulation
		Treatment with vasopressor agents
	Inhibition of ACTH synthesis	Glial cells/nitric oxide-mediated neuronal apoptosis
		Increased negative feedback from circulating cortisol following upregulation of ACTH-independent mechanisms of cortisol synthesis
		Drugs (e.g., sedatives, anti-infective, psychoactive agents)
		Innapropriate cessation of glucocorticoid treatment
Alteration of cortisol metabolism	Decreased cortisol transport	Downregulation of liver synthesis of cortisol-binding globulins and albumin
	Reduced cortisol breakdown	Decreased expression and activity of the glucocorticoid-inactivating 5-reductase enzymes in the liver with putative role of bile acids
		Decreased expression and activity of hydroxysteroid dehydrogenase in the kidney
Target tissue resistance to cortisol	Inadequate GR-α activity	Multifactorial etiology including reduced GR-α density and transcription and excessive NFκB activation

ACTH, adrenocorticotropic hormone; CRH, corticotrophin-releasing hormone; GR-α, glucocorticoid receptor α; NFκB, nuclear factor κ B.
Source: Reproduced from Annane et al [305] with permission of Springer Nature.

Table 42.14 Signs and symptoms of critical illness-related corticosteroid insufficiency (CIRCI)

General	Fever, asthenia
Neurological	Confusion
	Delirium
	Coma
Cardiovascular	Hypotension refractory to fluid resuscitation
	Decreased sensitivity to cathecolamines
	High cardiac index
Digestive	Nausea
	Vomiting
	Intolerance to enteral nutrition
Respiratory	Persistent hypoxia
Laboratory	Hypoglycemia
	Hyponatremia
	Hyperkalemia
	Metabolic acidosis
	Hypereosinophilia
Imaging	Hemorrhage or necrosis in hypothalamus, pituitary gland, or adrenal gland

Source: Reproduced from Annane et al [305] with permission of Springer Nature.

infusion, then hydrocortisone can be administered ideally after attaining a blood sample for subsequent determination of baseline cortisol concentration" [82]. Stress dose hydrocortisone is 50–100 mg/m²/day and can be continued and then tapered over 5–14 days with assistance from endocrinology consultation.

KEY POINTS: ENDOCRINE DISEASE

- Tight glucose control regimens in the PICU do not improve outcomes and hypoglycemia can cause harm; clinicians should avoid hypoglycemia and treat hyperglycemia
- DKA is treated by addressing shock, giving insulin infusion to reduce serum glucose, adding potassium in most patients, and being vigilant for cerebral edema
- Adrenal insufficiency can be a cause of catecholamine-resistant hypotension in shock states; stress dose hydrocortisone can be given

Gastroenterology and nutrition

The response to critical illness is characterized by increased protein breakdown and glucose and lipid intolerance, leading to a catabolic state with loss of lean body mass. Nutritional support in the PICU revolves around providing an adequate supply of nutrients that is balanced and adapted to the patient's needs.

Nutrition practices in critically ill children have been highly variable. In a worldwide survey disseminated to members of the World Federation of Pediatric Intensive and Critical Care Societies, with 189 respondents from 156 PICUs in 52

countries, nutritional protocols were available in 52%, and nutritional support teams were available in 57%, of the PICUs, respectively [309]. Important differences were found in macronutrient goals, equations used to estimate energy requirements, timing of nutrition initiation, and thresholds for supplemental parenteral nutrition [309].

In general, perceived barriers to initiation of nutrition are ongoing fluid resuscitation and need for frequent correction of electrolyte abnormalities. Safety concerns related to the use of vasoactive infusions have also impeded early initiation of enteral nutrition, although two single-center studies published in 2004 ($n = 52$) and 2016 ($n = 339$) suggested that enteral nutrition in children on continuous vasoactive infusions is not associated with adverse events and may be associated with improved survival [310,311].

Best practice recommendations for nutrition therapy in critically ill children were published in 2017, as a collaboration between the American Society for Parenteral and Enteral Nutrition and the Society for Critical Care Medicine [312]. The recommendations provide guidance on establishing a baseline nutrition status, and on the timing, type, and amount of nutrients to be provided to critically ill children [312]. It is recommended that PICU patients undergo detailed nutrition assessment within 48 h of admission, based on observational studies suggesting that malnutrition is associated with worse clinical outcomes, including higher risk of hospital-acquired infections, longer duration of ventilation, longer PICU and hospital stay, and increased mortality [312].

Resting energy expenditure, or the caloric requirement during a non-active 24 h period, increases during critical illness. Clinical guidelines recommend the use of indirect calorimetry to measure energy expenditure and guide prescription of the daily energy goal [312]. Indirect calorimetry in the PICU, however, can be technically difficult in children who are intubated, have temperature instability, or varying degrees of sedation and movement. When indirect calorimetry is not feasible, energy expenditure can be estimated using the Schofield or Food Agriculture Organization/World Health Organization/United Nations University equations, without the addition of stress factors [312].

Delivery of at least two-thirds of the prescribed daily energy requirement should be achieved by the end of the first week of PICU admission. Protein intake should be at least 1.5 g/kg/day, as higher protein intake has been shown to prevent cumulative negative protein balance. Infants and young children may require a much higher protein intake in order to achieve a positive protein balance. A negative protein balance can lead to loss of lean muscle mass, which is a poor outcome predictor in critically ill patients [312].

In recent years, mounting evidence suggests that early enteral nutrition is associated with improved outcomes, at least in part by reducing complications related to parenteral nutrition [313,314]. In a seminal multicenter, randomized controlled trial conducted in 1440 critically ill children, late parenteral nutrition (initiated 1 week after PICU admission) was compared with early parenteral nutrition [314]. Enteral nutrition was attempted early and intravenous micronutrients were provided in both groups. Mortality (not a primary end point) was similar in the two groups, but, compared with children randomized to early parenteral nutrition, children randomized to late parenteral nutrition had significantly lower new infection rates, shorter duration of ICU stay, and higher likelihood of an earlier live discharge from the ICU [314]. In addition, children in the late parenteral nutrition group had shorter duration of mechanical ventilation, a smaller proportion receiving renal replacement therapy, a shorter length of hospital stay, lower γ-glutamyltransferase and alkaline phosphatase plasma concentrations, and higher bilirubin and C-reactive protein plasma concentrations [314].

Based on the data presented above as well as other studies not detailed here, current clinical practice recommendations are to use enteral nutrition as the preferred mode of nutrient delivery to the critically ill child. Enteral nutrition should be initiated early (i.e. within 24–48 h of PICU admission), and follow a stepwise algorithm with criteria for: (1) eligibility for enteral nutrition; (2) timing of initiation of enteral nutrition; (3) detection and management of intolerance of enteral nutrition; and (4) the optimal rate of increase in enteral nutrition [314]. The gastric route for delivery of enteral nutrition is preferred over the transpyloric route, except for patients at high risk for aspiration and patients who do not tolerate gastric feeding [314].

Liver failure and extracorporeal liver support

Liver dysfunction is very common in the PICU and is multifactorial. Shock states, including from sepsis, cardiogenic causes, and postresuscitation hepatic injury, are some frequent etiologies. Hepatic failure may result in hepatorenal syndrome and hepatic encephalopathy. The etiologies and pathophysiology of end-stage liver disease and extracorporeal liver support ("hepatic dialysis") are discussed in Chapter 30.

Pancreatitis

Acute pancreatitis can be associated with a variety of critical illnesses, and although the mortality rate in children, unlike adults, is low, this condition can complicate and prolong ICU stay. In a very large, retrospective, multicenter cohort study of over 360,000 PICU admissions from 2009 to 2013, 2076 discharges (0.58%) had a diagnosis of acute pancreatitis [315]. Of these 16% were a primary diagnosis, and 84% a secondary diagnosis. The most common diagnoses associated with secondary acute pancreatitis were bacterial infections/sepsis, hypotension, seizure disorders, pneumonia/ARDS/acute lung injury, and trauma, accounting for over 50% of cases. Mortality in primary acute pancreatitis was 0.3%, and for patients with the secondary condition was 6.8%. Treatment of the primary condition, along with bowel rest and adequate parenteral nutrition, is usually effective.

Immunity and infection

Immune dysfunction in the critically ill child

Immune dysfunction is common in the PICU. Children may present with life-threatening infections due to primary immunodeficiency, have secondary immunodeficiency due to their medical condition or therapy, or have immunoparalysis associated with critical illness.

The incidence of primary immune disease is one in 2000 children aged less than 18 years [316]. Primary immune disorders are classified as antibody deficiency (B-cell disease) T-cell dysfunction, combined T- and B-cell disease, and phagocytic or complement disorders. Children with primary immunodeficiency present with recurrent infections with typical organisms or serious infections with rare organisms. When an immune disorder is known or suspected, antibiotic choices and other therapy can be tailored appropriately. Consultation with infectious disease expertise is often required to select empirical or treatment antibiotics for patients with primary immunodeficiency.

Secondary immune dysfunction is more common in the PICU and can be due to multiple causes. Patients are often immunosuppressed due to medical therapies such as during the treatment of oncological disease, immunosuppression for transplantation, cardiopulmonary bypass, or long-term steroid use. Diseases such as human immunodeficiency virus may also cause secondary immunodeficiency. Infection in this group of patients can be serious, and careful consideration of empirical antibiotic choice is indicated.

Another form of secondary immunodeficiency specific to the PICU is immunoparalysis associated with critical illness. The proinflammatory surge that accompanies critical illness is balanced by an anti-inflammatory response. When the anti-inflammatory response is out of proportion or prolonged, it can cause immunosuppression that has been termed "immunoparalysis." The degree of immunoparalysis is identifiable by blood laboratory tests. Immunoparalysis is typically treated by stimulation of the immune response and stopping any present immune-modulating therapies. Decision making regarding antibiotic coverage and immune-modulating therapies in this patient population is complex, and consultation is recommended [317].

Bacterial resistance and empirical antibiotics

The PICU population has a high rate of antibiotic-resistant bacterial colonization due to the large number of patients with multiple medical problems and medical care exposures. Vancomycin-resistant enterococcus colonization in the PICU population has been found to be as high as 5% [318]. Similarly, methicillin-resistant *Staphylococcus aureus* (MRSA) colonization has been reported in 4–10% of PICU patients. The rate of colonization with MRSA increases with previous hospitalization and family members who work in medicine [319,320].

Because of organ dysfunction, reliance on life-saving equipment and prevalent hemodynamic instability, concern for infection in PICU patients is common. Infection or sepsis can be a primary problem or secondary to critical illness or PICU interventions. Empirical antibiotic treatment is common, and antibiotic selection can be challenging. Factors that should be considered in empirical antibiotic treatment are: location of suspected infection, immune status of the host, degree of symptoms such as hemodynamic instability, previous bacterial culture sensitivities, and antibiotic exposure and colonization. Many PICUs have developed antibiotic stewardship programs to improve empirical antibiotic selection and treatment plans. Protocolized antibiotic selection, electronic medical record risk stratification, and antibiotic stewardship programs have been associated with improved antibiotic selection and time to treatment, decreased antibiotic duration, and reduced risk of bacterial resistance [321,322]. When caring for a PICU patient in the OR, discussion of current antibiotics and recommended empirical coverage with the intensivist may be helpful.

Transport of the critically ill pediatric patient

Anesthesiologists have expertise in the transport of patients and recognize the significant risks in moving critically ill patients. Monitoring and medication delivery can be less reliable than in stationary patients and risk of dislodging or disrupting life-sustaining therapy is present. In single-center studies, intrahospital transport of PICU patients, to and from the OR, procedure, or imaging area, has been associated with significant untoward event rates: change in hemodynamic parameters requiring treatment (13.9%), equipment-related adverse events (10%), urgent intubation (5%), loss of endotracheal tube (3.75%) or central line (3.75%), or cardiopulmonary resuscitation (7.5%) [323,324]. Preplanning, anticipation of potential problems, ensuring patient optimization prior to transport, and adequate staff are key to managing the risk and resultant untoward events associated with intrahospital transport.

Interhospital transport (typically from referring hospital to pediatric subspecialty service-associated hospital) is common in pediatric critically ill patients due to the centralization of subspecialty care for children. Pediatric subspecialty critically ill transport is a large practice with consensus statements on accreditation, medical direction, team composition, research, and economics [325,326]. Pediatric subspecialty teams bring critical care skill and expertise to the bedside of pediatric patients; patient transport with a pediatric subspecialty team is associated with less unplanned events than transport with non-pediatric specialty teams [327]. Anesthesiologists may interact with pediatric transport teams during interfacility transport when a pediatric patient needs urgent surgical intervention, sometimes being transferred directly into the OR. Similarly, an anesthesiologist at a non-pediatric subspecialty center may initiate interfacility patient transfer directly from the OR to a referral center when the patient condition or needs exceed resources available locally.

PICU outcomes

Survival following PICU admission has improved significantly over the last decades, with recent reports of 98% survival to PICU discharge and 97.6% survival to hospital discharge [328]. Of critically ill children requiring PICU admission, 4.8% suffer new morbidity, 3.4% acquire global cognitive disability, and 10.3% acquire global functional disability by Pediatric Cerebral Performance Category and by Pediatric Overall Performance Category at hospital discharge [328,329]. Intervention risk factors for acquiring cognitive and functional disability include mechanical ventilation, RRT, cardiopulmonary resuscitation, and ECMO [329]. Longer length of PICU stay is also associated with unfavorable neurofunctional outcomes [330].

KEY POINTS: GASTROENTEROLOGY AND NUTRITION, IMMUNITY AND INFECTION, AND OUTCOMES

- At least two-thirds of energy requirements, and adequate protein intake, should be met by the first week of admission, via enteral or parenteral nutrition
- Imuunoparalysis of critical illness and bacterial resistance from empirical antibiotic coverage are important causes of infection
- PICU survival has improved significantly, with 97–98% survival to hospital discharge; however, about 10% acquire a global functional disability

CASE STUDY

A 6-year-old, 20 kg girl with a history of severe bronchial asthma treated with daily inhaled β-agonists, inhaled corticosteroids, and montekulast was admitted to the PICU from the emergency department. She had a severe asthma exacerbation after an upper respiratory infection consisting of inspiratory/expiratory wheezing with poor air movement, severe retractions, hyperinflation on chest radiograph, and mild cyanosis with SpO_2 85% in room air, improving to 90% with non-rebreathing O_2 facemask at 10 L/min flow [331].

Rapid testing of nasal secretions revealed the presence of parainfluenza virus antigens. After inhaled β-agonist treatments, IV corticosteroids, and IV magnesium sulfate there was little improvement, and she was started on nasal BiPAP mask, with 100% oxygen, and pressure settings of 12/6 cmH_2O. A radial arterial line was placed, and arterial blood gas (ABG) on this therapy was pH 7.15, $PaCO_2$ 90 mmHg, and PaO_2 65 mmHg. Continuous albuterol inhalation was started, but her condition worsened over the next 4 h, with increasing use of accessory muscles, and tiring to the point that respiratory arrest was imminent. After preoxygenation by facemask with FiO_2 1.0, ketamine 2 mg/kg IV, and rocuronium 25 mg, her trachea was orally intubated with a 4.5 mm cuffed endotracheal tube (ETT). After intubation, chest radiograph revealed the ETT in midtrachea, and severe hyperinflation with areas of atelectasis in the right lower and left upper lobes, without pneumothorax or pneumomediastinum. Continuous albuterol, IV corticosteroids, and IV magnesium were continued, but gas exchange continued to worsen, with ABG pH 7.05, $PaCO_2$ 105 mmHg, and PaO_2 50 mmHg 4 h after intubation, on pressure control ventilation with peak inspiratory pressure (PIP) 38 cmH_2O, positive end-expiratory pressure (PEEP) 10 cmH_2O, I:E ratio of 1:4, and respiratory rate of 20 on FiO_2 1.0. Capnography tracing revealed a sharp upslope during expiration, and flow–volume loops indicated severe expiratory obstruction with an exhaled tidal volume of only 65 mL (3.25 mL/kg). Heart rate was 175 bpm, blood pressure 75/45 mmHg, and peripheral perfusion was abnormal with mottling and capillary refill time 3 s. A triple-lumen femoral central venous catheter was placed using ultrasound guidance, a fluid bolus of 20 mL/kg normal saline was administered, and low-dose epinephrine at 0.03 μg/kg/min was started, for inotropic support and bronchodilation. Ketamine, dexmedetomidine, and fentanyl infusions had been initiated for sedation. After a discussion among the ICU team about whether a course of volatile anesthetic agent treatment or venovenous ECMO was more appropriate, it was decided to consult with the anesthesia service and use inhaled sevoflurane [332].

Following the hospital's policy for inhaled volatile anesthetic agent treatment of asthma in the PICU, a late-generation anesthesia machine was brought to the PICU room, and respiratory gas and anesthetic gas scavenging lines were connected. Because the anesthesia machine ventilator was piston driven without a bellows, and had low internal deadspace and high driving pressures, initial settings matching the ICU ventilator were able to maintain the same gas exchange, albeit it was poor. Sevoflurane inhalation was stared at 0.5% inspired concentration, and increased over the next 2 h gradually to 3.5%. The continuous albuterol was gradually decreased and discontinued, as was the ketamine infusion. Blood pressure and heart rate were carefully monitored, and epinephrine gradually increased to 0.05 μg/kg/min to maintain systolic BP above 75 mmHg, and HR less than 180 bpm. The goal was to maintain end-tidal sevoflurane concentration at 3–3.5% for 4 h, and then decrease gradually if there was improvement in gas exchange and flow–volume loops. ABG was assessed every 30 min. $PaCO_2$ gradually decreased to 55 mmHg, PaO_2 increased to 205 mmHg, and pH improved to 7.30. End-tidal CO_2 waveform also improved and had only a slight upslope, and air exchange by auscultation also improved, with a decrease in inspiratory and expiratory wheezing. Finally, flow–volume loops improved, indicating much less expiratory obstruction, and exhaled tidal volumes increased to 140 mL (7 mL/kg) on a lower PIP of 30 cmH_2O. At the end of 4 h of steady-state sevoflurane, the volatile agent was gradually decreased over 2 h, then discontinued, with ongoing careful respiratory and hemodynamic monitoring, ensuring no deterioration of gas exchange and respiratory mechanics. Toward the end of the sevoflurane inhalation, continuous albuterol and ketamine infusion were restarted. The patient was transitioned to the ICU ventilator, and continued

to improve, with her trachea being extubated 48 h later. She was discharged from the ICU on the following day and home 3 days later.

This case demonstrates an approach to severe status asthmaticus with respiratory failure, use of multiple modalities to increase bronchodilation, and multidisciplinary decision making ultimately deciding on inhaled volatile anesthetic agent for treatment. Involvement of the pediatric anesthesiologist in ICU care, both for operative cases and in medical cases, is a major responsibility, and collaborative communication and planning with the ICU physicians facilitates patient care.

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A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 43

Anesthesia for the Patient with a Genetic Syndrome

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General approach to patients with a genetic syndrome

A syndrome is the occurrence of more than one recognizable phenotypic trait that occurs together in a specific association, with a cause that is thought to be from a specific genetic defect. A geneticist or dysmorphologist is usually able to determine a diagnosis from the phenotype of the patient, but as the science of molecular genetics advances, more of these syndromes have a known genetic cause and inheritance. It is presumed that many of those without a known cause will have their genetic bases determined in the near future. Definitive diagnosis of the more common genetic disorders is most often made from conventional karyotyping, chromosomal microarray, or fluorescence *in situ* hybridization (FISH), from peripheral blood lymphocytes. As newer genetic testing such as whole exome sequencing and whole genome sequencing becomes more clinically available because of lower cost, the precision of genetic diagnoses and the potential for "personalized medicine" is continuously improving [1,2]. Whole exome or genome sequencing has a diagnostic yield of 30–60% in infants and children in neonatal and pediatric critical care units, and may alter clinical care 50–70% of the time, with a turnaround time of several days to 2 weeks. It is likely that the clinical use of this approach will expand in the coming years [3].

An association is a constellation of several recognizable phenotypic traits, either without a known genetic cause, or with a variety of genetic causes. The distinction between a syndrome and an association is often not clear, and this chapter will use these terms interchangeably. The term "sequence" is also often used, as in "Pierre Robin sequence," but in modern terminology this term is also normally replaced with "syndrome." Because many of these children will require anesthesia or sedation for diagnostic or therapeutic procedures, the pediatric anesthesiologist will encounter patients with syndromes frequently, often almost on a daily basis. This chapter will first review the general approach to the patient with a genetic syndrome, and then review in more detail a few of the most common syndromes associated with challenges in anesthetic care. Finally, a listing of 120 syndromes associated with anesthetic management issues will be presented alphabetically (Appendix 43.1, see ebook).

Airway considerations

Management of the airway is always a central consideration for the pediatric anesthesiologist, and many patients with genetic syndromes have abnormal airways. Among the most common are syndromes with mandibular hypoplasia (see section "Micrognathia syndromes"), including Pierre Robin sequence, Treacher Collins syndrome, and Goldenhar syndrome (hemifacial microsomia). Other conditions include cleft lip and palate, high arched palate with small mouth opening, cervical vertebral fusion limiting neck movement, and soft tissue obstruction from macroglossia or other causes. A thorough preoperative history of airway problems, including snoring, airway obstruction during sleep, and acute life-threatening events is important to elicit. The history of previous anesthetics and tracheal intubations is crucial to understand, and whenever possible examination of previous anesthetic records, or speaking to the patient's previous anesthesiologist, otolaryngologist, or craniofacial surgeon is very important. Examination of the airway for mouth opening, and visualization of the pharynx and soft palate, as well as neck

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

range of motion, should be done carefully. Finally, any imaging studies such as chest, neck, and facial radiographs, computed tomography (CT) scans, or magnetic resonance imaging (MRI) scans should be reviewed. A management plan for the difficult airway should be developed. Details of difficult airway management are presented in Chapter 15. Details of anesthetic management for craniofacial surgery are presented in Chapter 35. Appendix 43.1 includes airway considerations for each of the syndromes listed.

Cardiac manifestations

A number of genetic syndromes have a cardiac component, and the importance of a thorough cardiac history and physical examination cannot be overemphasized. In the presence of an abnormal cardiac examination consisting most often of systolic and/or diastolic murmurs, the cardiac anatomy and pathophysiology must be understood, and any recent diagnostic studies such as echocardiography must be reviewed. In neonates without a cardiac diagnosis presenting for some types of surgery, e.g. a patient with VACTERL association (see later) presenting for tracheoesophageal fistula repair, cardiac consultation and echocardiography should be obtained if possible because of the high incidence of cardiac abnormalities of 30–40% [4]. Other common syndromes with patients presenting for non-cardiac surgery, with frequent cardiac involvement, include CHARGE, trisomy 13, 18, and 21, and velocardiofacial syndromes (see later). A discussion with the patient's cardiologist is indicated for severely affected patients. Details of cardiac development are reviewed in Chapter 5, and anesthetic management and pathophysiology in cardiac disease are discussed in Chapters 26 and 27.

Neurodevelopmental abnormalities

Many patients with genetic syndromes have malformations of the central or peripheral nervous systems, and for many without obvious malformations, there is associated neurodevelopmental delay. This may manifest as general intelligence lag, gross or fine motor problems, speech and language delay, and behavioral problems. It is important to understand neurodevelopmental status in any patient with a genetic syndrome; the chronological age may be very different than the developmental age and the approach to preoperative preparation, communication, premedication, and parental presence may need to be altered accordingly. Many of these patients have undergone multiple medical encounters and interventions, and may be very anxious in the preanesthetic period.

Vascular access

Patients with genetic syndromes may have limb abnormalities that preclude conventional intravenous access, and alternate sites may need to be planned. This may include external or internal jugular vein access if the limbs are not available. In addition, patients with genetic syndromes often have had multiple hospitalizations and procedures, and peripheral venous access may be very difficult, and central veins may also be thrombosed from previous catheters. The absence of typical superficial veins, and the presence of cutaneous collateral vessels, should increase suspicion for difficult access. If indicated, additional studies (i.e. ultrasound, MRI, or CT scanning) may be necessary to plan for vascular access. Ultrasound guidance for vascular access, including peripheral venous access, can greatly facilitate care of these patients. Chapter 18 contains a detailed discussion.

Orthopedic considerations

Scoliosis, hip dysplasia, and limb contractures are common in patients with genetic syndromes. Severe scoliosis should prompt an evaluation of the respiratory and cardiac status of the patient and may alter plans for postoperative ventilation and intensive care. Positioning of anesthetized patients with these problems must be done very carefully so as not to injure affected areas. Chapters 28 and 32 present spine and orthopedic considerations.

Other considerations

Particularly with rare disorders, or disorders with which the anesthesiologist is not familiar, it is important to consult a reference source whenever possible to become familiar with the basic problems of the particular syndrome, and to devise a rational anesthetic plan. Appendix 43.1 lists 120 syndromes, ranging from the most common (fetal alcohol syndrome, Down syndrome, autism spectrum disorder), to the most rare. Another excellent general source is the US National Institutes of Health MedGen website: https://www.ncbi.nlm.nih.gov/medgen/ [5]. The US National Institutes of Health online Mendelian Inheritance in Man database (www.ncbi.nlm.nih.gov/omim) and the US National Institutes of Health Genetic and Rare Diseases Information Center (https://rarediseases.info.nih.gov/) also have excellent information including the gene map locus, if known [6,7]. Many other published and electronic resources are available; including general review articles [8] and textbooks [9]. It behooves the pediatric anesthesiologist to have these resources at hand because of the frequent presentation of these patients on the day of surgery, when the luxury of time for a thorough search for information is not available. In addition, the parents and other caregivers are usually extremely knowledgeable about the patient, and often the condition itself, and can offer valuable information about how the patient has responded to particular interventions in the past. It is important to listen to the parents' and patient's requests and concerns when approaching the patient with a genetic syndrome.

KEY POINTS: GENERAL APPROACH TO PATIENT WITH A GENETIC SYNDROME

- Fluorescence *in situ* hybridization, chromosomal microarray, or newer genetic testing such as whole exome or whole genome sequencing can greatly increase diagnostic yield
- Airway and cardiac abnormalities are seen in a large number of genetic syndromes; careful evaluation is necessary for these organ systems
- Neurodevelopmental and orthopedic problems are also frequently seen in patients with genetic and dysmorphic syndromes

Management of common important syndromes

Down syndrome

Down syndrome (DS), or trisomy 21, is the most commonly identified genetic form of mental retardation, and the leading genetic cause of specific birth defects and medical conditions [10]. Approximately 95% of children with DS have an extra chromosome 21 due to abnormal segregation of chromosomes during gamete formation; about 4% due to chromosome 21 translocations, and 1% due to chromosome 21 somatic mosaicism [10]. The estimated maternal age adjusted prevalence of DS in the United States is 14 per 10,000 livebirths, or one in 732, suggesting that approximately 5400 infants are born annually with DS. Advanced maternal age is by far the most significant risk factor for DS.

DS patients experience a number of problems that result in them presenting to the anesthesiologist for diagnostic and therapeutic reasons, and common features which present a challenge to the anesthesiologist [11]. All DS patients by definition have the characteristic facial features of upslanting palpebral fissures, flat facial profile, and relatively large tongue, as well as mental retardation and hypotonia (Fig. 43.1) [12]. About 50% of DS patients have congenital heart disease (CHD) consisting of complete atrioventricular canal in the majority of patients, but ventricular septal defect, tetralogy of Fallot, and other lesions are also seen. Neonates with DS should be screened for CHD, and parents questioned about cardiac history before any anesthetic. Of particular note is that for reasons incompletely understood, DS patients develop pulmonary hypertension much earlier, and to a more severe degree, than patients without DS with the same cardiac lesion. Especially in unrepaired CHD in DS, an assessment of pulmonary artery pressures should be considered; echocardiography is often sufficient for this purpose. DS patients are more likely to experience bradycardia with sevoflurane induction, even if they do not have CHD; careful monitoring and availability of anticholinergic agents like atropine or glycopyrrolate is prudent [13]. Chapters 26 and 27 discuss anesthetic management in CHD.

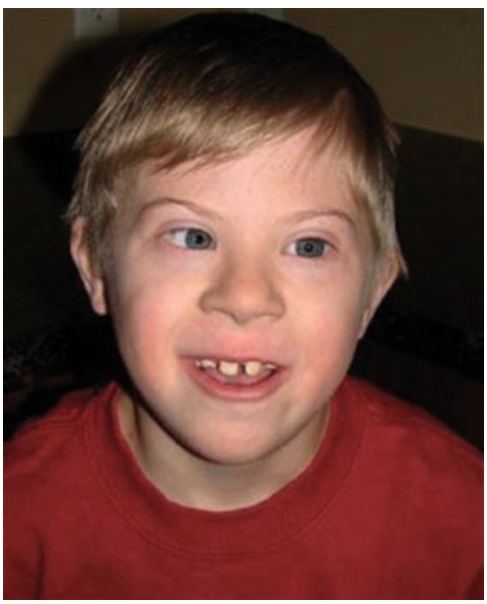


Figure 43.1 Typical facial features of Down syndrome. Note the epicanthal folds, upslanting palpebral fissures, flat facial profile, and relatively large tongue. *Source*: Reproduced from Davidson [12] with permission of Elsevier.

Airway obstruction is common in children with DS; caused by the relative midface flattening with constricted oropharyngeal space, small nasal passages, and relatively large tongue, tonsils, and adenoids [14]. This may lead to obstructive sleep apnea, which may further exacerbate any pulmonary hypertension. DS children present frequently for tonsillectomy and adenoidectomy; and may require special diagnostic testing, and postoperative admission and monitoring. Despite this propensity for upper airway obstruction, the vast majority of DS patients are suitable for a straightforward mask airway and tracheal intubation.

Atlanto-occipital instability occurs in up to 15% of DS patients, defined by excessive movement on cervical flexion–extension radiographs [14]. However, the vast majority of these patients are asymptomatic, and the many infants with DS who present for an anesthetic have incompletely ossified cervical spine vertebrae, and radiographs are not reliable. Therefore, cervical spine radiographs are not indicated in the asymptomatic DS patient before anesthesia. A careful history of neck pain or neurological symptoms, and previous anesthetics or tracheal intubations is important for every DS patient. If such a history is positive, elective anesthetics should be postponed until a thorough evaluation, often involving cervical spine radiography, CT scan, or MRI, is done. Very careful handling of the cervical spine during airway management, and surgical positioning is indicated. This includes avoiding extremes of flexion, extension, and rotation, and holding the cervical spine in a neutral position whenever possible. The majority of DS patients' tracheas can be intubated easily by direct laryngoscopy with these precautions.

Gastrointestinal problems occur in about 10% of patients with DS, with duodenal atresia and annular pancreas accounting for the majority of these findings [10]. Esophageal atresia/tracheoesophageal fistula may also be present in patients with DS. These conditions often result in a neonate with DS presenting for urgent surgery for bowel obstruction; a careful search for associated conditions, especially CHD, is important in such patients.

Down syndrome patients frequently have abnormal thyroid function, with about 2% having congenital hypothyroidism, and up to 25% of patients from birth to 10 years having compensated hypothyroidism, with elevated thyroid-stimulating hormone levels, and low normal T4 levels [14–16]. These patients often go undetected due to the other characteristics of DS, i.e. developmental delays, hypotonia, and obesity. Hypothyroidism is especially important in cardiac or other major surgery, where a subclinical state may be unmasked by the major stress in the perioperative period, which can affect myocardial function by desensitizing the heart to endogenous and exogenous catecholamines. Therefore, it is recommended that DS patients have screening thyroid function testing before major surgery.

Down syndrome children are at increased risk for acute leukemias, both myeloid (AML) and lymphocytic (ALL) [17]. DS children are different in their outcomes and response to treatments, as well as treatment toxicity and side-effects, compared to non-DS children. Survival and outcome is improved

in DS patients with AML, but equivalent to non-DS patients in ALL. Side-effects, particularly mucositis and severe infections, are more frequent in DS patients undergoing intensive chemotherapy-induction regimens. The anesthesiologist must evaluate the DS patient with leukemia for all of the other manifestations of DS noted above.

Finally, vascular access may be challenging in patients with DS, with peripheral venous access difficult due to increased adipose tissue, internal jugular access made difficult due to a short webbed neck and increased adipose tissue, and radial arterial access difficult due to the small size of this artery [18]. Again, ultrasound guidance can be extremely effective in facilitating peripheral and central venous, and arterial access.

In a recent study from a major US children's hospital, 9% of 479 anesthetics in children with complex special healthcare needs were for children with DS, representing 1.25% of all anesthetic cases [19]. This series indicates the frequency with which the pediatric anesthesiologist will encounter patients with DS, and a thorough understanding of the above noted disorders with DS is important to deliver appropriate anesthetic care to these patients.

Trisomy 18 and 13

Trisomy 18 (Edwards syndrome, incidence 1:6000–8000 live-births) and trisomy 13 (Patau syndrome, incidence 1:10,000) are the second and third most common autosomal trisomy disorders, after Down syndrome, in neonates who survive to birth [20]. Both syndromes have developmental delay, microcephaly, micrognathia, hypotonia, and a high incidence of CHD – of about 90% (Fig. 43.2). Atrial septal defects, ventricular septal defects, and patent ductus arteriosus, often with all three lesions together, represent the vast majority of lesions, at about 60–70% of CHD [21]. The majority of the remainder of CHD is found in two-ventricle anatomy such as aortic valve disease, coarctation of the aorta, double outlet right ventricle, tetralogy of Fallot, and complete atrioventricular canal. Single-ventricle disease, such as hypoplastic left heart syndrome, comprises less than 10% of CHD cases. Disorders in multiple other organ systems, including gastrointestinal, genitourinary, orthopedic, and neurological, are frequent. Both syndromes carry a poor overall prognosis, and median survival has been reported as 1–2 weeks for both syndromes. Mosaic or translocation-type trisomy 18 and 13 may confer improved survival versus complete trisomies.

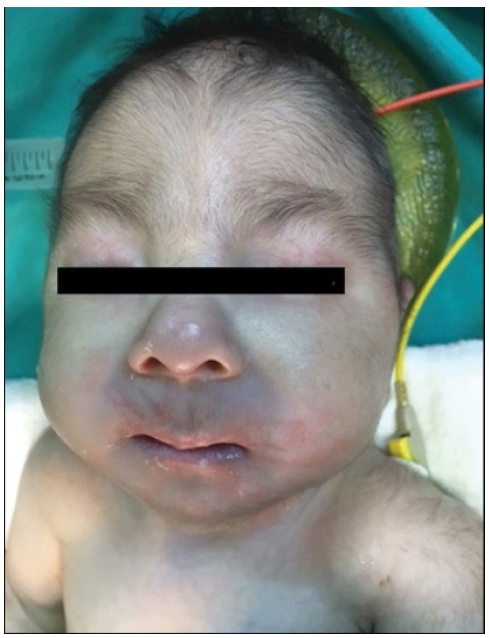


Figure 43.2 A 3 month old infant with trisomy 18 (Edwards syndrome). Note the microphthalmia, micrognathia, short neck, and failure to thrive. The infant was also hypotonic with club foot, and had ventricular and atrial septal defects. *Source*: Reproduced from Bali et al [25] with permission of Turk J Anaesthesiol Reanim.

The most common causes of death in trisomy 18 and 13 patients are pneumonia, apnea, and CHD. There are a number of recent reports about longer survival, including a large report of 10–12% 5–10-year survival for both trisomy 18 and 13. Although many of these patients will receive only comfort care, an increasing number are being actively treated, and will require anesthetic care [22]. Gastrostomy tube placement and cardiac repairs are among the most common surgeries, but major, intermediate, and minor surgery on essentially every organ system has been reported. This includes gastrointestinal, urological, spine, craniofacial (cleft lip and palate, maxillary reconstruction), tracheostomy, ventriculoperitoneal shunt, myringotomy, tonsillectomy, and many others. In a recent series of over 400 trisomy 18 and 13 patients in Ontario, Canada, 18% underwent at least one surgical procedure; 1-year survival after the first surgery was about 70% for both diagnoses [23]. Twenty to 40% of these children have four or more lifetime surgical procedures. In a large administrative database study of 1480 patients with trisomy 18 and 13, 90% had CHD, and CHD repair was performed in 7% of patients. In-hospital mortality was 48% in the unoperated CHD patients versus 21% in the repaired patients ($p < 0.03$) [21]. Anesthetic considerations include a thorough evaluation of all associated defects, particularly cardiac and airway considerations because of the high incidence of micrognathia [24–27]. Preparations for difficult airway management should be made as appropriate. A thorough discussion with the surgeon about planned procedures, and with the parents about the procedures and risks of the anesthetic, and the likely increased rate of major complications and mortality in the perioperative period, is essential. The expectations and wishes of the parents are crucially important to understand when approaching the care of trisomy 18 and 13 patients.

KEY POINTS: TRISOMY 21, 18, AND 13

- Common Down syndrome problems include cardiac disease, atlanto-occipital instability, pulmonary hypertension, hypothyroidism, duodenal atresia, and leukemias
- Trisomy 18 and 13 patients have a very high early infancy mortality, but increasingly are being treated for a variety of surgical conditions; congenital heart disease is present in 90%

VACTERL association

The VACTERL association was first proposed in 1972; the acronym comprises *V* for vertebral defects, *A* for anal or other intestinal atresia, *C* for cardiac defects, *TE* for tracheoesophageal

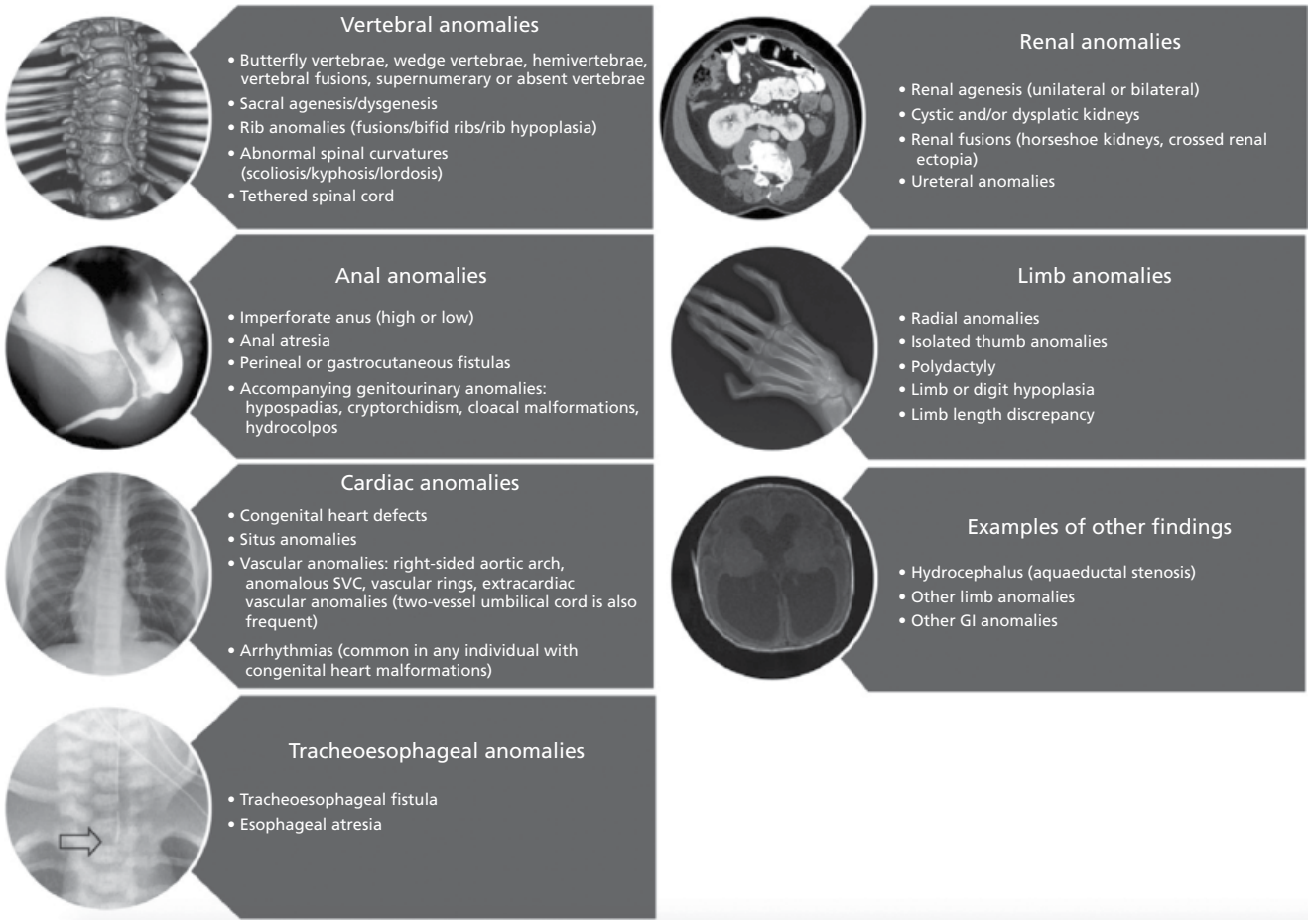


Figure 43.3 Examples of findings in the VACTERL association. The images in the circles represent radiological examples. Vertebral anomalies: 3D CT reconstruction showing thoracic segmentation anomalies; anal anomalies: contrast imaging showing rectoprostatic urethral fistula in a patient with ano-rectal malformations (ARMs); cardiac anomalies: chest radiograph showing midline heart in a patient with situs anomalies as part of the VACTERL association; tracheo-esophageal anomalies: radiograph showing the position of feeding tube placement (arrow) due to a tracheal pouch; renal anomalies: axial view from an abdominal CT showing horseshoe kidney; limb anomalies: skeletal anomalies affecting the radius, wrist, and thumb; examples of other findings: axial view from brain MRI showing hydrocephalus (due to aqueductal stenosis). GI, gastrointestinal; SVC, superior vena cava. *Source*: Reproduced from Solomon et al [31] with permission of Elsevier.

fistula (TEF), *R* for renal malformations, and *L* for limb defects. It was first proposed as the VATER association and this is occasionally still used; the frequent inclusion of cardiac and limb defects necessitated the change [28]. The incidence is estimated to be 1:10,000-40,000 livebirths. The genetics of this disorder are complex, but candidate genes in patients and animal models include defects or deletions in the sonic hedgehog gene on chromosome 7, FOX transcription gene cluster on chromosome 16, and Gli2 gene on chromosome 2 [29,30]. Not all patients have all features of this association, but the TEF is often accepted as essential for the diagnosis, along with at least one other major defect in one of the five additional categories. Recent publications have indicated an increased incidence of anomalies in these categories with more sophisticated imaging techniques to diagnose more subtle malformations (Fig. 43.3) [31,32]. In the other categories, cardiac lesions are the most prevalent, seen in 40–80% of patients [29]. Ventricular septal defect and tetralogy of Fallot are common, and most CHD is acyanotic at presentation. In the case of the VACTERL association with complex CHD with patent ductus arteriosus-dependent systemic or pulmonary circulation, mortality after TEF repair exceeds 50% [33]. Vertebral anomalies are seen in about 60–90% of patients, including hemivertebrae, fused or butterfly vertebrae, or extra vertebrae. Renal system anomalies are found in approximately 50–80% of patients and include horsheshoe kidney, renal agenesis, vesicoureteral reflux, hypospadias, dysplastic kidney, and cryptorchidism. Atresias of the gastrointestinal tract and other anorectal malformations are seen in approximately 55–90% of patients, with the significant majority of these being anal atresias. Limb anomalies are observed in about 40–55% of patients, with digital anomalies and absent radius the predominate defects.

The frequent and significant defects in the VACTERL association mean that these children are often presenting for repeated anesthetics for both diagnosis and treatment, necessitating a thorough preoperative evaluation encompassing an assessment of the lesions in all categories, and also of the developmental and emotional state of the child who has often endured multiple medical interventions. These children are most often developmentally normal.

CHARGE syndrome

The CHARGE syndrome was described in 1979, and the acronym is designated *C* for coloboma, *H* for heart defect, *A* for atresia choanae, *R* for retarded growth and development, *G* for genital hypoplasia, and *E* for ear anomalies/deafness (Table 43.1) [34,35]. Further refinement of diagnostic criteria in 1998 designated the major features seen in most CHARGE patients, but rare in other patients, as the four Cs: (1) coloboma of the iris or retina with microphalmia (80% of patients); (2) choanal atresia/stenosis, either unilateral or bilateral or membranous or bony; (3) cranial nerve anomalies – olfactory tract, facial paralysis, sensorineural deafness, and incoordination of swallowing; and (4) characteristic ear anomalies including cup-shaped ears (80–100% of patients). The minor criteria, seen less frequently in CHARGE syndrome and less specific, include cardiac malformations (75–80% of patients), most often conotruncal defects including tetralogy of Fallot, aortic arch anomalies, and atrioventricular canal; genital hypoplasia, including micropenis and cryptorchidism; cleft lip and palate; TEF; distinctive CHARGE facies and features (sloping forehead and flattened tip of nose); growth deficiency; and developmental delay [34,35]. Typical clinical features of the CHARGE syndrome are shown in Table 43.1 and Figure 43.4.

The incidence of CHARGE syndrome is estimated to be approximately one per 10,000 livebirths [34,35]. A leading candidate gene, discovered recently, is the *chromodomain helicase DNA binding protein 7* (*CHD7*) gene on the long arm of chromosome 8. This results in the expression of a protein that participates in chromatin remodeling during early development and allows a level of epigenetic control over target genes expressed in mesenchymal cells derived from the cephalic neural crest [36]. Mutations of this gene are found in 60–65% of individuals with the CHARGE syndrome, and over 150 mutations have been discovered that encode for short, nonfunctional CHD7 protein.

A thorough evaluation of all organ systems is required before anesthetizing a patient with CHARGE syndrome. Neonatal choanal atresia or stenosis may be particularly challenging – requiring repeated anesthetics for imaging, the repair itself, and re-evaluation and follow-up procedures. The cardiac procedures are particularly common. With the advent and more widespread use of the cochlear implant, many CHARGE patients will also undergo this procedure. Although mental retardation and other developmental delays are common, this feature is variable and some patients may have normal intelligence. Autism spectrum disorder behavioral syndromes are increasingly recognized in these patients [34,35].

Micrognathia syndromes

Among the most common causes for difficult airway management and tracheal intubation in pediatric patients is micrognathia, and an evaluation for this problem is done in

Table 43.1 Phenotypic features of the CHARGE syndrome

Features	Details	Frequency
Coloboma	Iris, retina, choroid, disk, or microphthalmia	75–90%
Choanal atresia/stenosis	Unilateral or bilateral, bony or membranous	65%
Cranial nerve anomalies	Facial nerve palsy, auditory, vestibular, or vagal (swallowing problems)	Facial: 50-90%
	CNS abnormalities can also involve arhinencephaly, holoprosencephaly spectrum, or forebrain and hindbrain abnormalities	CNS abnormalities 55–85%
Characteristic ear anomalies	Outer ear tends to be symmetrically misshapen, low set, anteverted, cup shaped, and wide with reduced vertical height	Outer ear 95–100%
	Triangular concha is a common finding	Inner ear: 90%
	Microtia, hypoplasia of the auditory canal, and preauricular tags can also be seen	
	Middle: ossicular malformation	
	Cochlear: Mondini defect	
	Temporal: absent/hypoplastic semicircular canals; highly predictive of the presence of a *CHD7* mutation	
Genital hypoplasia	Males: micropenis/cryptorchidism	50–70%
	Females: hypoplastic labia	
	Delayed puberty	
Developmental delay	IQ <70 is present in over 70%	70%
Cardiovascular malformation	Usually conotruncal, AV canal, and aortic arch abnormalities	50–85%
Growth deficiency	Hypothalamo-hypophyseal dysfunction leading to short stature and pubertal delay	70–80%
	Often birth centiles are low normal, around the 10th centile	
Orofacial cleft	Cleft lip/palate	15–20%
Distinctive facial features	Square face, prominent forehead, prominent nasal bridge and columella, and flat midface	NA
Additional features	Omphalocele/umbilical hernia	NA
	Bony scoliosis/hemivertebrae	
	Renal anomalies: dysgenesis or horseshoe/ectopic kidney	
	Hand and limb anomalies in 37%: polydactyly, J-shaped 'hockey stick' palmar flexion crease	
	Short neck, sloping shoulders, and nipple anomalies	
	Immune deficiency	

AV, atrioventricular; CNS, central nervous system; IQ, intelligence quotient; NA, not applicable.
Source: Reproduced from Hsu et al [35] with permission of John Wiley and Sons.

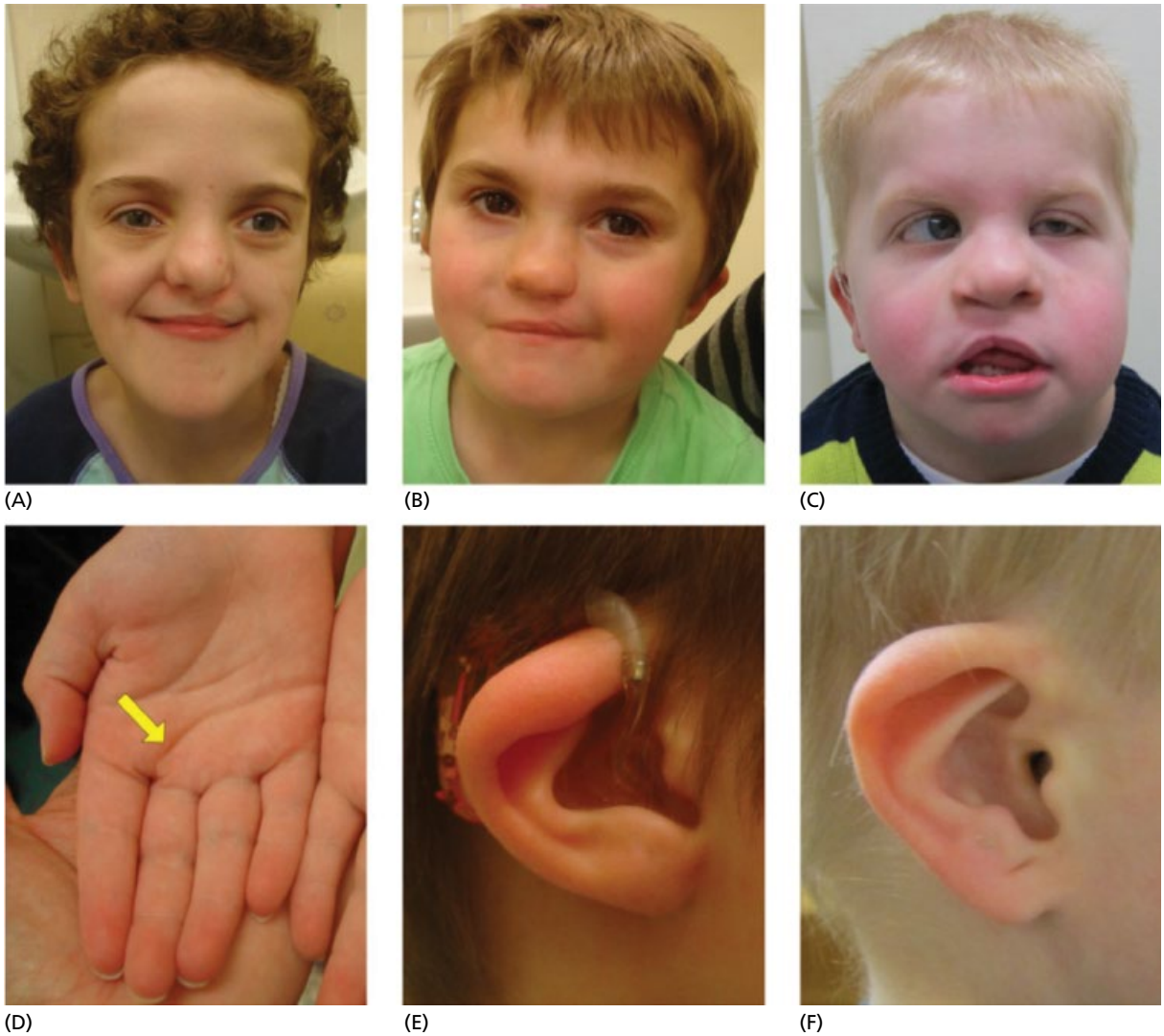


Figure 43.4 Clinical features of the CHARGE syndrome. (A) Cleft lip/palate repair, mild left facial palsy, and broad forehead in a 10-year-old girl. (B) Cleft lip/palate and square face with mild right facial palsy in a 6-year-old boy. (C) Left-sided microphthalmia, with prosthesis in situ, and a square face with broad forehead and broad nasal root in a 2.5-year-old boy. (D) 'J'-shaped hockeystick palmar crease (yellow arrow). (E) Typical CHARGE ear with hypoplastic, overfolded helix and lobe, and a triangular concha. (F) Less typical appearing ear with a squared superior helix and crease on the lobe. *Source*: Reproduced from Hsu et al. [35] with permission of John Wiley and Sons.

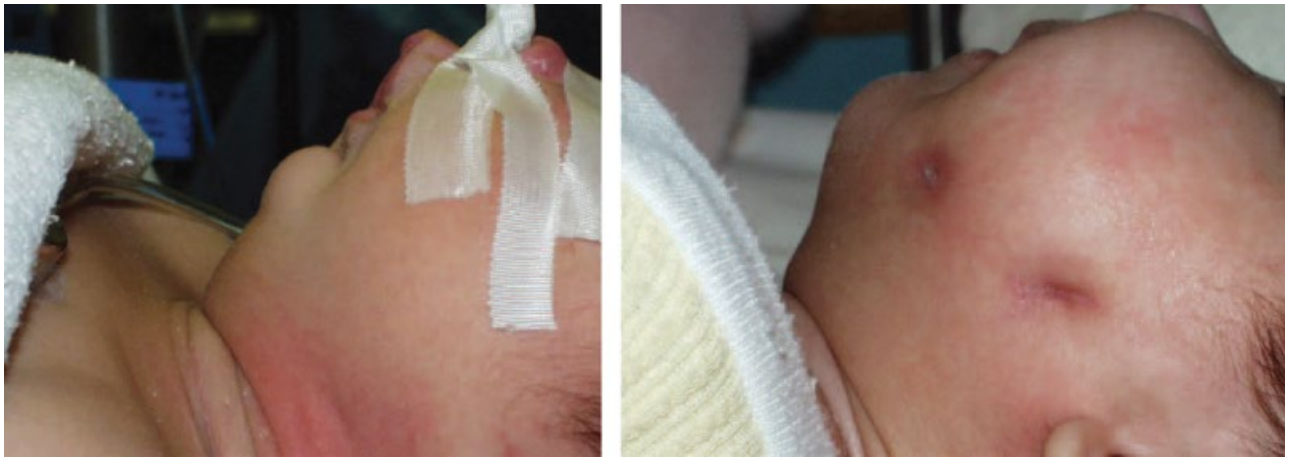
every patient. There are a number of craniofacial syndromes leading to micrognathia, including the Pierre Robin sequence, Treacher Collins syndrome, and hemifacial microsomia (Goldenhar syndrome).

Pierre Robin sequence

The Pierre Robin sequence (PRS) is defined as micro- or retrognathia, glossoptosis, and cleft soft palate. Isolated PRS does not have a known genetic cause and is not associated with other syndromes; the isolated form is seen in approximately half of the patients, but the published series vary from 11% to 81%. Incidence is approximately one per 8500 livebirths, with mortality during childhood at 2.2–26% [37]. PRS associated with genetic syndromes is most often associated with Stickler syndrome, Treacher Collins syndrome, and velocardiofacial syndrome. Fetal alcohol syndrome may also be associated with PRS [38]. Mildly affected patients may need minimal medical intervention, while severely affected patients manifest airway symptoms in the neonatal period. The constellation of upper airway anomalies frequently leads to obstructive apnea, and the intensity of medical intervention is proportional to the degree of upper airway obstruction. In significantly affected neonates, airway interventions such as prone positioning, nasal continuous positive airway pressure, endotracheal intubation, or tracheostomy may be required. Feeding difficulties are common, and feeding gastrostomy may be required. Airway surgery including cleft palate repair, veloplasty, tongue–lip adhesion, and mandibular operations may be necessary (Fig. 43.5) [38]. Airway management techniques such as laryngeal mask airway, video laryngoscope, fiberoptic intubation, or retromolar laryngoscopy technique may be required [39]. Details of difficult airway management are presented in Chapter 15.

Treacher Collins syndrome

Treacher Collins syndrome (TCS) is an autosomal dominant disorder of bilateral facial development, which affects approximately 1 in 50,000 livebirths; however up to 60% of



(A) (B)

Figure 43.5 Pierre Robin sequence in an infant. Clinical results of mandibular distraction: (A) before distraction and (B) after distraction. *Source*: Reproduced from Cladis et al [38] with permission of Wolters Kluwer.

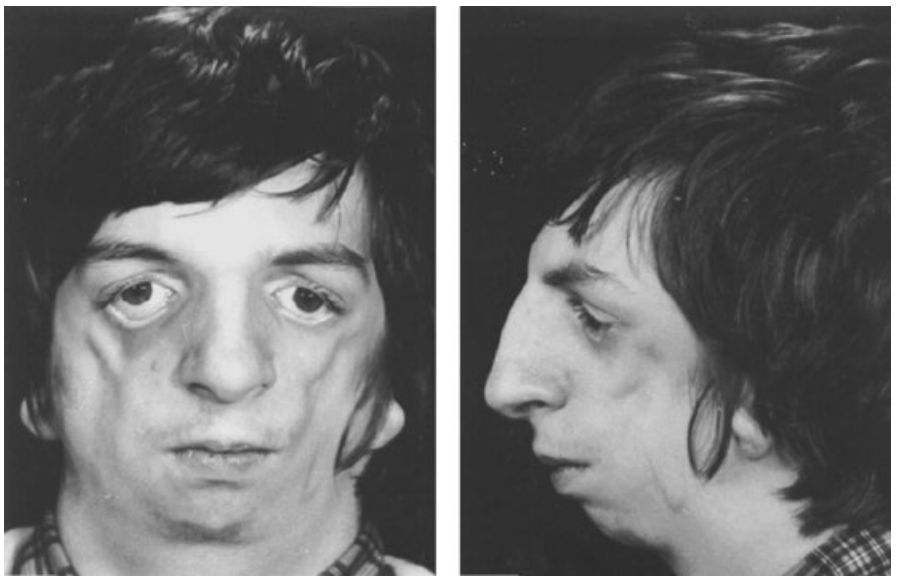


Figure 43.6 Treacher Collins syndrome in an adolescent. Note the hypoplasia of the maxilla, zygoma, and mandible, lateral downward sloping of the palpebral fissures, coloboma of the lower eyelids, and defects of the external and middle ears. *Source*: Reproduced from Marszalek et al [39].

cases appear to be a *de novo* genetic mutation. TCS is a genetic developmental disorder of the first and second branchial arches, resulting in extensive neural crest cell abnormal development. The TCS phenotype includes hypoplasia of the maxilla, zygoma, and mandible, lateral downward sloping of the palpebral fissures, coloboma of the lower eyelids, defects of the external and middle ears, and sensorineural deafness (Fig. 43.6). The protein coded by this gene is called Treacle, and the hypothesis is that it assists in ribosomal DNA transcription during particular stages in embryonic development, particularly that of the structures of the head and face [39,40]. These patients may require extensive bony and soft tissue facial reconstruction over multiple procedures, including orbital and zygomatic reconstruction before the age of 10, external ear reconstruction, and mandibular advancement as teenagers with bony growth is completed. Difficulties in airway management for the anesthesiologist arise from the mandibular hypoplasia and high arched palate frequently encountered in TCS patients. Video laryngoscopy has been reported to be successful for airway management in this syndrome [41].

Goldenhar syndrome

Goldenhar syndrome, also known as oculo-auriculo-vertebral syndrome, or hemifacial microsomia, is a developmental disorder of the first and second branchial arches that affects approximately one in 5600 livebirths. It is most frequently unilateral, and is characterized by malformations/hypoplasia of the external and middle ear often with sensorineural hearing loss, mandibular hypoplasia, eye abnormalities such as microphthalmus and epibulbar dermoids, and vertebral anomalies including cervical spine malformations and scoliosis (Fig. 43.7) [42]. Most cases of Goldenhar syndrome are sporadic, and heterogenous manifestations of the phenotype are common, ranging from very mild hemifacial asymmetry, preauricular ear tags or pits, to severe deformity and mandibular hypoplasia. Congenital heart disease is present in approximately one-third of patients, most commonly septal and conotruncal defects [42].

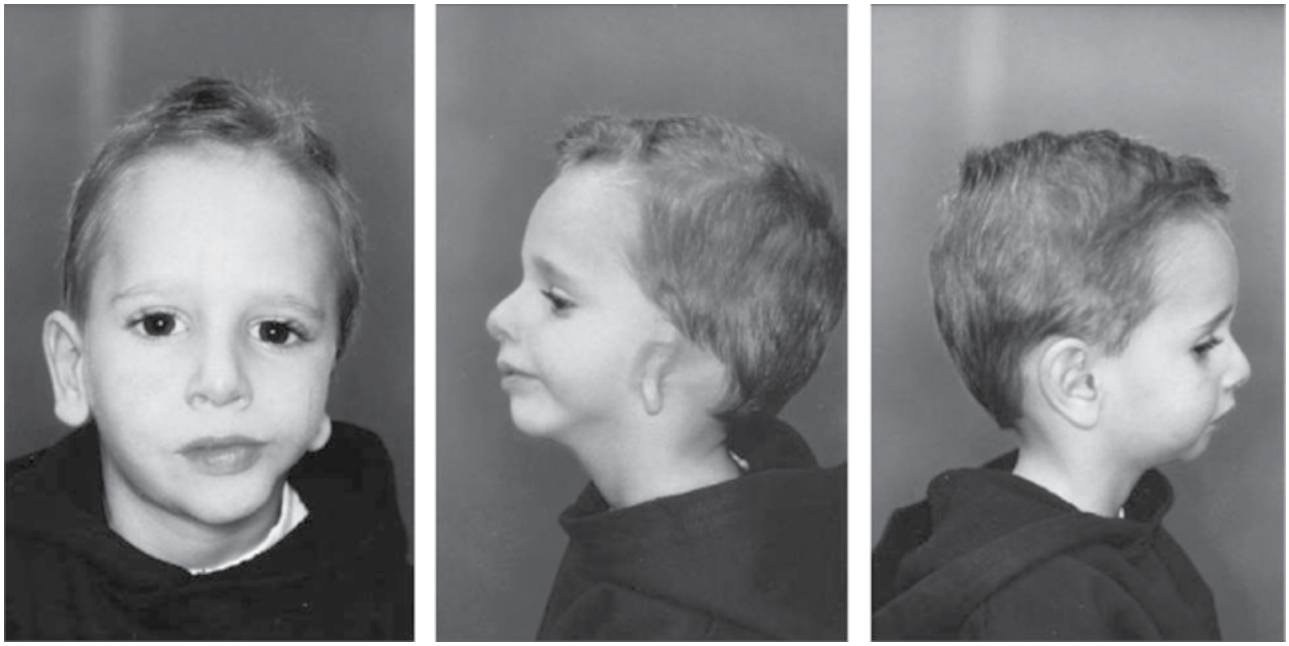


Figure 43.7 Goldenhar syndrome in a 7-year-old male. Note the facial asymmetry with hypoplastic mandible and ear deformity on the left side. *Source*: Reproduced from Vendramini-Pittoli and Kokitsu-Nakata [42] with permission of Wolters Kluwer.

Developmental delay and autism spectrum disorder is seen in some patients [43]. Difficulties with airway management and tracheal intubation are common in this syndrome due to the mandibular hypoplasia and lack of space for direct laryngoscopy. These patients frequently present for anesthesia and sedation for diagnostic and therapeutic procedures for ear, facial, and cardiac anomalies. Techniques such as fiberoptic or video-assisted laryngoscopy are frequently required for airway management [44,45]. In a series of 13 patients with Goldenhar syndrome undergoing cardiac surgery, six had difficult intubation: two required surgical tracheostomy after multiple failed intubation attempts; one required retrograde intubation; the other three required 2–5 attempts with direct laryngoscopy [46]. It should be noted that video laryngoscopy was not available in this series and would likely have facilitated airway management, as noted earlier.

Figure 43.8 Williams syndrome facies in a young child. Note the periorbital puffiness, flat nasal bridge, long philtrum, wide smile, full cheeks, and full lower lip. *Source*: Reproduced from Waxler et al [48] with permission of SLACK Incorporated.

KEY POINTS: VACTERL, CHARGE, AND MICROGNATHIA SYNDROMES

- VACTERL association varies widely but tracheoesophageal fistula plus one other major defect must be present; cardiac disease is seen in 40–80%
- CHARGE syndrome major criteria are coloboma, choanal atresia, cranial nerve anomalies, and cup-shaped ear
- Micrognathia syndromes are among the most common causes of difficult tracheal intubation

Cardiac syndromes

Williams syndrome

Williams syndrome is a genetic syndrome whose phenotype involves supravalvular aortic stenosis, and characteristic facial features including periorbital puffiness, flat nasal bridge, long philtrum, full cheeks, and full lower lip (Fig. 43.8). Other features include developmental delay, friendly or outgoing personality, hypercalcemia, hypotonia, joint laxity, and hypertension. Williams syndrome affects approximately one in 10,000 livebirths, and has been localized to a 1.5 Mb base pair deletion on one copy of chromosome 7, involving 26–28 genes, including the elastin gene, at 7q11.23 [47]. This deletion can arise from a spontaneous mutation, or inherited as an autosomal dominant familial form. Fifty to 75% of patients with Williams syndrome have cardiac disease, most frequently supravalvar aortic stenosis, and peripheral pulmonary artery stenosis. These changes

are characterized as an elastin arteriopathy, and the usual large quantity of elastin present in the medial layer of the large arteries is absent, resulting in limited distensibility and stenosis of the artery. In addition, adhesion of the aortic valve leaflet edges to the narrowed sinotubular junction can result in obstruction of the coronary artery ostia, resulting in impaired coronary blood flow [48]. It is this feature that leads to sudden death in Williams syndrome patients, both spontaneously, and during diagnostic and therapeutic procedures requiring anesthesia and sedation [49]. The patients with highest anesthetic risk have severe supravalvar aortic stenosis (mean gradient >40 mmHg), electrocardiogram (ECG) findings or symptoms of coronary ischemia, coronary disease on imaging, severe left ventricular hypertrophy, biventricular outflow tract obstruction, and prolonged corrected QT interval [50].

Careful anesthetic management to balance myocardial oxygen supply and demand, including avoidance of excessive tachycardia, hypotension, and hypovolemia, are important principles. The peripheral pulmonic stenosis is often present during infancy but improves over time. Details of anesthetic management for left heart obstructive lesions are presented in Chapters 26 and 27.

Noonan syndrome

Noonan syndrome is characterized by cardiac disease and distinctive facial features including hypertelorism with downslanting palpebral fissures, ptosis, and low-set posteriorly rotated ears. The cardiovascular manifestations are most commonly valvar pulmonary stenosis in about 60%, hypertrophic cardiomyopathy in 20%, atrial septal defects and ventricular septal defects in approximately 10% and 5%, respectively, and patent ductus arteriosus in 3% [51]. Other defects include webbed neck, shield chest, and abnormal lymphatic drainage resulting in lymphedema. The syndrome occurs in approximately one in 1000–2500 livebirths, and may occur sporadically, or with an autosomal dominant inheritance, predominately by maternal transmission. Approximately 50% of cases have a missense mutation in the *PTPN11* gene on chromosome 12, which encodes for a protein, tyrosine phosphatase SHP-2. This enzyme is involved in a variety of signal cascades for receptors for hormones, cytokines, and growth factors and is involved in a number of developmental processes [51]. Intervention requiring anesthesia is most commonly balloon valvuloplasty or surgery for pulmonary valve stenosis.

Velocardiofacial syndrome

Velocardiofacial syndrome (VCFS) is also known as DiGeorge syndrome or sequence, 22q11 deletion syndrome, CATCH 22, and conotruncal anomalies face syndrome. This disorder has a wide spectrum of phenotypic findings with more than 180 clinical features. It is one of the most common multiple anomaly syndromes, with incidence estimates of approximately 1:2000 livebirths. VCFS is inherited as an autosomal dominant disorder, and is caused by a microdeletion at chromosome 22q11.2 [52]. The phenotype is extremely variable, and there is no single clinical feature present in 100% of cases, and so the diagnosis is defined by the chromosome defect itself. Congenital heart disease is present in 70% of cases, and constitutes a high percentage of all conotruncal cardiac anomalies, including more than 50% of cases of interrupted aortic arch, over 15% of patients with tetralogy of Fallot, about 50% of truncus arteriosus cases, and about one-third of posteriorly malaligned ventricular septal defects. Hemizygosity of the gene *TBX1* is responsible for the cardiac defects. Other defects commonly encountered are cleft palate, most commonly submucous clefts, and facial anomalies often associated include high arched palate, low-set ears, and occasionally varying degrees of micrognathia (Fig. 43.9). Other important features present in a variable percentage of patients are partial hypoparathyroidism resulting in neonatal hypocalcemia, and relative immunodeficiency from abnormal lymphocyte function. Developmental delay is common in VCFS, although in some patients intelligence may be normal. Average mean full-scale IQ is 70–75, with about 55% having an IQ of 70–100; 45% have an IQ of 55–70, and a few have moderate to severe disability [53]. Individuals with VCFS are at an increased risk for developing several psychiatric disorders including attention deficit with hyperactivity disorder, autism spectrum disorder, anxiety and mood disorders, and psychotic disorders and schizophrenia. Patients with the cardiac diseases noted above should be tested for the 22q11.2 deletion using FISH or chromosomal microarray. The other defects, especially hypocalcemia and immune dysfunction, leading to increased infection risk, should be sought as well as these may affect anesthetic management. In patients with simpler forms of CHD and VCFS, i.e. tetralogy of Fallot, ventricular septal defect, and simple truncus arteriosus, surgical outcomes are not worse than patients without a chromosome defect. However, in interrupted aortic arch, surgical outcomes are worse with the 22q11.2 deletion. Finally, the later neurodevelopmental outcomes at 1 year or more after cardiac surgery are definitely worse overall with 22q11.2 deletion [54,55]. In spite of the known mild craniofacial anomalies in this syndrome, airway management and tracheal intubation is most often straightforward.

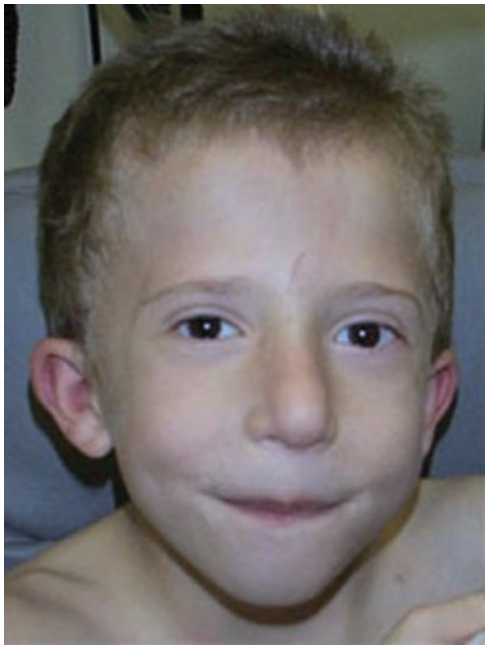


Figure 43.9 Facial features of the velocardiofacial syndrome. Note the small low-set posteriorly rotated ears and slight retrognathia; the patient also has a high arched palate with submucous cleft. *Source*: Reproduced from Shprintzen [53] with permission of John Wiley and Sons.

KEY POINTS: CARDIAC SYNDROMES

- Williams syndrome is a frequent cause of cardiac arrest and death with anesthesia due to coronary ischemia from supravalvar aortic stenosis
- Noonan syndrome is accompanied by pulmonic stenosis in the majority of patients; hypertrophic cardiomyopathy can also be seen
- Velocardiofacial, or DiGeorge, syndrome is a common cause of conotruncal anomalies; these patients may have mild micrognathia but are not usually problematic for endotracheal intubation

Autism spectrum disorder

Autism spectrum disorder (ASD) is an increasingly recognized neurodevelopmental disorder of empathy that encompasses autism, Asperger syndrome, atypical autism, and pervasive developmental disorder not otherwise specified. ASD is characterized by impairments in social communication and social interaction of varying degrees, and also includes restricted and repetitive behaviors and impairments of imaginary thought [56]. Ritualistic and repetitive behaviors include the need for fixed routines and a constant environment, stereotypical repetitive movements (such as hand-flapping), and intense special interests [56]. These behaviors may be an attempt to impose order for their internal world, but the underlying reasons may vary for different children. Children with ASD are more likely to be anxious and exhibit unwanted behaviors if their routine or repetitive behavior is interrupted. On the positive side, introducing predictability of events and environment for a child with ASD can minimize unwanted behaviors and enhance interaction. Autistic children may have problems with managing sensory input. They may over- or under-react to sensory stimulation, including tactile, auditory, visual, gustatory, and vestibular or proprioceptive input. On the other hand, some sensory experiences can evoke intense pleasure, such as the visual input from toys with spinning lights. Parents may report that their child has hyperacusis, and some may find some everyday sounds unbearable, like a vacuum cleaner or hair dryer. The child may dislike to be touched, e.g. hugs from parents or siblings. The texture of some fabrics may cause distress. With the expansion of diagnostic criteria for ASD, the long-held view that the vast majority of patients have significant intellectual disability, defined as an IQ <70, has been challenged. A recent report assessed 156 children aged 10–14 years with ASD. They found 55% of the 75 children with ASD had IQ <70, only 16% had moderate to severe intellectual disability (IQ <50), 28% had average intelligence (IQ 85–115), and 3% had above average intelligence (IQ >115) [56]. Epilepsy is present in about 30% of patients with ASD.

The US Centers for Disease Control and Prevention now estimates the prevalence of ASD in the USA as one in 68 children, with boys affected 4.5 times more frequently than girls (1:42 in boys versus 1:189 in girls) [57,58]. Studies in Europe, Asia, and North America also put the prevalence at between 1% and 2%. There is increasing evidence that ASD has a genetic basis, including data indicating that the relative risk to siblings is 25 times higher than the general population, and twin studies showing higher rates in concordant twins. Genome association studies have identified several candidate genes on different chromosome regions, including 2q, 7q, 15q, 15p14.1, and X. In addition, syndromes such as fragile X, Down syndrome, velocardiofacial syndrome, and others, account for 1–2% of ASD patients [55]. Multiple approaches to behavioral therapy have been used in ASD, and there is also evidence that pharmacological interventions can be effective in reducing some of the negative behaviors [56]. Medications may include risperidone for irritable and aggressive behavior, selective serotonin reuptake inhibitors/selective norepinephrine reuptake inhibitors such as fluoxetine for repetitive behaviors, methylphenidate derivatives for attention-deficit hyperactivity symptoms, and clonidine for hyperactivity and irritability [56].

Anesthetic management of patients with ASD, especially preoperative preparation, premedication, and induction of anesthesia, presents problems unique to this population [59]. When possible, parents of patients with ASD should be contacted in advance of the anesthetic to gain some understanding of the degree of their ASD, their particular behaviors, and interventions to avoid. Outpatient surgery whenever possible, and returning the patient to their home environment and routines as soon as possible, are important for the ASD patient. Parental presence, and/or premedication with oral midazolam, ketamine, clonidine, or in some cases intramuscular ketamine, are reported to be effective in this population. The most common procedures in the ASD population include dental restorations, otorhinolaryngological procedures, electroencephalography, and brain MRI scans [59]. Scheduling these patients first in the day, admitting them a short time before induction of anesthesia to a quiet secluded recovery area, removing intravenous catheters whenever possible, parental presence for induction and in the recovery room, and discharging home as soon as possible are all reported to help in minimizing behavioral disruptions in the ASD population. Recommendations for the preoperative approach to ASD patients are displayed in Table 43.2 [56,60]. Despite the well-founded concerns that ASD children would have a greater degree of anxiety and behavior change after outpatient surgery, a recent controlled prospective study of 60 children (32 ASD, 28 normal development), revealed greater patient anxiety only in the holding area and poorer induction compliance, but no difference in negative behavior change at 1 and 7 days postoperatively [61]. No special preparation was done for the ASD patients, but more children with ASD received a premedication (87% versus 64%), and were much more likely to receive a non-standard medication, usually intramuscular ketamine.

Epidermolysis bullosa

Epidermolysis bullosa (EB) is a group of hereditary bullous skin disorders distinguished by blister formation as a result of mechanical trauma. Although there are over 20 subtypes of EB, it can be divided into three major types: EB simplex (mutations in keratin 5 and 14 genes) where the epidermis only is affected; junctional EB (mutations in laminin 5 or type XVII collagen genes) where the basement membrane is involved; and dystrophic EB (mutations in type VII collagen genes) in which the dermis is primarily involved. Mutations in 10 additional genes encoding protein components of the basement

Table 43.2 Common presentations of the autism spectrum disorder and their management in the perioperative setting

Behavior	Impact on anesthetic	Management
Persistent deficit in social communication	Inability to comprehend accurately the events and communicate their fears	Use simple clear language, visual aid, social story
Restrictive and repetitive interests, behaviors, and activities	Can be irritable with change in routine	Use special interest to comfort and to motivate and for comfort, especially computer/I pad
Sensory hypersensitivity		
Touch	The feeling of hospital gown/local anesthetic cream maybe unpleasant	Change of clothes can be stressful, avoid anything that triggers challenging behavior
Taste	May not tolerate oral premedication, especially bitter midazolam and ketamine	Give clonidine first, it has no taste and can be given in water. Other premedications can be given later (15–30 min later)
Light	Can have temper tantrum (feeling of pain from the light that they cannot express)	Avoid fluorescent lights. Admit in a semi-dark, quiet room and recover in the same environment. Peaceful and low stimulation
Noise	As above, the sound of crying children in particular is very distressing	Admit and recover in a single quiet room
Associated mental health problems		
Anxiety	May not want to come to hospital and be distrustful	Premedication Preparation for 1 week minimum with social story that is factual and calming and includes coping/relaxation skills
Anger	Disruptive and agitated	Premedication including antipsychotic. Preparation as above
Intellectual impairment	Inability to understand and communicate	Use simple language/visual aid and repeat
Epilepsy	Possible risk in perioperative period	Make sure epilepsy is well controlled

Source: Reproduced from Taghizadeh et al [57] with permission of John Wiley and Sons.

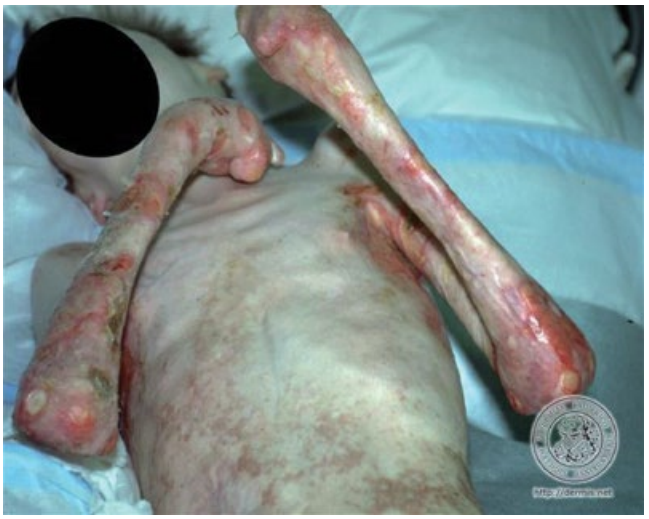


Figure 43.10 Dystrophic epidermolysis bullosa. Note the severe blistering with hypertrophic scarring and contractures in the axillae and antecubital fossae. Note also pseudosyndactyly from severe chronic contractures. *Source*: Reproduced from DERMIS Dermatology Information System [64].

membrane have also been implicated in various subtypes of EB [62]. Clinical manifestations vary from mild to severe, with dystrophic EB the most severe and the form most frequently requiring surgical and anesthetic intervention (Fig. 43.10) [63]. The majority of patients with dystrophic EB have blisters and wounds that are present at birth or shortly after, with a variety of blister sizes that heal with atrophic scars, and development of contractions [64]. These occur commonly on the dorsum of the hands, feet, elbows, and knees. Friction caused by scratching, or other mechanical forces, is very damaging in EB. Oral, pharyngeal, and esophageal blistering is common in EB, leading to contractures of the mouth and tongue. The pain associated with these blisters leads to decreased oral intake and poor nutrition. Esophageal strictures, and dental caries and gum disease are also common in dystrophic EB. Contractures on the extremities can cause severe scarring to the point that a pseudosyndactyly is created. Corneal scarring can also occur. General management of EB involves teaching the family to avoid friction and shearing forces, special clothing and feeding techniques, draining of blisters and treatment with silver sulfadiazine for large infected blisters, special dressings with hydrofiber foam with silicone coating, and topical corticosteroids. Feeding via open gastrostomy, dental treatment, and analgesia as well as a multidisciplinary approach are crucial to optimize outcomes for this complicated patient population.

All of these problems lead to the need for anesthesia and sedation for diagnostic and therapeutic procedures, which can be very challenging, and are best carried out in a specialized center that cares for large numbers of these patients. However, these patients may present in a number of settings, and may require emergency interventions and so the pediatric anesthesiologist must be familiar with their care. Common surgical procedures in EB include dressing changes, casting, repair of contractures and pseudosyndactyly, dental restoration, esophagoscopy and esophageal dilation, open gastrostomy, long-term indwelling central venous access, skin biopsy, and eye surgery [64].

The most important principle of anesthetic care of children with EB is that friction and shearing forces, and not direct pressure, are responsible for new bullae formation [65]. Airway management problems are frequent, secondary to

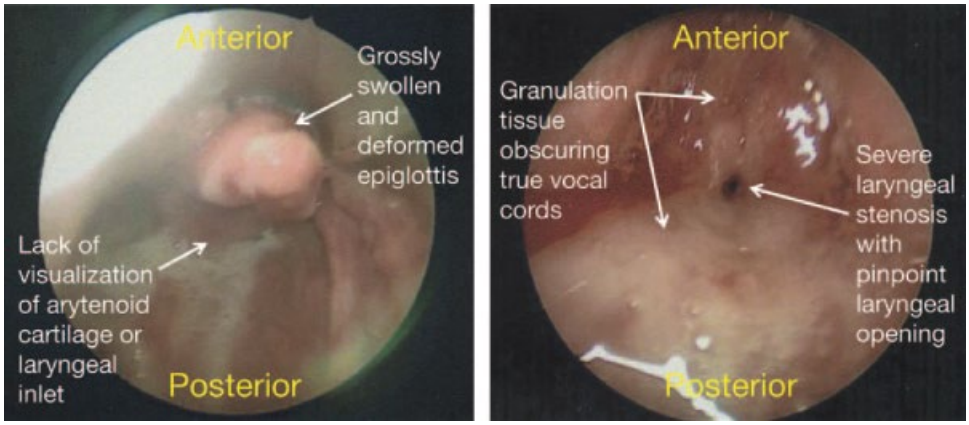


Figure 43.11 Microlaryngoscopic (A) and bronchoscopic (B) views of laryngeal stenosis in epidermolysis bullosa. *Source*: Reproduced from Aronson [66] with permission of Wolters Kluwer.

neck contractures and pharyngeal bullae. After thorough evaluation of preoperative condition, an oral premedication can be given if needed. Veins are often easily visualized and cannulated in these patients and are often an option for premedication and anesthetic induction. The number of transfers of the patients should be minimized, as sliding causing shearing forces between stretcher and operating room bed, for example, may contribute to bullae formation. For the attachment of monitors, IV cannulas, or airway devices, adhesives should be assiduously avoided. It is often preferable to secure a peripheral IV cannula with a single suture. A clip-on pulse oximetry probe is used. ECG electrodes can be used by cutting away the adhesive portion and laying only the gel part on the skin, or covering the skin with paraffin gauze or a gel pad. Non-invasive blood pressure is used, but the skin should be first padded with Webril® soft gauze. Conformable foam dressings such as Mepilex® (Mölnlycke Health Care, Norcross, GA, USA) can also be used to protect the face or facemask placement, and other sensitive areas for protection from monitoring devices. Nasopharyngeal and rectal temperature probes are avoided. Inhalation induction can be used, but the facemask must be thoroughly lubricated with petrolatum jelly or protected with Mepilex, and great care should be taken to avoid shearing forces on the skin of the face and neck. In general, tracheal intubation has been the preferred airway management method, with the tube half a size smaller than normal; with gentle laryngoscopy the incidence of new laryngeal or pharyngeal bullae is low [64].

Anticipated difficult airway management because of contractures or severe intraoral bullae must be accompanied by a careful plan, including the availability of video laryngoscopy, fiberoptic bronchoscopy, and laryngeal mask airways. The laryngeal mask airway can also be used for airway maintenance successfully with little risk of new severe intraoral bullae, but maintenance of the airway with a facemask for long periods of time should be avoided. Non-depolarizing muscle relaxants can be used, but succinylcholine should be avoided. Standard intravenous induction agents, maintenance agents, and opioid and regional anesthesia may be used safely in these patients. Emergence from anesthesia and tracheal extubation must be done carefully, again avoiding shearing forces on the face; intraoral suctioning must be done gently. Avoidance of use of conventional facemasks for oxygen administration in postanesthesia recovery is important; increasing oxygen concentration by blowing humidified oxygen over the face from a 22 mm corrugated oxygen tubing is an effective method.

Evaluation for new bullae and communication with the patient's dermatologist about any changes in treatment plan after an anesthetic is very important. Airway lesions can be particularly challenging, with laryngeal stenosis, obstruction, or stricture seen in as many as 10–40% of patients with junctional EB (Fig. 43.11) [66]. There is a case report of a video laryngoscope rescuing a failed fiberoptic intubation in a 13-year-old with dystrophic EB undergoing elective syndactyly repair and dental surgery [67]. A Glidescope® with GVL stat 3 blade (Verathon Medical, Bothell, WA, USA) was able to visualize the glottis (direct laryngoscopy had been grade IV Cormack–Lehane view), and allow the nasal endotracheal tube to be directed into the airway using the fiberscope, after fiberoptic visualization of the vocal cords proved extremely difficult and ultimately unsuccessful. The soft tissues were extremely friable resulting in obscured visibility.

A recent single-center series of 14 children with dystrophic EB undergoing 148 anesthetics is instructive [68]. Common procedures were esophageal dilation (38%), syndactyly (9%), percutaneous endoscopic gastrostomy (6%), or combinations of these procedures (26%). General anesthesia was utilized for 55% of cases: of these, 81% were endotracheal intubations using direct laryngoscopy, 15% fiberoptic intubations, and 4% laryngeal mask airways. Intubation difficulties were encountered in a third of patients undergoing general anesthesia. Sedation was used for 45% of the cases (wound dressing change and esophageal dilation were the most common sedation procedures), with midazolam and ketamine the most frequently used agents. New oropharyngeal blisters were seen in 10% of patients receiving general anesthesia, versus 1/67 receiving sedation. The same group reported a series of 19 syndactyly procedures in nine EB children performed with sedation plus ultrasound-guided axillary block with excellent intraoperative and postoperative analgesia [69].

CASE STUDY

A 6-month-old female presented for an MRI of the brain, spine, and heart. She was born at 39 weeks' gestation weighing 3.4 kg with polyhydramnios and multiple congenital anomalies. Because an orogastric tube could not be passed, yet there was abdominal gas present on radiograph, a diagnosis of type C esophageal atresia with distal tracheoesophageal fistula (TEF) was made. She did not have respiratory distress, and room air oxygen saturation was 92%. Other findings included a systolic II/VI cardiac murmur, and an echocardiogram revealed a double outlet right ventricle, with large subaortic ventricular septal defect, and large patent ductus arteriosus, as well as a hypoplastic aortic arch. Additional findings on renal ultrasound were bilateral hydronephrosis with a multicystic and dysplastic right kidney and an enlarged and abnormally positioned left kidney. She also had imperforate anus and ambiguous genitalia. On chest and abdominal radiograph it was evident that she had vertebral anomalies, including partial fusion of C5 and C6 vertebrae, complete fusion of L3–4 vertebrae, and sacral agenesis beginning at the S4 level. Finally, she exhibited rocker bottom feet.

A diagnosis of VACTERL association was made. PGE1 infusion was begun in the neonatal period, and repair of the TEF was done as the first priority on the first day of life, via a right thoracotomy. No ventilation difficulties were encountered, and a small TEF was ligated and divided, and the esophageal atresia was repaired primarily without problems. Then, a colostomy and a feeding gastrostomy were performed, again without incident. The patient's trachea was left intubated, and 5 days later she was taken to the cardiac operating room for an aortic arch repair, and pulmonary artery banding via median sternotomy on cardiopulmonary bypass, and again did well with postoperative oxygen saturations of 80–85% on room air, and an appropriate mean echocardiographic gradient of 3.5 m/s across the pulmonary artery band. Ten days postoperatively from the cardiac repair, she underwent placement of a percutaneous left nephrostomy tube because of progressive hydronephrosis, to preserve renal function until more definitive surgery could be done. After a 4-week hospitalization she was discharged home.

On the day of the MRI the patient's only medication was trimethoprim/sulfamethoxazole for urinary tract infection prophylaxis. She had undergone three additional anesthetics to replace the nephrostomy tube, all without incident. The MRI was scheduled to image her spine defects in detail, and rule out any brain anomalies. She was alert and responsive, room air saturation was 76%, HR 135, RR 24, and she was afebrile; her weight was 6.5 kg (10th percentile). Examination of the airway revealed no abnormalities; her mandible was normal size. Her neck appeared slightly short but had full range of motion. Lungs were clear to auscultation bilaterally, and she had no signs of respiratory distress. There was a long harsh IV/VI systolic murmur at the right sternal border. There were well-healed right thoracotomy and median sternotomy scars, as well as a colostomy and gastrostomy button, and a percutaneous nephrostomy tube. She had significant kyphoscoliosis. The echocardiogram done at the cardiology clinic visit the week before revealed good biventricular function, a large subaortic ventricular septal defect (VSD) measuring 12 mm, and a 4.8 m/s pulmonary artery band gradient. Plans had been made for a complete biventricular repair vsersus bidirectional cavopulmonary connection when she was 8–9 months of age. Laboratory studies at that time included a hemoglobin concentration of 17 g/dL, normal electrolytes, BUN of 11 mg/dL and creatinine 0.3 mg/dL. Cardiac MRI was requested to further define the size of the left ventricle, and the anatomical relationship of the VSD to the great vessels, to assist in determining whether a full biventricular repair was possible.

Because of the approximately 3 h planned scan time, the patient's age and cardiac lesion with requested apnea for the cardiac imaging, general endotracheal anesthesia was chosen. Emergency drugs were available, including epinephrine, phenylephrine, and atropine, as well as isotonic crystalloid solutions and 5% albumin for intravascular volume expansion. After application of standard monitors, inhalation induction was initiated with sevoflurane in the MRI suite outside the scanner room. The pediatric anesthesia fellow managed the airway while the faculty anesthesiologist attempted peripheral intravenous access. Inhalation induction proceeded slowly with FiO_2 1.0 and increasing inspired sevoflurane concentrations up to 5%. After three attempts a 22 G peripheral IV was started in the left saphenous vein above the ankle using ultrasound guidance. During induction systolic blood pressures were 60–80 mmHg, and HR 120–150 with sinus rhythm. SpO_2 began at 65% with crying, but quickly improved to 80–85%. Rocuronium 1 mg/kg was administered and the trachea intubated with a 3.5 mm cuffed endotracheal tube. After a period of 5 min observation and ongoing stability, she was moved into the MRI scanner with MRI-compatible monitoring. The brain and spine scans were completed first, with 90 min scan time. Brain MRI was normal, and the vertebral anomalies were confirmed and tethered spinal cord noted. Anesthesia was maintained with 1.5–2% end-tidal sevoflurane, and FiO_2 at 0.5. Two periods of mild hypotension and arterial desaturation to SpO_2 70–75% were treated with decreasing the inspired anesthetic, and intravenous boluses of 10 ml/kg lactated Ringer's solution. Intravenous contrast was not used during this phase because of the concern over her renal function. During the cardiac MRI the patient was stable with SpO_2 80–85%. Two 30 s periods of apnea were requested, and were accomplished with preoxygenation with FiO_2 1.0, and manual hyperventilation. A reduced dose of gadolinium MRI contrast was administered, and excellent cardiac images were obtained with the patient stable throughout. After a 3 h 10 min anesthetic, the patient's trachea was extubated with the patient awake after reversal of neuromuscular blockade with neostigmine 70 μg/kg and glycopyrrolate 14 μg/kg. The patient spent 3 h in the recovery area, returned to baseline room air saturations of 75–80%, and was alert, responsive, in no distress, and had resumed gastrostomy and nipple feeds.

After the cardiac surgery, additional procedures planned were colostomy takedown and repair of imperforate anus, and repair of hydroureter. No interventions for the spine or feet were planned at this time. This patient with all the manifestations of VACTERL association illustrates the complex multisystem nature of the disorders of some patients with syndromes, along with the need for multiple anesthetics for therapeutic and diagnostic procedures. A thorough evaluation of all systems, including access to all previous medical records, is important in planning care of these patients.

Listing of 120 syndromes encountered by the pediatric anesthesiologist

Appendix 43.1 lists, in alphabetical order, 120 syndromes encountered by the pediatric anesthesiologist. Please refer to the downloads on the book's product page at the following link, www.wiley.com/go/gregory, for a full version of this appendix which includes considerations for anesthesia noted by organ system, emphasizing airway, cardiac, pulmonary, and neurological disease associations.

Appendix 43.1 120 Genetic and dysmorphic syndromes

No.	Syndrome: name, eponyms, inheritance, incidence, gene locus, gene product
1	**Achondroplasia** autosomal dominant, but almost 90% are spontaneous mutations; mutation chromosome 4p16.3; 1:25,000; fibroblast growth factor receptor 3 (FGFR3)
2	**Adrenoleukodystrophy** X-linked recessive; 1:42,000 males; mutation chromosome Xq28; ABCD1 transporter protein
3	**Alagille syndrome** autosomal dominant; 1:70,000; chromosome 20p12 microdeletion
4	**Angelman syndrome** happy puppet syndrome; maternally inherited chromosome 15 deletion; chromosome 15q11-13 deletion; 1:10,000–20,000; UBE3A ubiquitin pathway
5	**Antley–Bixler syndrome** autosomal recessive; very rare disorder; chromosome 10q26; fibroblast growth factor receptor 2 (FGFR2)
6	**Apert syndrome** acrocephalosyndactyly; Apert–Crouzon syndrome; Vogt cephalodactyly; 1:160,000–200,000; sporadic/autosomal dominant; chromosome 10q26; fibroblast growth factor receptor 2 (FGFR2)
7	**Arnold–Chiari malformation** Chiari II malformation; 1:1000–5000; association with connective tissue disorders, myelomeningocele
8	**Arthrogryposis multiplex congenita** congenital arthromyodysplasia; congenital multiple arthrogryposis; fibrous ankylosis of multiple joints; Guerin–Stern syndrome; Guérin–Stern syndrome; myodystrophia fetalis deformans; Otto syndrome; Rocher–Sheldon syndrome; Rossi syndrome; can be autosomal recessive or dominant; X-linked inheritance, sporadic, or not inherited; 1 in 3000; multiple causes
9	**Ataxia telangiectasia** Louis Bar syndrome; AT1; autosomal recessive; 1:300,000; chromosome 11q22.3 mutations in the ATM gene
10	**Autism spectrum disorder** Asperger syndrome; atypical autism; pervasive developmental disorder; 1/68 to 1/42 boys; 1/189 girls; candidate genes on chromosomes 13, 15, 17, 3, 7, 1, 21, 16, and others
11	**Becker muscular dystophy** benign pseudohypertrophic muscular dystrophy; X-linked recessive; 1:20,000–30,000 males; mutation dystrophin gene; Xp21.2
12	**Beckwith–Wiedemann syndrome** Exophthalmos–macroglossia–gigantism syndrome; 1:13,700; chromosome 11p15.5 mutations, multiple variants; insulin-like growth factor II (IGF2) likely involved
13	**Carpenter syndrome** acrocephalopolysyndactyly type II; Summitt syndrome; autosomal recessive; 1:1 million; chromosome 6p11
14	**Cat eye syndrome** trisomy 22; Schmid–Fracarro syndrome; chromosome 22 partial tetrasomy; sporadic-spontaneous three or four copies of short arm and section of long arm; between 1:50,000 and 1:150,000; cat eye syndrome critical region gene-7 (CECR7) protein
15	**Catel–Manzke syndrome** X-linked recessive; rare: approx. 30 cases reported
16	**Central core disease** central core myopathy; autosomal dominant or recessive; chromosome 19q13.1; mutations in the ryanodine receptor-1 gene
17	**Cerebrocostomandibular syndrome** rib gap defects with micrognathia; autosomal dominant and recessive; fewer than 100 cases reported; heterozygous mutation in the SNRPB gene on chromosome 20p13
18	**Charcot–Marie–Tooth disease** hereditary sensorimotor neuropathy; peroneal muscular atrophy; multiple modes of inheritance; 1:2500; duplication chromosome 17p12 (75%); PMP22; 38 other gene mutations in neuronal proteins: myelins or axons
19	**CHARGE association** parental gonadal mosaicism in some cases; spontaneous mutation; 1:10,000; heterozygous mutation in the CHD7 gene on chromosome 8q12; chromodomain helicase DNA binding protein 7 (CHD7) gene: neural crest epigenetic chromatin remodeling
20	**Cockayne syndrome** Weber–Cockayne syndrome; Neill–Dingwall syndrome; autosomal recessive; 1:250,000; mutation chromosome 5q12; 10q11.23 (80%)
21	**Cornelia de Lange syndrome** De Lange syndrome; Brachmann–de Lange syndrome; typus degenerativus amstelodamensis; sporadic mutation or autosomal dominant; 1:30,000; mutation chromosome 5p13.1
22	**Costello syndrome** faciocutaneoskeletal syndrome; spontaneous mutation; 300 reported cases; mutation chromosome 11p15.5; mutation Harvey rat sarcoma viral oncogene (HRAS) gene: proteins controling cell growth and division
23	**Cri du chat syndrome** chromosome 5p deletion syndrome; 5p minus syndrome; Lejeune syndrome; sporadic deletion: new mutation (88%); 1:20,000–50,000; deletion chromosome 5p15.2
24	**Crouzon syndrome** craniofacial dysostosis type; autosomal dominant; some are new mutations with advanced paternal age; 1:60,000; heterozygous mutation in the gene encoding fibroblast growth factor receptor-2 (FGFR2) on chromosome 10q26; fibroblast growth factor receptor 2 (FGFR2)
25	**Cystic fibrosis** Mucoviscidosis; autosomal recessive; 1:4000

(*Continued*)

No.	Syndrome: name, eponyms, inheritance, incidence, gene locus, gene product
26	**Diastrophic dysplasia** diastrophic dwarfism; diastrophic nanism; autosomal recessive; 1:100,000; homozygous or compound heterozygous mutation in the DTDST gene (SLC26A2) on chromosome 5q32
27	**DiGeorge (22q11–) syndrome** velocardiofacial syndrome; CATCH-22; conotruncal anomaly face syndrome; sporadic or autosomal dominant; 1:2000; 1.5–3.0 Mb hemizygous deletion of chromosome 22q11.2; TXB1 deletion causes most cardiac defects and other phenotypic features; T-box genes are transcription factors involved in the regulation of developmental processes
28	**Down syndrome** trisomy 21; errors in meiosis that lead to trisomy 21 are overwhelmingly of maternal origin; only about 5% occur during spermatogenesis; 1:650–1000
29	**Duchenne muscular dystrophy** pseudohypertrophic progressive muscular dystrophy; recessive X-linked; 1:3500 males; mutation chromosome Xp21; absent dystrophin
30	**Dutch–Kentucky syndrome** Hecht–Beals syndrome; congenital contractural arachnodactyly; trismus pseudocamptodactyly syndrome; distal arthrogryposis type 7; sporadic inheritance; very rare syndrome
31	**Ehler–Danlos syndrome (EDS)** ***EDS – classic type*** ***EDS – hypermobility type*** autosmal dominant or recessive mutation in tenascin X gene ***EDS – vascular type*** autosmal dominant mutation in type III collagen gene: 1:100,000-250,000 ***EDS – kyphoscoliosis type*** ***EDS – arthrochalasia type*** mutation in type I collagen gene; fewer than 30 cases ***EDS – dermatosparaxis type*** 10 cases reported; 13 subtypes recognized in 2017 reclassification
32	**Ellis van Creveld syndrome** chondroectodermal dysplasia; mesoectodermal dysplasia; autosomal recessive; 1:60,000; mutation in EVC or EVC2 gene on chromosome 4p16
33	**Epidermolysis bullosa (EB)** ***EB simplex*** mutations keratin 5 and 14 genes ***EB junctional*** mutations laminin 5 or collagen XVII genes ***EB dystrophic*** 1:50,000 overall incidence
34	**Fabry disease** Anderson–Fabry disease; angiokeratoma corporis diffusum; α-galactosidase A deficiency; X-linked recessive; 1:55,000 males; mutation chromosome Xq22; alpha-galactosidase A
35	**Familial dysautonomia (Riley-Day syndrome)** hereditary sensory and autonomic neuropathy, type III; autosomal recessive; 1:3700 Ashkenazi Jewish ancestry; mutation chromosome 9q31-33
36	**Familial periodic paralysis (FPP)** autosomal dominant myopathy; variable penetrance ***FPP: hypokalemic*** mutation chromosome 1q32; HOKPP gene ***FPP: hyperkalemic*** mutation sodium channel gene SCN4A on chromosome 17 ***FPP: Anderson syndrome*** Anderson–Twail syndrome, long QT syndrome 7, Andersen cardiodysrhythmic periodic paralysis; mutation chromosome 17q23.1-q24.2
37	**Fibrodysplasia (myositis) ossificans progressiva syndrome** autosomal dominant; complete penetrance; 1:1.5 million; heterozygous mutation in ACVR1 gene on chromosome 2q24.1
38	**Fetal alcohol syndrome** teratogenic syndrome from exposure *in utero*; GABA receptor binding and neuroapoptosis thought to be etiology; 1:100
39	**Fragile X syndrome** X-linked mental retardation; marker X syndrome; Martin–Bell syndrome; X-associated tremor–ataxia syndrome; X-linked dominant; 1:3600 males; 1:4000–6000 females; mutation chromosome Xq27.3
40	**Fraser syndrome** cryptophthamos–syndactyly syndrome; cryptophthalmos syndrome; autosomal recessive; 1:230,000; FRAS1 or FREM 2 genes (extracellular matrix proteins); mutation chromosome 13q13.3 or 4q21
41	**Friedreich ataxia** autosomal recessive; 1:50,000
42	**Glycogen storage diseases (GSD)** ***GSD type 0***: glycogen synthase deficiency ***GSD type I***: von Gierke disease glucose-6-phosphate deficiency; 1:50,000–100,000 ***GSD type II***: Pompe disease acid maltase deficiency; 1:60,000–140,000 ***GSD type III***: Debrancher deficiency (Cori or Forbes disease) glycogen debrancher deficiency; 1:100,000

No.	Syndrome: name, eponyms, inheritance, incidence, gene locus, gene product
	GSD type IV: brancher deficiency (Andersen disease) glycogen branching enzyme deficiency; very rare ***GSD type V***: McArdle syndrome muscle glycogen phosphorylase deficiency; 1:100,000 ***GSD type VI***: Hers disease liver glycogen phosphorylase deficiency; 1:65,000–85,000 ***GSD type VII***: phosphofructokinase deficiency (Tarui disease) muscle phosphofructokinase deficiency; very rare ***GSD type VIII (IX)***: phosphorylase kinase deficiency phosphorylase kinase deficiency; very rare
43	**Goldenhar syndrome** hemifacial macrosomia; oculo-auriculo-vertebral syndrome; facio-auriculo-vertebral syndrome; most cases are sporadic mutations; autosomal recessive or autosomal dominant reported; 1: 5600; mutation in hemifacial microsomia gene on chromosome 14p32 in some patients
44	**Hajdu–Cheney syndrome** arthrodento-osteodysplasia; Cheney syndrome; acro-osteolysis syndrome; autosomal dominant; rare: 50–100 cases reported; heterozygous mutation in the NOTCH2 gene on chromosome 1p12
45	**Hallermann–Streiff syndrome** Francois dyscephalic syndrome; autosomal recessive; 200 reported cases; genetic defect not known
46	**Hallervorden–Spatz disease** neurodegeneration with brain iron accumulation; pantothenate kinase-associated neurodegeneration; autosomal recessive or X-linked autosomal dominant; 1–3:1 million
47	**Hemophilia** ***Hemophilia A*** X-linked recessive; 1:5000 males; mutation chromosome Xq28; factor VIII gene ***Hemophilia B*** Chirstmas disease; X-linked recessive; 1:30,000 males; mutation chromosome Xq27.1-q27.2; factor IX gene
48	**Hereditary angioedema (C1 esterase inhibitor deficiency)** hereditary angioneurotic edema; autosomal dominant; 1:10,000–50,000; deficiency C1 esterase inhibitor gene
49	**Holt–Oram syndrome** heart–hand syndrome; cardiac–limb syndrome; atriodigital dysplasia; autosomal dominant; 1:100,000; heterozygous mutation in TBX5 gene on chromosome 12q24.21
50	**Homocystinuria** cystathionine β-synthase deficiency; autosomal recessive; 1:344,000; mutation chromosome 21q22.3 ***Type I and II***: B6 (pyridoxine) responsive and non-responsive types ***Type III*** with tetrahydrofolate reductase deficiency
51	**Hunter syndrome** mucopolysaccharidosis type II; X-linked recessive; 1:110,000–320,000 males; mutation in the gene encoding iduronate 2-sulfatase (IDS) on chromosome Xq28; deficient enzyme, iduronate-2-sulfatase, is involved in the lysosomal degradation of the glycosaminoglycans heparan sulfate and dermatan sulfate
52	**Hurler syndrome** mucopolysaccharidosis type I; autosomal recessive; 1:100,000; homozygous or compound heterozygous mutation in the gene encoding α-L-iduronidase (IDUA) on chromosome 4p16.3; iduronidase deficiency: hydrolyzes the terminal a-L-iduronic acid residues of the glycosaminoglycans dermatan sulfate and of heparan sulfate; Hurler–Scheie and Scheie are milder forms of disease
53	**Jeune syndrome** asphyxiating thoracic dystrophy; short-rib thoracic dysplasia; thoracic–pelvic–phalangeal dystrophy; autosomal recessive; very rare; mutation 15q13; multiple genes can be affected
54	**Kabuki syndrome** Kabuki make-up syndrome; Niikawa–Kuroki syndrome; autosomal dominant; 1:32,000 Japanese individuals; heterozygous mutation in MLL2 gene on chromosome 12q13.; lysine (K)-specific methyltransferase 2D
55	**Kartagener syndrome** primary ciliary dyskinesia; immotile cilia syndrome; dextrocardia, bronchiectasis, and sinusitis; Polynesian bronchiectasis; Siewert syndrome; autosomal recessive or heterogeneous; rare; no estimates of incidence in literature; dynein arms of the primary ciliary apparatus
56	**Kearns–Sayre syndrome** mitochondrial cytopathy; ophthalmoplegia plus; oculocraniosomatic disease; oculocraniosomatic neuromuscular disease with ragged red fibers; spontaneous inheritance; 1:125,000; various mitochondrial DNA deletions transmitted from mother
57	**King–Denborough syndrome (KDS)** malignant hyperthermia susceptibility 1; King syndrome; autosomal dominant; 1:5000–15,000 children
58	**Kleeblattschladel syndrome** cloverleaf skull syndrome; autosomal dominant or sporadic; gene locus not identified
59	**Klinefelter syndrome** 47, XXY, XXY trisomy; variants with XXXY, XXXXY, and XXYY karyotypes
60	**Klippel–Feil syndrome** autosomal dominant and recessive forms; some sporadic; 1:1500–5000; mutation chromosome 8q22.1 or 12p13 (dominant); or 17q21 or 22q12(recessive) or GDF6 or GDF3 gene (dominant) or MEOX1 or MYO18B gene (recessive); cartilage and bone growth factor proteins
61	**Klippel–Trenaunay–Weber syndrome** angio-osteohypertrophy syndrome; sporadic inheritance; mutation on chromosome 8q22.3; rare, several hundred cases reported; AGGF1: angiogenic factor 1 gene may be involved

(*Continued*)

No.	Syndrome: name, eponyms, inheritance, incidence, gene locus, gene product
62	**Larsen syndrome**
	autosomal dominant; a recessive form also exists
63	**LEOPARD syndrome**
	multiple lentigenes syndrome; cardiomyopathic lentiginosis; autosomal dominant; very rare: approximately 100 reported cases; heterozygous mutation in the PTPN11 gene on chromosome 12q24.13; protein-tyrosine phosphatase, non-receptor-type 11 (PTPN11): regulates intercellular signaling
64	**Limb–girdle muscular dystrophy**
	autosomal recessive or dominant; 1–9:100,000
65	**Loeys–Dietz syndrome**
	Furlong syndrome; autosomal dominant
66	**Long QT**
	prolonged QT syndrome including Jervell–Lange–Nielson, Romano–Ward, and Andersen syndromes; autosomal dominant or recessive; approx. 1:10,000; at least 12 different mutations mostly of sodium and potassium channel protein genes
67	**Marfan syndrome**
	variable inheritance; often autosomal dominant; 1:3000–10,000; mutation fibrillin-1 gene: connective tissue protein
68	**Maroteaux–Lamy syndrome**
	mucopolysaccharidosis VI; arylsulfatase B deficiency autosomal recessive 1:238,000–433,000 homozygous or compound heterozygous mutation in the ARSB gene on chromosome 5q14.1 deficient arylsulfatase B; lysosomal enzyme that removes the C4 sulfate ester group from the N-acetylgalactosamine sugar residue at the non-reducing terminus of the glycosaminoglycans dermatan sulfate and chondroitin sulfate
69	**McCune–Albright syndrome**
	somatic mosaicism, not inherited; rare, 1–9:1 million; encoding guanine nucleotide-binding protein, α-stimulating polypeptide; stimulatory G protein involved in numerous adenylyl cyclase-mediated intracellular functions, including ACTH, TSH, FSH
70	**MELAS syndrome**
	spontaneous inheritance; rare disease; various mitochondrial DNA deletions transmitted from mother
71	**Menkes kinky hair syndrome**
	kinky hair syndrome, Menkes disease; steely hair disease; copper transport disease; X-linked recessive; 1:254-357,000; mutation chromosome Xq21.1
72	**MERFF syndrome**
	myoclonic epilepsy with ragged red fibers; spontaneous inheritance; 1:400,000; various mitochondrial DNA deletions transmitted from mother
73	**Miller syndrome**
	postaxial acrofacial dysostosis syndrome; Genee–Wiedemann syndrome; autosomal recessive; extremely rare; compound heterozygous mutation in the DHODH gene on chromosome 16q22.2
74	**Moebius syndrome**
	variable inheritance; 1:50,000; mutation chromosome 13q12.2-q13; gene product unknown
75	**Morquio syndrome**
	mucopolysaccharidosis IV, mucopolysaccharidosis IVA, galactosamine-6-sulfatase deficiency; autosomal recessive; 1:216,000–640,000 (A and B); mutation chromosome 16q24.3; deficiency in galactosamin-6-sulfatase; lysosomal enzyme involved in the catabolism of keratan and chondroitin sulfate
	Mucopolysaccharidosis IVB
	autosomal recessive; 1:216,000–640,000 (A and B); mutation chromosome 3p22.3
76	**Myotonic dystrophy, type I**
	Steinert disease; congenital myotonic dystrophy; autosomal dominant, variable penetrance; all forms: 1:8000, congenital variety is a small proportion; DMPK gene: myotonic dystrophy protein kinase
77	**Nager syndrome**
	mandibulofacial dysostosis with proximal limb anomalies; autosomal dominant and recessive reported; very rare disorder: approximately 100 reported cases; heterozygous mutation in the SF3B4 gene on chromosome 1q21.2; ZFP37 candidate gene; protein for cartilage development
78	**Neurofibromatosis (NF)**
	neurofibromatosis type 1
	von Recklinghausen disease; autosomal dominant; 50% arise as new mutations; 1: 3500; mutation chromosome 17q11.2; neurofibromin gene 1: GTPase activating enzyme
	neurofibromatosis type 2
	autosomal dominant; 50% arise as new mutations; 1:50,000–120,000; mutation chromosome 22q12.2; neurofibromin 2 gene; merlin: cytoskeletal protein
79	**Noonan syndrome**
	male Turner syndrome; female pseudo-Turner syndrome; Turner phenotype with normal karotype; autosomal dominant; 1:1000–2500; heterozygous mutation in the PTPN11 gene on chromosome 12q24.13 (about 50% of patients); wide genotypic and phenotypic variability; PTPN11 gene: protein tyrosine phosphatase SHP-2: modulates intercellular signaling including epidermal growth factor receptor
80	**Oral–facial–digital syndrome (OFDS)**
	OFDS type 1
	Papillon–Leage syndrome; Psaume syndrome; X-linked recessive; very rare; mutation chromosome Xp22.2; CXORF5 gene: unknown gene product
	OFDS type 2
	Mohr syndrome; sporadic inheritance; very rare; chromosome defect not identified

No.	Syndrome: name, eponyms, inheritance, incidence, gene locus, gene product
81	**Osler–Weber–Rendu syndrome** hereditary hemorrhagic telangiectasia; autosomal dominant; 1:5000–8000; HHT 1; mutation cromosome 9q34.1; ENG gene: endoglin, a receptor of TGF-β1; HHT2 mutation chromosome 12q11-14; ACVRL1 gene: codes for Alk-1, a TGF-β1 receptor
82	**Osteogenesis imperfecta** brittle bone disease; autosomal dominant; 1:20,000; mutation chromosome 17q21.31-q22, 7q22.1; COL1A1 or 1A2 gene: abnormal amount collagen I
83	**Pallister–Hall syndrome** hypothalamic hamartoblastoma; hypopituitarism; imperforate anus; postaxial polydactyly; autosomal dominant; very rare; heterozygous mutation in the GLI3 gene on chromosome 7p14.1; GLI3 gene (Gli-Kruppel family member 3): protein controlling gene expression: zinc finger transcription factor that functions in the hedgehog signal transduction pathway
84	**Pentalogy of Cantrell** thoracoabdominal syndrome; Cantrell pentalogy; sporadic; some cases X-linked; very rare, 5.5:1 million; mutation chromosome Xq25-q26.1 in some patients
85	**Pfeiffer syndrome** acrocephalosyndactyly type V; Noack syndrome; autosomal dominant; 1:100,000; mutation chromosome 8p11.23 in some patients; FGFR1 gene: fibroblast growth factor receptor 1; mutation chromosome 10q26.13 in some patients; FGFR2 gene
86	**PHACE association** posterior fossa malformations–hemangiomas–arterial anomalies–cardiac defects–eye abnormalities–sternal cleft and supraumbilical raphe syndrome
87	**Pierre Robin syndrome** Robin sequence; sporadic if non-syndromic, familial if syndromic; 1:8500–14,000; mutation chromosome 17q24.3-q25.1 in some patients; candidate genes: SOX9, KCNJ2, KCNJ16, MAP2K6
88	**Potter syndrome** oligohydramnios sequence; Potter sequence; sporadic; syndrome from many causes of oligohydramnios
89	**Prader–Willi syndrome** sporadic or autosomal dominant; 1:16,000–45,000; absence of paternal genes from the 15q11-q13 segment; SNRPN, P, UBE3A, and necdin gene involvement
90	**Progeria** Hutchinson–Gilford syndrome; sporadic; 1: 8 million; de novo heterozygous mutation in the lamin A gene (LMNA) on chromosome 1q22; lamin A gene: componenet of nuclear envelope
91	**Proteus syndrome** partial gigantism of hands and feet, nevi, hemihypertrophy, and macrocephaly syndrome; sporadic; very rare, about 200 reported cases; mosaicism for a somatic activating mutation in the AKT1 gene on chromosome 14q32.33; AKT1 gene; antogonizes PI3K and MAPK signaling
92	**Prune-belly syndrome** Eagle–Barrett syndrome; autosomal recessive or sporadic; 1:29,000; CHRM3: muscarinic acetylcholine receptor 3
93	**Rett syndrome** austism, dementia, ataxia, and loss of purposeful hand use syndrome; X-linked dominant; 1:15,000–20,000 females; surviving males have Klinefelter's (XXY); mutation chromosome Xq28
94	**Rubinstein–Taybi syndrome** broad thumb–hallux syndrome; broad thumbs and great toes, characteristic facies, and mental retardation; mostly sporadic from *de novo* mutations; autosomal dominant also reported; 1:100,000–125,000; heterozygous mutation in the gene encoding the transcriptional coactivator CREB-binding protein (CREBBP) on chromosome 16p13.3; CREB-binding protein: a nuclear protein participating as a coactivator in cAMP-regulated gene expression
95	**Russell–Silver syndrome** Russell–Silver dwarf; Silver–Russell dwarfism; sporadic or uniparental disomy (10%);1:300–100,000; mutation chromosome 11p15.5 (20–60% of cases), parental disomy 7p11.2 (10% of cases); gene: epigenetic changes of DNA hypomethylation
96	**Saethre–Chotzen syndrome** acrocephalo-syndactyly, type 3; acrocephaly, skull asymmetry, and mild syndactyly; autosomal dominant; heterozygous mutation in the TWIST1 gene on chromosome 7p21, or a mutation in the FGFR2 gene on chromosome 10q26.13; class of transcriptional regulators that recognize a consensus DNA element called the E-box
97	**Schwartz–Jampel syndrome** chondrodystrophica myotonia; myotonic myopathy, dwarfism, chondrodystrophy, and ocular and facial abnormalities; autosomal recessive; very rare; mutation in the gene encoding perlecan (HSPG2) on chromosome 1p36.12; HSPG2 gene, which codes for perlecan, a heparin sulfate proteoglycan
98	**Sickle cell disease** autosomal recessive; mutation chromosome 11p15.4; beta-globin
99	**Smith–Lemli–Opitz syndrome** Rutledge lethal multiple congenital anomaly syndrome; polydactyly, sex reversal, renal hypoplasia, and unilobar lung; lethal acrodysgenital syndrome; autosomal recessive; 1:20,000–40,000; homozygous or compound heterozygous mutation in the gene encoding sterol delta-7-reductase (DHCR7), on chromosome 11q13.4
100	**Sotos syndrome** cerebral gigantism; chromosome 5q35 deletion syndrome; sporadic, autosomal recessive, or dominant; 1–9:100,000
101	**Spinal muscular atrophy (SMA) types I and II (Werdnig–Hoffmann disease)** autosomal recessive; all types: 1:10,000 total incidence ***SMA I***: acute Werdnig–Hoffman disease, acute infantile SMA autosomal recessive; 1:25,000; gene: SMN1; regulates telomeres ***SMA II***: chronic Werdnig–Hoffman disease, intermediate SMA compound heterozygous mutation in the SMN1 gene on chromosome 5q13.2

(*Continued*)

No.	Syndrome: name, eponyms, inheritance, incidence, gene locus, gene product
102	**Spinal muscular atrophy (SMA) type III (Kugelberg–Welander disease)** juvenile spinal muscular atrophy; mild SMA; Kugelberg–Welander disease; autosomal recessive; gene: SMN1; regulates telomeres
103	**Stickler syndrome** arthro-ophthalmopathy, hereditary progressive; autosomal dominant; 1:7500–9000; mutation chromosome 12q13.11; genes: COL2A1, COL11A1, COL11A2, COL9A1; abnormal collagen type II and XI
104	**Sturge–Weber syndrome** encephalotrigeminal angiomatosis; sporadic; some casued by somatic mosaic mutation in the GNAQ gene on chromosome 9q21.2; 1:50,000
105	**Thrombocytopenia–absent radii syndrome** TAR syndrome; inheritance unclear, some autosomal recessive; 1:250,000; chromosome deletion at 1q21.1
106	**Treacher Collins syndrome** mandibulofacial dysostosis; Franceschetti–Klein syndrome; autosomal dominant, 50% *de novo* mutations; 1:50,000; mutation chromosome 5q32-q33.1; TCOF1 gene (treacle): ribosomal DNA transcription
107	**Trisomy 13** Patau syndrome; sporadic: meotic non-dysjunction; 1:10,000; chromosome 13 trisomy
108	**Trisomy 18** Edwards syndrome; sporadic: meotic non-dysjunction; 1:6000–8000; chromosome 18 trisomy
109	**Tuberous sclerosis** autosomal dominant; 1:12,000–14,000; mutation chromosome 9q34 (TSC1) or 16p12 (TSC2); gene: TSC1–hamartin, TSC2–tuberin–tumor-suppressing proteins
110	**Turner syndrome** XO syndrome; gonadal dysgenesis; meotic non-dysjunction, mosaicism; 1:2500 females; monosomy chromosome X; half of patients are mosaic (45 XO/46 XX) with milder manifestations
111	**Uhl anomaly** arrythmogenic right ventricular dysplasia; autosomal dominant
112	**VACTERL/VATER** sporadic inheritance; 1:17,000; possible defects at chromosome 2, 7, 16 (animal models); candidate genes: SHH, FOX gli
113	**von Hippel–Lindau syndrome** autosomal dominant; 1:36,000–45,000; heterozygous mutation in the VHL gene on chromosome 3p25.3; tumor suppressor gene
114	**Weaver syndrome** Weaver–Smith syndrome; sporadic inheritance; very rare syndrome; heterozygous mutation in the EZH2 gene on chromosome 7q36.1; histone methyltransferase that initiates epigenetic silencing of genes involved in cell fate decisions
115	**Whistling face syndrome** Freeman–Sheldon syndrome; craniocarpotarsal dysplasia; whistling face–windmill vane hand syndrome; craniocarpotarsal dystrophy; craniocarpotarsal dysplasia; distal arthrogryposis type 2A; sporadic or autosomal dominant; very rare syndrome; mutation chromosome 17p13.1; gene: myosin heavy chain 3
116	**Williams syndrome** Williams–Beuren syndrome; autosomal dominant or spontaneous inheritance; 1:10,000; deletion chromosome 7q11.23; gene: elastin
117	**Wilson disease** hepatolenticular degeneration; autosomal recessive; 30:1 million
118	**Wiskott–Aldrich syndrome** eczema–thrombocytopenia–immunodeficiency syndrome; immunodeficiency 2; IMD2; X-linked recessive; 1:250,000 males; mutation chromosome Xp11.23; gene: Wiscott–Aldrich syndrome protein
119	**Wolff–Parkinson–White syndrome** WPW; pre-excitation syndrome
120	**Zellweger syndrome** cerebrohepatorenal syndrome; autosomal recessive; very rare disorder; mutations chromosome 1p36.2, 1q22, 6p, 6q, 7q21, 8q, 12; genes: multiple peroxisome genes, PEX1 most common

ACTH, adrenocorticotrophic hormone; FSH, follicle-stimulating hormone; GABA, γ-aminobutyric acid; IM, intramuscular; TGF, transforming growth factor; TSH, thyroid-stimulating hormone; VSD, ventricular septal defect.

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A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 44
Pediatric Anesthesia in Developing Countries

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Organization

Children under 15 years constitute more than half the population in many developing countries [1–3]. Many of these children are victims of circumstance, orphaned by human immunodeficiency virus (HIV) [3,4], natural disasters, war, social unrest, economic crises, and famine. Providing anesthesia for children in the developing world can be very challenging [5–9] because for the most part anesthetic practice has not kept pace with the advances made in the developed countries [7]. Our understanding of anesthesia in the developing world is based on personal experience or anecdotal reports provided by local healthcare workers or visitors on medical missions. This reflects the low incentive to publish in the face of a heavy clinical workload and staff shortages.

Many developing countries have a colonial history and were exploited for their raw materials. The infrastructure was developed for the benefit of the colonial power and not the country or region [2,3]. As a result, many of these countries are today characterized by poverty, poor housing and educational standards, and limited health resources and social services (Figs 44.1 and 44.2) [1,5,7–13]. Of the world's poorest countries, 70% are in sub-Saharan Africa [11–13], an area ravaged by HIV, malaria, and tuberculosis [4].

Access to safe anesthesia and pain relief following surgery is considered a basic human right. International standards for the safe practice of anesthesia, adopted by the World Federation of Societies of Anaesthesiologists (WFSA), are seldom met in developing countries [5,14]. As recently as 2015, the World Bank and Lancet Commission on Global Surgery and World Health Assembly have prioritized surgery in low income countries (LIC) and low middle income countries (LMIC) [15,16]. This is consistent with the shift in the global burden of disease from communicable to non-communicable disease [17]. Also for the first time surgery and anesthesia received prominence at the World Health Assembly [15].

Essential surgery needs to be performed safely. Provision of safe anesthesia requires trained anesthetists, essential equipment, consumables, and drugs [18–23]. These essentials are not always available in the operating rooms of the developing world [20–23]. Many issues published in previous decades persist and, in many instances, are remarkably similar to those seen today [2,13,22–25]. Improving the safety of surgery and anesthesia worldwide, but particularly in the developing world, has become the focus of the World Health Organization (WHO), WFSA, and other organizations [19–23].

Different countries have different problems demanding different solutions. Conditions may even vary significantly within the same country [2,5]. The essential differences include the medical personnel and their level of training, the spectrum and nature of disease, the facilities, including access to electricity, running water, and oxygen, the equipment available, and access to cheap, generic, and perhaps outmoded drugs (Fig. 44.3) [8,17,24–26,28–30]. The ratio of anesthetists to population varies greatly (Fig. 44.4). Perioperative mortality and morbidity are high by developed world standards and, not surprisingly, inversely related to the anesthetic manpower (Table 44.1) [31]. The expectations of the local population are often commensurate with the facilities and quality of the available care. Patients may refuse surgery simply because the cost is prohibitive in the face of a meager salary, difficulty in borrowing money from family or the community, or the need to support other children [32].

Anesthesia does not enjoy a high profile and lacks the voice to demand access to resources in developing countries [17]. Anesthesia is not perceived to be an attractive career for many undergraduates [33–35] who receive little, if any, exposure to the specialty [36–38]. Indeed, even today, very few developing countries can afford specialist anesthesiologists, except perhaps in the principal hospitals [14,15,29,39,40]. The "pediatric anesthesiologist" is invariably someone who may have a special interest or affinity for children or simply allocated to

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

pediatric anesthesia for the day because there is no one else. Pediatric anesthesiologists per se are a luxury.

Some two decades ago the Education Committee of the WFSA set out to establish pediatric anesthesia fellowship training programs. The aim was to train individuals from a medically disadvantaged country in a more medically advanced country, ideally in their own language [21]. Whether this training should take place on site within a given country or off site in an established program has been a topic of debate recently [38–49].

Figure 44.1 Victims of war. Mutilating injuries acquired over two decades ago during the Rwandan genocide received basic treatment only. Child survivors face an intense struggle for survival as a consequence of displacement, separation from or loss of parents, poverty, hunger, and disease in countries that are subject to total collapse of economic, health, social, and educational infrastructures.

Through a WFSA-driven sponsorship program, a cohort of pediatric anesthesiologists is being trained in Chile [46], Tunisia, South Africa, and Kenya [21,41,44]. In addition, many institutions and organisations have created partnerships in the LIC and LMIC countries to improve education and training in both surgical and anesthesia care with the overarching goal of sustainability [45]. The advantage of this training is that the trainees are exposed to similar problems to those they would encounter in their own country. On completion of their training, they must return to their country of origin and champion the development of pediatric anesthesia as a speciality [2,21,41]. In those countries where a training program has been developed, the value of a pediatric anesthesiologist is enormous [21,44].

The vast majority of anesthetics are still delivered by non-physicians [2,5,13,50–52], a reality that has remained constant over many decades. Supervision of "non-physician anesthetists" or "anesthetic officers" is invariably inadequate [38,41,51,53,54] and access to textbooks, journals, or other medical literature is limited [2,5,13]. Internet access and communication has made access to educational material easy but is hindered by unreliable electrical supply and telecommunication networks.

Some countries, such as Nigeria, Kenya, and India, have trained significant numbers of physician anesthetists, but these physicians tend to practice in large hospitals in urban areas [2,6,39]. The majority of anesthetics in rural communities are still provided by nurses or unqualified personnel, with little medical background, who are "trained on the job" [2,5,13,39,50]. In many African [17,39,55] and Asian countries [56], the doctor/patient ratio is so low that the ideal of employing a physician specifically to provide routine anesthesia is out of the question [2,31,34]. Salaries are insufficient to attract suitably trained and qualified practitioners for more than short periods. The emigration of scarce trained personnel to developed countries in search of better salaries and an improved lifestyle exacerbates these shortages [2,33,34,57].

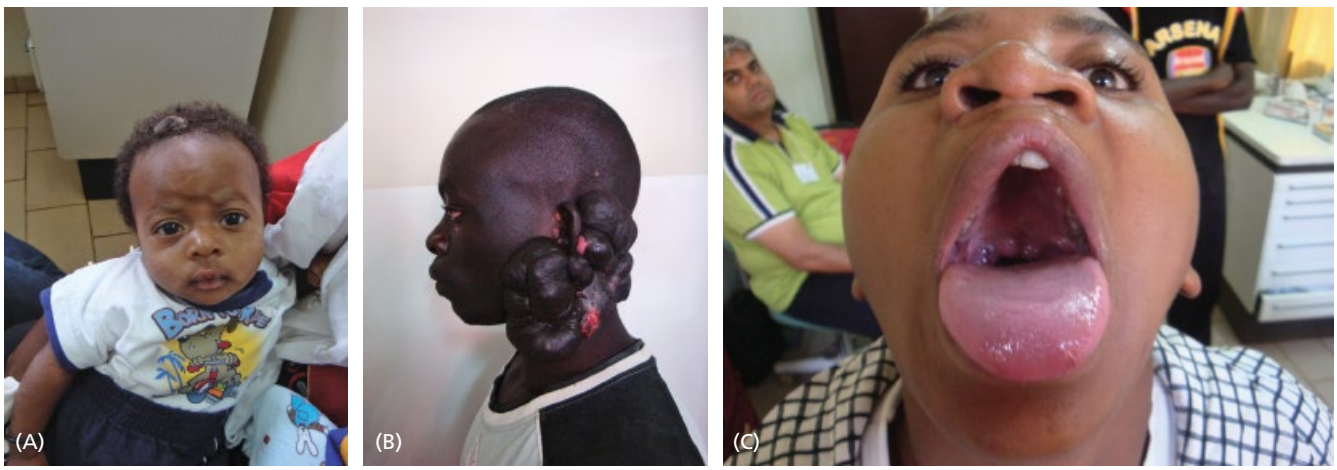

Figure 44.2 Traditional healers and tribal customs. Traditional healers play a significant role in healthcare. (A) A potion had been placed over this baby's fontanelle to close it. (B) Extensive keloid formation after injury or tribal scarification is a common complication in Africa. Tribal ear piercing as a child led to this disfiguring keloid formation. Access to specialist treatment is limited. (C) This child had a uvulectomy performed to ward off "evil spirits" and treat a sore throat.

Figure 44.3 Anesthesia equipment. (A) Boyles machine. Considered obsolete in many developed countries, this machine was used to provide anesthesia for a newborn. The 2 L bag on the T-piece was patched with zinc oxide tape and was used by the author to successfully resuscitate a newborn delivered by emergency caesarean section. (B) Drug cupboard. Anesthetic supplies are basic, similar colored glass ampoules are poorly labeled and almost illegible. The risks of administering the wrong drug, as a result, are high. (C) Diathermy. A steel plate with poor connections places the child at risk of an electrical burn.

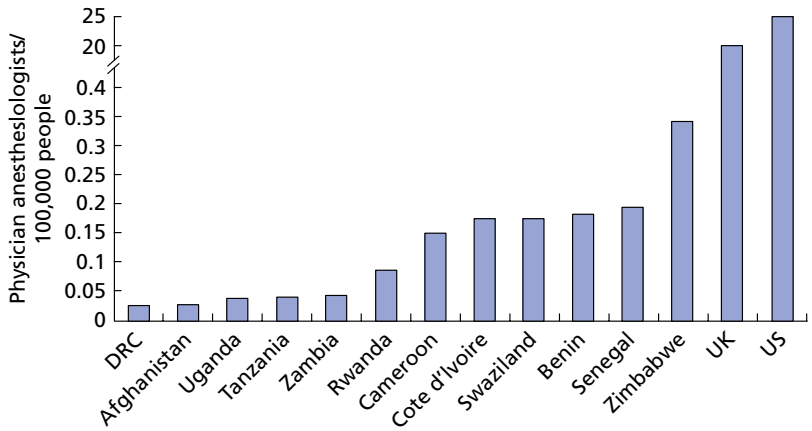

Figure 44.4 Anesthesia providers per 100,000 people. *Source*: Reproduced from Dubowitz et al [31] and Bridenbaugh [133] with permission of Springer Nature.

Table 44.1 Anesthetic mortality per 100,000 and the year reported [25,121,130–132]

Year	Country	Anesthetic death rate	Hospital setting	Reference
1987	Zambia	1:1925	University/teaching	25
2000	Malawi	1:504	Central	25
1994–2001	Zimbabwe	1:482	District	25
2006	Nigeria	1:387	Teaching	25
2005	Togo	1:133	Teaching	25
2007	Pakistan	1: 5556	University	25
2002	Ghana	1:1250		121
2007	Benin	1:103	University	130
1996–2004	Brazil	1:1020	Tertiary/teaching	131
1992–2006	Pakistan	1:2888	University/teaching	132
1987	United Kingdom	1:185,000		25

KEY POINTS: ORGANIZATION OF ANESTHESIA SERVICES

- Most of the children undergoing anesthesia in developing countries do so by inadequately trained people
- Several organizations are working to improve the number of trained anesthetists, but it will take many years to provide them
- Trained anesthetists often leave for better opportunities in developed countries

Equipment procurement and maintenance

Essential equipment to provide safe anesthesia for children, particularly neonates, is often lacking (Fig. 44.3) [2,12–14,20,30,39,50,58–63]. Neonatal or pediatric ventilators are virtually non-existent outside the main centers [12,59,60,62]. Syringe pumps and other control devices are impractical in environments that have an erratic electricity supply. Laryngoscopes, both metal and plastic, are usually available but generally not well maintained. Even batteries may be in short supply and light bulbs unreliable. Endotracheal tubes in the full pediatric range are seldom available; disposable endotracheal tubes are consequently recycled as there is little or no alternative [18,63]. Laryngeal mask airways (LMAs) in pediatric sizes are considered a luxury. Intravenous fluids are expensive if not manufactured locally, and many developing countries do not have any local production facilities [6]. The choice of intravenous fluid is therefore limited and in relative short supply.

Unreliable electrical supplies add to the challenges in the developing world. In many hospitals, particularly in rural areas, neither mains electricity nor reliable and functional back-up generators are available [2,5,14,17,61,64]. General facilities for infection control, such as running water, disinfectants, or gloves (sterile or non-sterile), are not constantly available even though the reuse of disposable equipment is "normal" practice in many countries [5,13,18,65].

Anesthetic machines fall into two categories: modern sophisticated machines or simple low-maintenance equipment [64]. Modern electronic machines, provided by well-meaning international donors, have a poor track record in austere environments [1,2,12,13,18]. Sophisticated equipment needs to be understood but operating manuals provided in a foreign language are of no benefit. Sophisticated machines require maintenance and technicians trained to repair them. Service contracts are not considered viable. Unfortunately, these machines are consequently discarded when the first fault occurs. Guarantees are unlikely to be honored and faults are considered too expensive to repair. Poorly maintained equipment becomes hazardous and even life threatening in untrained hands [64].

Simplicity and safety have long been the key to anesthetic equipment in developing countries [6,13,18,66–68]. Ideally the anesthetic machine should be inexpensive, versatile, robust, able to withstand extreme climatic conditions (temperature (hot or cold), humidity, dust and altitude), able to function even if the supply of cylinders or electricity is interrupted, easy to understand and operate by those with limited training, economical to use, and easily maintained by locally available skills [68--70]. The cheapest, most practical, and most widely used anesthetic is inhalational anesthesia administered through an EMO (Epstein Macintosh Oxford) or OMV (Oxford miniature vaporizer) draw-over vaporizer [18]. Oxygen concentrators supplement oxygen delivery and eliminate the need for expensive oxygen cylinders whose reducing valves are often faulty or destroyed in austere environments. The most appropriate ventilator is the Manley multivent ventilator, which essentially functions like a mechanical version of the OIB (Oxford inflating bellows) and can be used with a draw-over system [70].

A general scheme for inhalation anesthesia in developing countries is shown in Figure 44.5 [71], first proposed by Ezi Ashi et al [72]. Four different modes can be used and can be modified according to the available supplies and services. The basic mode A is for use when there is no electricity and no supply of compressed gases. The apparatus consists of a low-resistance vaporizer, linked by valves to the patient to act as a draw-over system with room air as the carrier gas. The self-inflating bag or hand bellows makes it possible to provide artificial ventilation while the vaporizer remains as a draw-over. The addition of low-flow oxygen to the inspired gas (mode B) is dependent on the availability of an oxygen cylinder. The addition of a length of reservoir tubing to the circuit enables oxygen to be stored on expiration, to be used on the next inspiration, making it substantially more economical [73]. When electricity is available (mode C), the operation of the anesthetic apparatus can be extended by permitting (1) the use of an air compressor to provide continuous gas flow (which in turn will allow the use of a Boyles apparatus and plenum vaporizer); (2) oxygen concentrator; and (3) ventilators. When nitrous oxide is available (mode D) all types of inhalation anesthesia currently available in developed countries can be practiced. In situations where services and supplies are interrupted it is possible to change from one mode to another without requiring other anesthetic apparatus.

Draw-over anesthesia enables inhalation anesthesia to be administered using atmospheric air as the carrier gas [18]. The essential features of this system consist of a calibrated vaporizer with sufficiently low resistance (EMO and OMV) to allow the negative pressure created by the patient's inspiratory effort to draw room air through the vaporizer during spontaneous ventilation. Positive pressure ventilation can be provided by means of a self-inflating bag or bellows (OIB), with a valve to prevent the gas mixture re-entering the vaporizer, as well as a unidirectional valve at the patient's airway to direct expired gases to the atmosphere, preventing rebreathing (mode A, Fig. 44.5). In this way an anesthetic can be administered in the absence of compressed gases. The vaporizer has an inlet for supplementary oxygen that can be attached to the oxygen output tube of an oxygen concentrator, or oxygen cylinder if available (modes B and C, Fig. 44.5).

The EMO and OMV (both Penlon Ltd, Abingdon, UK) are the more commonly used low-resistance vaporizers [18]. The EMO is only calibrated for ether but its performance is linear for other agents. The OMV is calibrated for a variety of agents [68,70]; despite the lack of temperature compensation, its performance is stable under most conditions. Both these vaporizers have been used successfully in pediatric anesthetic

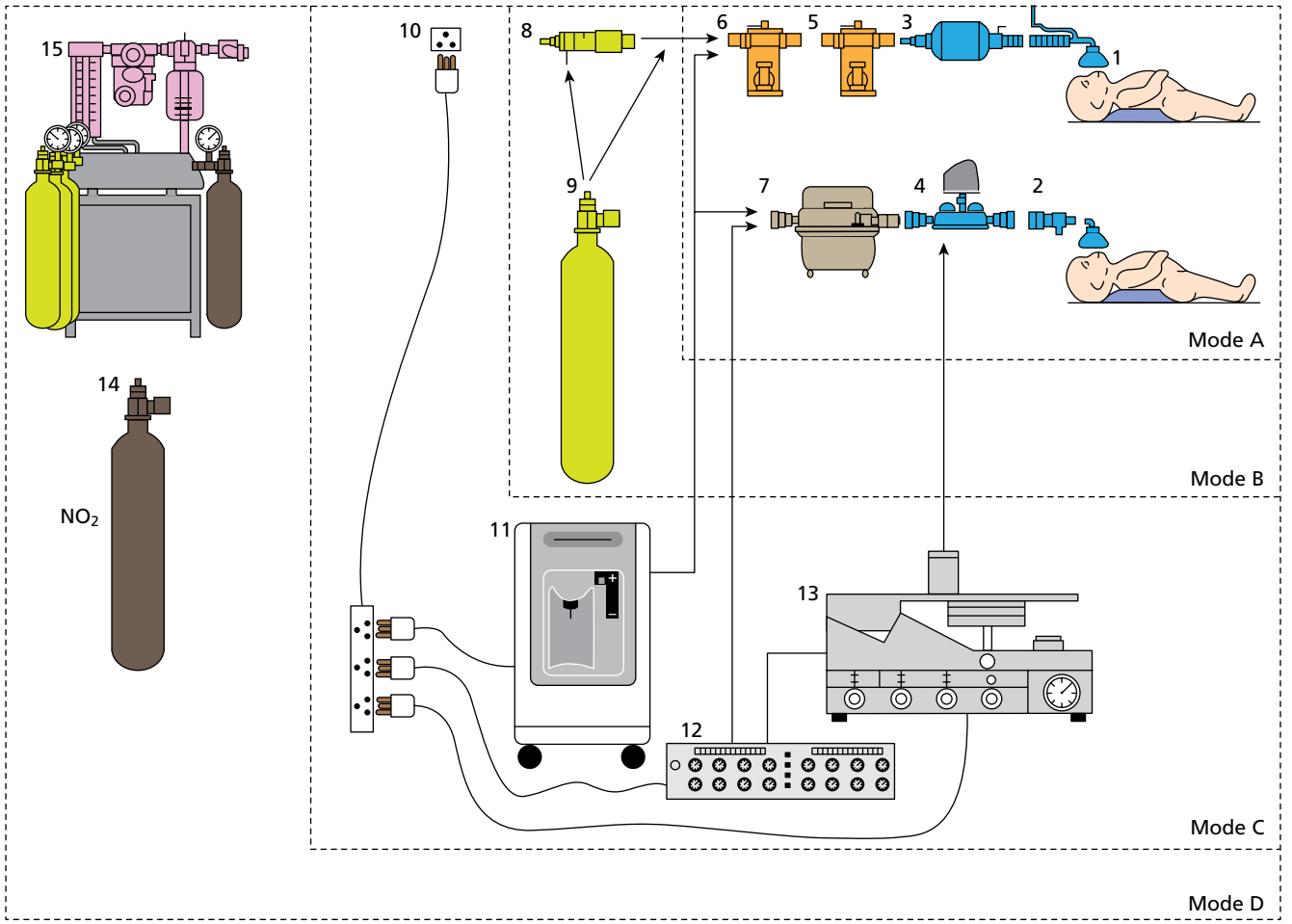

Figure 44.5 A schematic diagram of anesthetic systems that could be used, depending on available resources. Mode A provides basic inhalation anesthesia with air, spontaneous ventilation, or self-inflating bags. Draw-over vaporizers are required. Mode B provides oxygen enrichment but requires the availability of oxygen cylinders. Plenum vaporizers can be used. Mode C requires electricity to power the oxygen concentrator, air compressor, and/or ventilator. A mechanical ventilator (e.g. Manley) does not require electrical power. Mode D requires a Boyles machine and nitrous oxide cylinders. 1, T-piece with reservoir tube and facemask; 2, Ambu paedi valve; 3, self-inflating bag (Ambu); 4, Oxford inflating bellows; 5, Oxford miniature vaporizer (OMV) with halothane; 6, OMV with trichloroethylene; 7, EMO (Epstein Macintosh Oxford) vaporizer with ether. These circuits and manual ventilators are interchangeable and ether, halothane, and trichloroethylene can be used on their own or in series. 8, Farman's entrainer with an oxygen cylinder (9) can be used to supplement oxygen, or an electrical power source (10) is available with an oxygen concentrator (11), air compressor (12), or Manley ventilator (13). Nitrous oxide (14) and Boyles apparatus (15) allow anesthesia practice equivalent to that of developed countries.

practice [27], but it is recommended that they be converted to form a T-piece for greater safety.

The OMV has been evaluated as a simple draw-over system for pediatric anesthesia. Wilson and Walker [58] showed that when a self-inflation bag is used in a draw-over mode, more efficient vaporization occurs despite vaporizer cooling. However, the respiratory efforts of neonates or weak infants are insufficient to operate the valve mechanisms of the self-inflating bag, e.g. Ambu-bag, necessitating continuous assisted ventilation even in the presence of ether, which stimulates ventilation.

Oxygen concentrators can improve oxygen availability, independent of compressed gas and electrical power supply, by linking oxygen concentrators to a draw-over anesthetic apparatus as first described by Fenton [74]. Maintenance requirements are low and servicing is recommended only after approximately 10,000 h of usage. The benefits are enormous, but a reliable electricity supply is critical.

The concentrator functions by using a compressor to pump ambient air alternately through one of two canisters containing a molecular sieve of zeolite granules that reversibly absorb nitrogen from compressed air [70,75]. The controls are simple and comprise an on/off switch for the compressor and a flow-control knob to deliver 0–5 L/min. Flow of oxygen continues uninterrupted as the canisters are alternated automatically so that oxygen from one canister is available while the other regenerates. A warning light on a built-in oxygen analyzer illuminates if the oxygen concentration is <85% and the concentrator switches off automatically when the oxygen concentration is <70%. This is heralded by visual and audible alarms. Air is then delivered as the effluent gas. Modern machines are relatively silent.

The oxygen output of the concentrator depends on the size of the unit, the inflow of oxygen, the minute volume, and pattern of ventilation. The addition of dead space (or oxygen economizer tube) at the outlet improves the performance, and predictable concentrations >90% oxygen can be obtained with flows between 1 and 5 L/min independent of the pattern of ventilation. Much lower concentrations and less predictability were noted when the dead space tubing was omitted [73].

The possible hazards of oxygen concentrators are few, provided they are positioned in the operating room so that the in-draw area is free from pollutants. Failure of power supply or failure of the zeolite canisters will result in the delivery of ambient air. A bacterial filter at the outlet combined with the use of dust-free zeolite should prevent contamination of the delivered gas. Dirty internal air filters may produce lower oxygen concentrations and must be checked. An oxygen storage tank and booster pumps afford protection against the vagaries in electrical supply.

Intravenous fluid administration must also be given careful consideration [2]. Small intravenous cannulas are a precious commodity and butterfly needles are still used (and in some cases reused) [76]. Syringe pumps and other control devices are impractical in environments that have an erratic electricity supply [2]. Unmonitored IV lines can have disastrous consequences including volume overload, sepsis, tissue loss, compartment syndrome, or even loss of limb [2]. The choice of intravenous fluid is often limited and in short supply [2,70,77,78].

KEY POINTS: EQUIPMENT

- Drugs, oxygen, and facilities (e.g. intensive care units) are often unavailable
- Equipment for providing anesthesia for children (masks, endotracheal tubes, etc.) is often absent
- Monitors are often not available; when they are, they may not function because they are broken and cannot be repaired or because the electricity is unreliable
- Much of the equipment donated by developed countries is non-functional and cannot be repaired

Evaluation of patients

The burden of disease in the poorest countries is formidable. Children of the developing world are victims of circumstance, natural disasters, war, social unrest, and economic crises [8,12,79-82]. An estimated 10 million children die annually before their 5th birthday [5,81,83]; that is one of every six children born in Africa, and one of every 12 children born in South Asia [5]. Approximately 50% of these deaths occur in the neonatal period [5] and birth asphyxia, prematurity, sepsis, and tetanus are the major causes. In the older child, diarrhea, pneumonia, malaria, HIV/AIDS, measles, and trauma are major causes [5,81,84].

For many in rural areas, timely access to medical care is a remote possibility (Figs 44.1 and 44.6) [76,77]. Fear, poor understanding, and lack of education often result in delayed presentation to medical facilities [13,85–87]. Illiterate people in rural areas may simply not be aware that surgical treatment is possible [18]. Superstition may also play a role in compounding the anesthetic risk. Frequently, well-meaning traditional healers have had prior involvement, exposing the child to additional risk (see Fig. 44.2) [2,19,88] caused by potions that may be hepatic-renal toxins or enemas that may perforate the bowel [89–91]. Further delays are engendered when patients have to undertake long journeys to hospital. As a result, dehydration, infection, sepsis, and complications

Figure 44.6 In many developing countries worldwide, the failure to provide surgical services may lead to lifelong disability, social exclusion, or even premature death. This family all had an isolated cleft lip that had remained unrepaired until they were successfully treated during a volunteer mission with Operation Smile South Africa.

compound the surgical problem and the anesthetic risk. Tertiary referral is often only made when complications arise [8,12,13,50,64,90–92].

Perinatal mortality in some parts of the developing world is 10 times greater than that in developed countries [5,59,60,83]. The common denominators include early child-bearing, poor maternal health and, above all, the lack of appropriate and quality medical services. One-third of pregnant women still have no access to medical services during pregnancy, and almost 50% do not have access to medical services for childbirth [12,78,82]. The majority of parturients deliver at home or in rural health centers [78] where basic neonatal resuscitation equipment is often deficient or non-existent [12]. Those who require surgery may need to be transferred, but specialized transport teams rarely exist.

The safe administration of anesthesia should take into account the pre-existing condition of the child. Preoperative investigations are generally limited, perhaps stretching to hemoglobin and screening for malarial parasites. There are few functional laboratories in the rural areas and trained technicians are virtually non-existent. Similarly, radiographic studies are often rudimentary and of poor quality [2,9,18]. Even an experienced anesthesiologist with minimal access to laboratory or radiographic investigations and limited in the choice of resuscitation fluid would be challenged to manage these children.

Co-morbidities need to be excluded or treated prior to elective surgery. Tuberculosis (TB) remains an important cause of morbidity and mortality [50,93]. The epidemiology of pediatric TB is shaped by risk factors such as age, race, immigration, poverty, overcrowding, and HIV/AIDS [65,93–96]. The emergence of drug-resistant TB adds to the burden and is a constant danger to healthcare workers in general and anesthesiologists in particular. Primary TB infection usually does not produce clinical illness in well-nourished immunized children, whereas reactivated pulmonary TB is a chronic or subacute disease, which may present a variety of challenges for the anesthesiologist. These range from a need to prevent transmission by contamination of the anesthetic

circuits to the risks associated with pleural effusions, pulmonary cavitation, and bronchiectasis. Mediastinal and hilar lymphadenopathy may severely compromise the airway. Primary TB and its complications are more common in children than in adults. Once infected, young children are at risk of progression to extrapulmonary disease [93,94]. *Mycobacterium tuberculosis* can cause symptomatic disease in any organ, and is usually a reactivation of a latent site of infection. The most common sites of reactivation are lymph nodes, bones, joints, and the genitourinary tract. Less frequently, the disease may involve the gastrointestinal tract, peritoneum, pericardium, or skin. TB meningitis and miliary TB, both more common in children, carry a high mortality [93]. In view of the high prevalence of HIV infection in tuberculous children, HIV testing should be performed on all children with TB; conversely the presence of TB should be sought in all HIV-positive children [95].

Rheumatic heart disease is more common than congenital heart disease in many developing countries, reflecting the socioeconomic problems of poverty, overcrowding, malnutrition, and lack of antibiotics. Children often present late with life-threatening symptoms secondary to repeated infections and superimposed endocarditis. The acute deterioration precipitated by endocarditis may be the factor that prompts the search for medical attention. Valve replacement can be life saving but long-term follow-up of anticoagulant therapy is not feasible without laboratory facilities nearby.

Malaria is caused by one of four species of malaria parasites: *Plasmodium falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. Effective and safe prophylaxis against malaria has become increasingly difficult because the species that causes the most severe illness, *P. falciparum*, has become widely resistant to chloroquine and in some areas to other antimalarial drugs as well [97]. Severe malaria, even when optimally treated, carries a mortality of 10–25% [97]. Prompt diagnosis and early treatment are important determinants of outcome. Uncomplicated malaria usually presents with flu-like symptoms (fever, headache, dizziness, and arthralgia). Gastrointestinal symptoms may predominate and include anorexia, nausea, vomiting, and abdominal discomfort or pain that may mimic appendicitis. Malaria in children can present with an acute life-threatening disease or run a chronic course with acute exacerbations. The acute manifestations include three overlapping syndromes: respiratory distress secondary to a severe underlying metabolic acidosis (pH <7.3), usually a lactic acidemia, severe anemia (hemoglobin <5 g/dL) that can develop hypovolemia very rapidly even within hours [98], and neurological impairment as a manifestation of cerebral malaria. Seizures are an important presenting feature in 60–80% of cases. Prolonged seizures that are refractory to treatment and those that occur on antimalarial treatment are ominous signs and are usually associated with neurological sequelae or death [98].

Children with chronic malaria adjust physiologically to low hemoglobin levels but may decompensate rapidly when challenged with a febrile illness or surgery. The characteristic physical findings in children with severe anemia are respiratory distress and a hyperdynamic circulation. Blood transfusion may need to be administered rapidly in children with metabolic acidosis since most have a depleted intravascular volume. Although controversial, exchange transfusion has been advocated for severe malaria. Unfortunately, many malaria endemic areas also have a high prevalence of HIV, adding significantly to the risk of blood transfusions.

Chronic recurrent malarial infections may manifest with splenic enlargement. This may cause delayed gastric emptying and pose an aspiration risk on induction of anesthesia. The spleen may also enlarge acutely or rupture spontaneously during coughing, vomiting, or defecation. Rupture during external cardiac massage has also been described. Malaria may cause bloody diarrhea with massive loss of fluid resembling dysentery in children. Development of renal failure with severe malaria is not uncommon. Malaria may present preoperatively or may complicate the postoperative course. Children in endemic areas who develop postoperative fever must be investigated for malaria. This is especially true if they have had a blood transfusion.

KEY POINTS: EVALUATION OF PATIENTS

- The burden of disease is great in developing countries, complicating surgery and anesthesia
- Starvation, chronic infections (HIV/AIDS, TB), and malaria are common and often untreated
- Rheumatic heart disease is still present and often affects the outcomes of surgery and anesthesia

Types of surgery

An estimated 85% of children in developing countries will require surgery of some sort before their 15th birthday [4]. Congenital anomalies, trauma (road traffic accidents, assaults, falls, burns, bites, fractures), and infections (abscess, osteomyelitis) make up the bulk of the surgical workload [11–13,85,88,99]. Burns, particularly in young children, affect resources in many developing countries [77] but especially in sub-Saharan Africa [76,99].

While the burden of disease is dominated by infections and malnutrition [65], pediatric trauma has low advocacy and as such is given scant attention [5,12,50,85]. Socioeconomic advances in some countries have introduced a new danger in the form of faster, more powerful vehicles without the necessary maintenance culture or road discipline. Trauma prevention strategies are given low priority despite the acknowledged impact trauma has on the economy of any country. Road traffic accidents are thus inevitable. Additionally, many developing countries are at war and this has led to massive trauma and injuries to children who are both participants in the fighting and innocent bystanders. Effective systems to handle the polytrauma victims that result are hard to find [50]. Even simple bone fractures may have disastrous outcomes. Inappropriate management by traditional bonesetters can result in compartment syndromes or even gangrene [88].

Many pathological conditions, seldom seen in industrialized countries, are more prevalent in developing countries because of poor health education, malnutrition, the close proximity of livestock to humans, earth-floored homes, poor sanitation, and contaminated water supplies.

In some hospitals, neonates are not considered candidates for surgery because "they always die" [73] whereas, in others,

they undergo surgery without anesthesia [100] or under local anesthesia [101] because "it's safer" and some still believe that neonates do not feel pain. When surgery is performed on neonates, there are additional challenges, particularly in emergency situations [78]. Not only is there a lack of appropriately sized equipment [50], but it may be extremely difficult to maintain normothermia even in relatively warm climates, let alone provide ventilatory support.

Regrettably, even neonates who have skillful anesthesia and surgery may die because of inadequate postoperative care [13,102]. Overwhelming infection, sepsis, respiratory insufficiency, and surgical complications are the main causes of morbidity and mortality [12,78]. The development of highly specialized neonatal anesthetic and surgical services [67,100,102], essential for a good outcome after neonatal surgery [12,50,78], is a low priority.

KEY POINTS: TYPES OF SURGERY

- Congenital anomalies, trauma (road traffic accidents, assaults, falls, burns, bites, fractures), and infections (abscess, osteomyelitis) constitute most of the surgery done
- Trauma (especially from wars) is common and requires surgery. Outcomes may be poor due to lack of basic equipment
- In some countries neonates do not receive surgery because it is believed that they will "all die"

Anesthesia monitoring and drugs

Recent surveys have shown that many anesthesiologists in developing countries were not able to provide safe anesthesia for children [2,30,61–63,103,104]. Minimal requirements for anesthesia were an oxygen supply, suction apparatus, a pulse oximeter, a tilting table, a pediatric breathing circuit, a laryngoscope, facemasks, endotracheal tubes, oropharyngeal airways, and intravenous cannulas suitable for use in children [2]. Implausible as these findings may seem to those who have not experienced the austere conditions in some parts of the developing world, many anecdotal reports, both recent and in the past, bear witness to this stark reality.

Monitoring is therefore very basic – a precordial stethoscope or a finger on the pulse [6]. Electrocardiogram (ECG) monitoring is used when available but is also dependent on a constant supply of electricity, ECG pads, and proper maintenance. Appropriately sized blood pressure cuffs are scarce, non-invasive blood pressure monitors even more so. Even though pulse oximetry has been shown to be the most useful monitor, and should be available in all centers where pediatric surgery is performed [6,12], this ideal is far from reality. The Lifebox project, introduced as part of a WHO initiative (Millennium Goal 4) [5,24] to introduce pulse oximetry globally, has been shown to be effective [105,106].

The supply of anesthetic gases and drugs, particularly to rural medical facilities, is erratic and unreliable [5,18]. Furthermore, the cost of many drugs, particularly the modern agents, has risen beyond the reach of most health budgets. Anesthesiologists in developing countries therefore have to resign themselves to using cheaper agents or generics. Halothane remains the mainstay of anesthesia in many countries [2,9,13,27,75], although there are arguments for maintaining the use of the cheaper ether [107]. Unfortunately, ether, and more recently halothane, has virtually disappeared from operating rooms in the developed world. As a result, the demand for these cheaper agents has fallen and lack of profitability claimed by some manufacturers has threatened the withdrawal of halothane [1,18]. While this may make commercial business sense, these agents sustain the anesthesia services for millions of patients in the developing world and their loss would have a huge negative impact [1,18].

In many remote rural areas anesthesia for children remains largely ketamine based [5,13,18,100,108,109], even when halothane or ether is available. Lack of airway equipment such as tracheal tubes, facemasks, or breathing circuits and the perception that intravenous access is not necessary are further reasons for ketamine's popularity in this setting [5,86,110]. Ketamine is simple to use, relatively inexpensive, provides anesthesia, analgesia, and cardiovascular stability, and some preservation of the airway reflexes [2,6,86]. Ideally, ketamine should be used with midazolam to reduce the hallucinatory side-effects. Benzodiazepines, however, are not commonly available.

For developing countries, the cost of nitrous oxide is prohibitive in terms of storage, erratic delivery, and budgetary constraints [72,74]. Closed or semi-closed anesthetic systems are considered dangerous in an environment where the oxygen supply is uncertain [57] and agent monitors are not available [18,64]. The erratic supply of soda lime and compressed gas cylinders further limits the use of nitrous oxide. Consequently, the potential benefits and cost savings of low-flow anesthesia are lost [72]. Scavenging of waste anesthetics is almost non-existent.

The choice of muscle relaxants is also limited [13]. Succinylcholine, gallamine, curare, alcuronium, or pancuronium are the most likely options, and the choice is dictated by their availability or the availability of reversal agents. For this reason, muscle relaxants are not commonly used. Other drugs considered basic to anesthesia are seldom available in the developing world [2,5,13,27]. These include induction agents (propofol), analgesics (morphine, meperidine), reversal agents (naloxone), and long-acting local anesthetics (bupivacaine, ropivacaine). Opioid analgesia may not be permitted in some cultures. The ability to deal with complications, such as malignant hyperthermia, is virtually non-existent. Dantrolene is simply too expensive and the shelf-life too short to be cost-effective.

Regional anesthesia has many benefits in terms of safety, cost savings, and immediate postoperative analgesia [6,12,50,53,78,102,111–114]. Generally, children in developing countries are very accepting of this form of analgesia. However, there seems to be a general reluctance to perform regional anesthesia in children [13,50,53,115] in some institutions in the developed world. Possible reasons include lack of training or expertise, fear of failure, and the unavailability of drugs, disposables, and other ancillary equipment (nerve stimulators, portable ultrasound) [53]. Improvisation may be the key. Access to the epidural space can be obtained if the appropriate equipment is not available by using a technique first described before the introduction of pediatric epidural needles into clinical practice. A catheter can be threaded well

into the epidural space through an intravenous cannula inserted into the caudal space via the sacral hiatus in neonates and small infants [116]. Furthermore, cheap non-insulated needles can be used with a nerve stimulator for peripheral nerve blocks when more expensive insulated needles are not available [117].

KEY POINTS: ANESTHESIA MONITORING AND DRUGS

- Some countries cannot consistently (if ever) supply oxygen, suction apparatus, pulse oximeter, pediatric breathing circuit, laryngoscope, facemasks, endotracheal tubes, oropharyngeal airways, and intravenous cannulas suitable for use in children
- Choice of anesthetic is often limited to halothane or ketamine alone
- Regional anesthesia is not used as often as possible for many reasons

Postoperative pain relief

Posptoperative pain management in children is another factor that divides the developed world from the developing world. Providing pain relief in the face of limited resources, a limited spectrum of analgesics (if available at all), and inadequately trained staff is a challenge [2,13,18]. Attempting to apply similar standards to those used in sophisticated units is fraught with difficulty. Illiteracy, malnutrition, poor cognitive development, differing coping strategies, and pharmacogenetic, cultural, and language differences all add to the complexity of the problem [118,119].

Children of the developing world learn to cope with vastly different problems. Their attitude towards pain, and tolerance thereof, is different. Children from an impoverished background seem more stoical and indifferent to even severe pain. Following cardiac surgery, for example, some appear to need very little pain relief and are easily soothed by lollipops or play therapy [79]. Pain assessment of children from an impoverished background is difficult and may be inaccurate [118–120]. Many children in acute pain do not show facial expression. Is this stoicism or simply a reflection of malnutrition, lack of social stimulation, severity of illness, or even cultural attitude? Language difficulties, cultural barriers, willingness to share information, emotional expressiveness, and outdated attitudes of the caregiver may sanction this quandary [118,119]. Some societies convey pain readily, while others teach that expression of pain is inappropriate; in many parts of Africa, boys are not supposed to express pain. Reporting the pain of testicular torsion, for example, may be delayed and would be considered taboo if the boy lives with his mother only.

Although there are many pain assessment instruments available, few have been validated in children from the developing world [118,119]. There is an urgent need not only to make analgesics universally available but also to develop strategies that can be safely applied to the children living in these areas. Local conditions will dictate their use and applicability. Simple pain management strategies may produce the most benefit with the least risk, whereas more complex techniques that offer the most benefit require a minimum standard of monitoring and regular reassessment to allow individualized titration of analgesia. These are seldom available. The final choice of analgesia, unfortunately, is dictated by economic pressures or by the facilities available rather than what would be considered in the best interest of the child. In many environments, family members must purchase the analgesics used. Financial constraints often make this difficult or impossible. Nonetheless, it is morally, ethically, and physiologically beneficial to provide children with effective analgesia despite the immense inequalities that exist in our world [118].

KEY POINTS: POSTOPERATIVE PAIN RELIEF

- Postoperative pain relief for children is often unavailable
- Some people still believe children do not feel pain
- Nurses often have little or no training in the use of narcotics and monitoring on the ward is left to the parents. Consequently, narcotics are seldom used

Follow-up care

Perioperative morbidity and mortality are understandably high by developed world standards [5,13,64,66,109]. Facilities considered mandatory for the surgical care of children, such as the provision of adequate analgesia, a recovery area for immediate postoperative observation, ventilatory support, or high-level care following surgery [9,12,13,18], are inadequate or non-existent in many parts of the developing world. In some countries, pediatric surgery is considered too expensive in itself, to justify these additional needs [12,13].

There is precious little information on the anesthesia morbidity or mortality in developing countries [13,66,68,120]. Fisher et al reported on the incidence of anesthesia-related problems seen by volunteer services working over in developing countries over a period of 18 months [66] that reflects the quality assurance data of trained anesthesia providers working in the developing countries. This is vastly different to the reality where the risks associated with surgery and anesthesia vary widely (see Table 44.1) [26,31]. For example, in Ghana, a 0.08% mortality for elective surgery was recently reported [121], while there was a 20% mortality for intestinal obstruction of the newborn in a Nigerian teaching hospital [122].

We have little idea of the incidence of problems associated with anesthesia provided by non-physicians, nurses, or unqualified personnel "trained on the job" [13,26,123,124]. In some areas, even today, neonatal surgery may be performed without anesthesia [102], or simply under local infiltration only in an attempt to improve outcome [122,125,126]. Understandably, late presentation, respiratory failure, infection, or anesthetic complications [102,125,126] are still the major contributors to a poor outcome.

Follow-up care is generally poor. The follow-up visit is usually not considered worth the added financial burden. Long distances, lack of transport, and poor telecommunications prevent patients from returning. Even patients who live

nearby are lost to follow-up and seldom return unless there are complications.

KEY POINTS: FOLLOW-UP CARE

- Perioperative mortality/morbidity is often high due to lack of personel to care for the patients and lack of equipment and facilities (e.g. no postanesthetic care unit)
- Perioperative statistics on mortality/morbidity are lacking in most developing countries. This makes it difficult to know how to improve things
- Postoperative follow-up is poor for many reasons

Summary

The practice of anesthesia in a developing country will always be challenging, particularly for those who provide anesthesia for children. The challenges vary and it is wise to expect the unexpected and have the flexibility to improvise in the face of an ever-changing world racked by famine, war, violence, natural disasters, and political unrest. The nuances of practice in different communities will inevitably vary and may even challenge some fondly held beliefs in pediatric anesthesia.

Different standards may emerge from different parts of the world. Such standards need not necessarily be considered inferior but may well open the way for the assimilation of new ideas [127]. A safe anesthetic is not necessairly the most expensive one. After all, it is generally not the agents that we use but the skill with which we use them that determines outcome. It should never be necessary to depart from the dictum *primum non nocere*. Simplicity may be the key, but there is no place for double standards. Guidelines evolved over time in the UK, USA, and Australia [127,128] may be untenable in many parts of the world, but every attempt should be made to exercise the same standard of care as expected in the developed countries. The children deserve no less!

What can be done to improve the lot of children who undergo anesthesia in the developing world? Audits of morbidity and mortality are the first steps towards improvement, provided action is taken to address the problems uncovered. Publications reflecting outcomes in developing countries have increased over the past decade (see Table 44.1) [129–132]. Sending money is another suggestion [129] but unfortunately, with all the goodwill in the world, there is no guarantee that money will ever reach the right people and be put to the best use. Purchasing equipment without subsequent maintenance is wasteful. Disposables are short-lived even if they are recycled. Human resources are needed.

Attracting trained anesthesiologists to work in the developing world is the challenge [1,132–134]. Temporary sojourns with volunteer medical groups are for the most part stimulating but few, if any, of these volunteers are likely to return for longer periods, let alone permanently. Is it the environment? Is it the lack of home comforts? Is it the family that finds it difficult? How much influence does political uncertainty have? Unfortunately, until these questions and many others can be addressed, anesthesia in the developing world, particularly for children, is unlikely to advance [1].

The WHO has also recognized that surgery is a public health issue and has launched the "Safe Surgery Saves Lives" program. The WHO has also emphasized that safe surgery does not exist without safe anesthesia [2,23–25]. Training anesthesiologists in the skills required for pediatric anesthesia is a slow process. It is hoped that the WFSA program [129,134], the World Bank, the Lancet Commission, and the many universities and organisations involved in healthcare in LMICs can build sustainable programs that will snowball so that children undergoing surgery in developing worlds may reap the benefit.

CASE STUDY

A 1.8 kg newborn male with gastroschisis presented to the emergency room of the regional hospital. The baby had been delivered in a remote hut in a village some 5 h away. His mother, an 18-year-old primigravida, had not attended antenatal clinic because she lived at least a 1 h walk away from the nearest clinic. Her HIV status was unknown. The baby, whose gestational age was unknown, was delivered by a "traditional midwife" who after resuscitation had wrapped the baby in towels and sent the mother to the nearest clinic for further management. On arrival at the clinic after an hour's walk, the baby was clearly hypothermic, had a weak cry, and the bowel, which had extruded further, was covered with a green film suggesting meconium staining.

At this point the baby's lower body was placed in a plastic bag and the local ambulance driver was notified that the baby needed to be transported to the regional hospital. The ambulance was undergoing repairs and would only be ready in an hour. There were no IV fluids or antibiotics available at the clinic. There were no laboratory facilities to check the blood glucose, hematocrit, electrolytes, or acid–base status; the bottle of "Dextrostix" had expired. The initial examination had been conducted in semi-darkness because of another temporary power outage.

The ambulance finally arrived 2 h later and needed to refuel en route. On arrival at the regional hospital, the baby's temperature was 34.1°C. The blood glucose measured 25 mg/dL, the urea was elevated, and the hematocrit was 54%. No incubator was available, but the child was warmed with an overhead radiant heater. The gastroschisis was wrapped in cling film, and the child was prepared for surgery. The surgeon was not immediately available because he was busy with an ectopic pregnancy.

A peripheral IV line was started and a bolus of 10 mL/kg Ringer's lactate was given for resuscitation. Glucose was added after the initial resuscitation. Antibiotics in the form of ampicillin and gentamicin were given intravenously. The general surgeon, who had been working all night, became available after completion of the ectopic pregnancy. The baby was taken to the operating room, anesthesia was induced with halothane, and the trachea was intubated

after succinylcholine administration. No other muscle relaxants were available. The lungs were hand-ventilated with a modified Ayre's T piece by the anesthetist who had recently completed his 6 months of "training on the job." There was no scavenging system or suitable ventilator for postoperative ventilatory support. The surgeon aimed to achieve primary closure to improve the chances of survival. A caudal block using 2.5 mL/kg 0.25% bupivacaine with epinephrine 1:400,000 was placed by the visiting anesthesiologist using a 22 G scalp vein needle. The surgeon, in an attempt to reduce the bowel volume, managed to "milk" approximately 30 mL of meconium from the bowel using normal saline irrigation through a Jacques red rubber catheter (Fig. 44.7). The bladder was also emptied (3 mL) using Crede's method since there were no urinary catheters available. If primary closure was not possible the surgeon aimed to fashion a "silastic" bag from an intravenous bag. Fortunately this was not needed.

Primary closure was achieved with difficulty. The abdomen was tense but the dorsalis pedis pulse was palpable and there was good capillary refill of both feet. The baby was able to breathe spontaneously but there was no way to measure the increase in airway pressure, blood gases, or capnography to evaluate respiratory function. The residual effects of the caudal provided analgesia and some degree of motor block without respiratory depression. Ideally, a caudal catheter could provide continuous or intermittent blockade, but neither a caudal catheter nor a functional infusion pump was available.

The closure was completed within 9 h of delivery. Although closure was achieved as soon as possible, the delay was expected to have a negative influence on the outcome because of the high risk of sepsis [102,135]. The mother's positive HIV status became apparent and both mother and child were started on antiretroviral therapy. The HIV status was not expected to affect the baby's outcome [96].

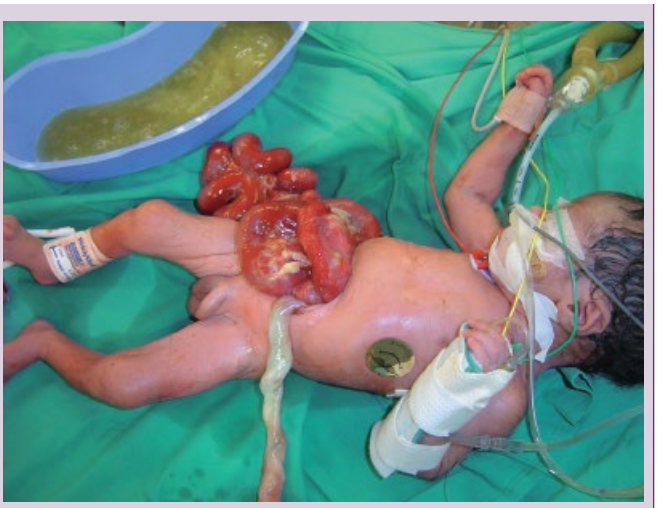

Figure 44.7 Gastroschisis is a major problem in the developing world. The outcome is poor because of a paucity of facilities for neonates. This baby with significant intrauterine growth retardation was not diagnosed antenatally and presented late for closure. The risk of sepsis is high. The bowel content (in the kidney dish) was emptied as far as possible to facilitate closure. Postoperative ventilatory support was not available.

Early initiation of total parenteral nutrition (TPN) would have been ideal but was not possible because of the budgetary limitations in the regional hospital. Furthermore, neither central venous access nor peripherally inserted central catheters (PICCs) were available nor could these procedures be performed at this hospital. Ten percent glucose in quarter normal saline was the only IV fluid available to provide some calories, but its use placed the infant at significant risk of hyponatremia-induced convulsions.

The postoperative course was stormy, punctuated by episodes of sepsis related to infiltrated peripheral IVs, wound sepsis, and minor dehiscence. Enteral nutrition was tolerated by 28 days of age and the baby was discharged after 40 days in hospital and referred for follow-up at the surgery and HIV clinics.

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 45
Clinical Complications in Pediatric Anesthesia

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Introduction

Complications in the perioperative care of children range from very minor to devastating. This chapter describes some of the most common and severe complications that may be encountered in the daily care of children within the perioperative environment. While limited space prohibits an exhaustive topical review, for many complications, data, especially pediatric-specific data, are either lacking or insufficient to provide the reader with thoughtful guidance. Nonetheless, data are available for many common and serious clinical complications in pediatric anesthesia to allow clinicians to minimize risk and provide the best care possible to the children under their care. The perioperative complications covered in this chapter include the following: cardiac arrest, temperature control, malignant hyperthermia, propofol infusion syndrome, local anesthetic toxcity, positioning injuries, perioperative vision loss, anaphylaxis, and latex allergy.

Cardiac arrest

The risk of morbidity or mortality in both adults and children undergoing general anesthesia has declined dramatically over a generation. The decline in mortality, the most robust outcome measure in pediatric anesthesia, observed in children over the past 50 years is depicted in Figure 45.1 [1–14]. The improved safety of pediatric anesthesia over the past several decades has been attributed to improved monitoring, sophisticated equipment, easily titratable anesthetics, and growing subspecialization and regionalization of pediatric care [15,16]. Despite these advances, anesthetic-related complications occur more often in children compared with adults [17]. Specifically, infants and children less than 3 years of age and children with co-morbid conditions are at the highest risk of morbidity associated with general anesthesia [17–19]. Anesthesia-associated cardiac arrest in children has been reported to be between 0.7 and 8/10,000 anesthetics and is inversely proportional to age [13,18,20,21]. In a retrospective review of over 90,000 anesthetics administered between 1988 and 2005 at a tertiary care center, the incidence of perioperative cardiac arrest in neonates undergoing non-cardiac surgery was 39.4/10,000 anesthetics compared with 8.7/10,000 anesthetics for children <1 year of age and 1.9/10,000 anesthetics for children older than 10 years [13]. A prospective cohort study of more than 280,000 anesthetics administered to children more recently between 2000 and 2011 in another tertiary pediatric hospital also found anesthesia-related cardiac arrests were higher in infants <1 year of age, with the highest rates in those younger than 6 months of age [20]. These findings were similar to those of Odegard et al in Boston [22], Tay et al in Singapore [23], Braz et al in Brazil [24–26], and Sanabria-Carretero et al in Spain [27].

The most important contribution to the existing knowledge related to pediatric cardiac arrest in the operative setting comes from the Pediatric Perioperative Cardiac Arrest (POCA) Registry. The POCA Registry was created at the

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

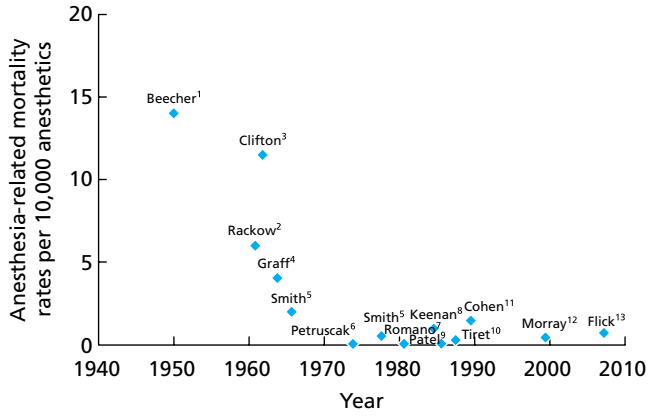

Figure 45.1 Anesthesia-related mortality rates in children from studies published between 1950 and 2010 [1–13]; the year of publication is indicated by the author's surname. *Source:* Reproduced from Morray [14] with permission of Elsevier.

University of Washington in 1994 as an extension of the American Society of Anesthesiologists (ASA) Closed Claims Project and was supported by the American Academy of Pediatrics Section on Anesthesiology and Pain Medicine. In 1985, the ASA Committee on Professional Liability, with the cooperation of 28 insurance providers, began collecting data obtained from closed malpractice cases in the United States. In 1993, Morray and colleagues reported a comparison of pediatric and adult closed claims and found that claims in children disproportionately involved infants, healthy children (ASA physical status [PS] 1), death or permanent injury, and deficiencies in anesthesia care 17]. Claims paid for malpractice involving pediatric care tended to be higher than those paid for adults.

To further study the complications that may arise during the anesthetic care of children, the POCA Registry has subsequently provided valuable insights into the risk factors and outcomes associated with pediatric perioperative cardiac arrest [12]. The registry, now closed, collected data from pediatric anesthesia practices throughout the United States and Canada and reported their findings. The initial report was made in 2000 and provided data gathered from 63 institutions that had submitted a total of 289 cases of cardiac arrest in children [12]. A subsequent report was published in 2007 with cardiac arrest data from as many as 79 academic institutions and information on 397 cases covering a 7-year period [28].

Reports from the POCA Registry grouped events as either related or unrelated to anesthesia and focused the analysis primarily on those judged to be anesthesia related. When comparing data from the first report (289 cases, 1994–1997) to the second report (397 cases, 1998–2004; 193 anesthesia related), the distribution of cases judged to be anesthesia related was similar at 52% and 49%, respectively. These rates are higher than those observed by Flick et al [13] (18%) when the POCA Registry definition of anesthesia related was applied to the Mayo data. Likewise, in a series of 41 arrests among children undergoing cardiac procedures, Odegard et al [22] found that 26.8% were anesthesia related, and Braz et al [24] found that 20% were anesthesia related [29]. The designation of anesthesia related is obviously subjective but allows for the elimination of cases from review that might obscure important patterns, risk factors, or causes.

The children at greatest risk have been identified by Morray et al [12] and others [13,23,28] and include higher ASA PS rating, young age (neonates and infants), presence of congenital heart disease, and the need for emergency procedures. In the initial report from the POCA Registry, 32% of anesthesia-related cardiac arrests occurred in children who were ASA PS classes 1 and 2, whereas in the subsequent report, the frequency of cardiac arrest in PS 1 and 2 children had fallen to 25% [12]. Over a similar time period, Braz et al [24] found in all cardiac arrests that only four of 35 arrests (11%) occurred among the healthiest children. Flick et al [13] found that among those undergoing non-cardiac surgery, half the 26 cardiac arrests occurred in children of ASA PS 3 or less. Clearly, a higher ASA PS is associated with a greater risk of complications of all types, including cardiac arrest [10]. It would appear that fewer healthy children are experiencing cardiac arrests than in the past. This has been attributed by some to the shift from the use of halothane to sevoflurane as the primary inhalational anesthetic used in children [14,30].

Coexisting disease, as reflected by the ASA PS, is without question the strongest predictor of risk for cardiac arrest and death, particularly for those children with congenital heart disease [31,32]. The incidence of anesthesia-related cardiac arrest is high in cardiac patients even when undergoing non-cardiac surgery [33–35]. The decline in the frequency of cardiac arrest among children undergoing cardiac surgical procedures over the 15-year study period in the Mayo Clinic cohort [13] was attributed to the more aggressive use of extracorporeal membrane oxygenation (ECMO) for failure to wean from cardiopulmonary bypass (CPB) [36]. Patients who previously may have experienced cardiac arrest during a cardiac procedure are now placed on ECMO and are no longer captured in analyses of perioperative cardiac arrest. A study of more than 70,000 patients aged less than 18 years from 97 centers participating in the Society of Thoracic Surgeons Congenital Heart Surgery Database (2007–2012) found that 2.6% had postoperative cardiac arrest, and that lower volume centers have increased mortality after cardiac arrest [37].

Unquestionably, neonates and infants are at greater risk. In the study by Olsson and Hallen [38], the risk of cardiac arrest among infants was found to be 17 per 10,000 anesthetics, more than three times the risk for older children and almost six times that of adults less than 60 years old. More recent studies have found somewhat lower rates, ranging from nine to 15 per 10,000 anesthetics [13,24]. More than 50% of cardiac arrests in the 2007 POCA Registry report occurred in infants younger than 6 months (43%) [28]. Among neonates, rates are dramatically increased to as high as 200 per 10,000 anesthetics [24]. Beyond 12 months, rates appear to decline rapidly to levels similar to those found in young adults.

Emergency procedures have been found by some to be associated with greater risk of cardiac arrest and other major complications [13,23,38]. Additionally, Morray et al [12] found in the initial report of the POCA Registry that the odds of mortality from cardiac arrest increased almost fourfold among those experiencing such a problem during an emergency procedure. Similarly, time of day appears in some studies to affect risk, such that those children undergoing procedures during off-hours (typically after 5 pm) and on weekends are at increased risk for cardiac arrest [39]. The cause of this elevated risk is unclear; however, one can speculate that the acuity of

illness and the lack of availability of resources such as experienced personnel and equipment may be less during those times [13]. A recent study of survival rates following pediatric in-hospital cardiac arrests at 354 hospitals participating in the American Heart Association's Get With the Guidelines© – Resuscitation registry from January 1, 2000 to December 12, 2012 found that the rate of survival to hospital discharge was lower for pediatric events occurring at night than for those cardiac arrest events that occur during daytime or evening hours [40].

Of great interest to the pediatric anesthesia community is the question of provider and risk for cardiac arrest. The benefit of specialty-trained pediatric anesthesiologists has been examined, as has the presence of trainees. The data are insufficient, however, to draw clear conclusions. Sprung et al [41] found in a study of adults and children that the provider at the time of the arrest was not predictive of ultimate survival after intraoperative cardiac arrest. Alternatively, Olsson and Hallen [38] suggested that the incidence of cardiac arrest was inversely proportional to the availability of specialist anesthetists. In a pediatric study, Keenan et al [42] examined the effect of subspecialty pediatric anesthesia care on the occurrence of cardiac arrest among infants cared for at a major academic center. They found that of the four cardiac arrests observed in the cohort all occurred in the non-pediatric anesthesiologist group (incidence 19.7 per 10,000 anesthetics; $p = 0.048$). A follow-up study [43] found a similar relationship when the frequency of bradycardia was compared between pediatric and non-pediatric anesthesiologists, and a large study by Mamie et al [44] demonstrated a reduction in critical events among children cared for by specialist pediatric anesthesiologists, especially during ear, nose, and throat surgery.

Analysis of correctable causes of cardiac arrests may lead to improvements in anesthetic care. In the 1950s, deaths related to administration of curare were reported and led to changes in practice [1]. Later in the 1960s and 1970s, airway obstruction and aspiration were common antecedents to cardiac arrest [3,4]. Over subsequent decades, improvements in perioperative care resulted in a reduction in the incidence of cardiac arrest, especially in the predominance of inadequate ventilation and anesthetic overdose as frequent causes [8,38]. Data from the Closed Claims Project in the 1990s [17] suggested a decline in respiratory causes of cardiac arrest; this decline was confirmed by subsequent analysis of POCA Registry and other data [12,14,28,45]. The change may be attributable to the introduction of pulse oximetry and later capnography. Medication-related cardiac arrest declined after the late 1990s and was reflected in the subsequent report of the POCA Registry [14], suggesting that the conversion from halothane to sevoflurane may have been responsible.

The decline in respiratory- and medication-related cardiac arrest was accompanied by a concomitant rise in the proportion of events related to cardiovascular causes in the data reported by Bhananker et al [28] from the POCA Registry. These were primarily related to blood loss and replacement (hyperkalemia secondary to massive transfusion). Similar findings were observed in the Mayo Clinic series [13]. The findings reinforced the need for adequate hemodynamic and electrolyte monitoring as well as avoidance of the use of whole, irradiated, or old blood whenever possible (Fig. 45.2 and Table 45.1).

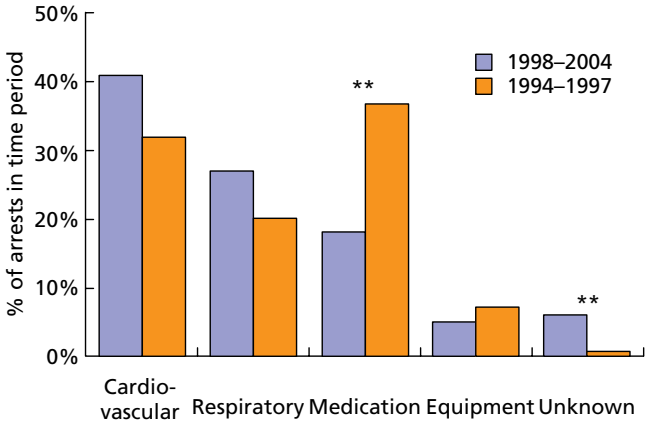

Figure 45.2 Causes of perioperative cardiac arrest from the Pediatric Perioperative Cardiac Arrest Registry, 1994–1997 and 1998–2004. *Source:* Reproduced from Bhananker et al [28] with permission of Wolters Kluwer.

Table 45.1 Causes of cardiac arrest 1998–2004 in 193 cases

Cause	No. (% of 193)
Cardiovascular	79 (41)
Hypevolemia associated with blood loss	23 (12)
Electrolyte imbalance	10 (5)
Hypovolemia (non-hemorrhage)	5 (3)
Air embolism	4 (2)
Other CV	11 (6)
Presumed CV unclear mechanism	26 (13)
Respiratory	53 (27)
Airway obstruction – laryngospasm	11 (6)
Airway obstruction – other	5 (3)
Inadequate ventilation or oxygenation	9 (5)
Inadvertent or premature extubation	7 (4)
Difficult intubation	4 (1)
Esophageal or endobronchial intubation	3 (2)
Bronchospasm	4 (2)
Pneumothorax	2 (1)
Aspiration	2 (1)
Other	1 (1)
Presumed respiratory, unclear mechanism	5 (3)
Medication	35 (13)
Halothane-induced CV depression	5 (5)
Sevuflurane-induced CV depression	6 (3)
Other single medications	9 (5)
Medication combination	7 (3)
Allergic reaction	2 (1)
Intravascular injection of local	2 (1)
Equipment	9 (5)
Central catheter	5 (3)
Kinked or plugged ET tube	2 (1)
Peripheral IV catheter	1 (1)
Breathing circuit	1 (1)
Multiple events	3 (2)
Miscellaneous	2 (1)
Unknown	12 (6)

CV, cardiovascular; ET, endotracheal; IV, intravenous.
Source: Reproduced from Bhananker et al. [28] with permission of Wolters Kluwer.

Respiratory events, although proportionately less common, continue to be an important source of cardiac arrest in children. Laryngospasm was the most frequent antecedent event identified in the POCA Registry data. This is supported by other large series that examine adverse events such as those

by Mamie et al [44], Tay et al [23], and Murat et al [45]. These arrests may be attributed to the failure to rapidly recognize and effectively treat laryngospasm before the onset of bradycardia.

Outcomes of cardiac arrests among children in the perioperative setting are dependent on the cause. The following is overall survival reported in the extant literature: 21% Flick et al [13], 28% Bhananker et al [28], 37% Braz et al [24], 57% Tay et al [23], and 92% Odegard et al [22]. The higher survival reported by Odegard et al [22] was among cardiac surgical cases and did not include those that failed to wean from CPB or were placed directly onto ECMO support. In a recent, large, multicenter study, only half of pediatric cardiac patients who suffered a cardiac arrest survived to hospital discharge [46]. In general, the outcome of in-hospital cardiac arrest among children is better than that of adults, and arrest occurring in the operative setting has improved outcomes compared to arrest occurring elsewhere in the hospital [47]. Cardiac arrest in children outside the hospital has a poor outcome, with only a 12% survival to discharge; this survival rate is based on a meta-analysis by Donoghue et al in 2005 [48]. Survival following cardiopulmonary arrest is reported to be lower for cardiac-induced cardiac arrest than respiratory-induced cardiac arrest [49].

As more robust methods of capturing clinical events become more widely available and organizations such as the Society for Pediatric Anesthesia and others develop and support methods of capturing these data across multiple institutions, the ability to quantify and study these rare events will improve, along with the care of children. See Chapter 48 for further discussion of databases and outcomes research; for treatment of cardiac arrest, see Chapter 13.

KEY POINTS: CARDIAC ARREST

- Cardiac arrest in the pediatric perioperative period is rare
- The improved safety of pediatric anesthesia over the past several decades has been attributed to improved monitoring, sophisticated equipment, easily titratable anesthetics, and growing subspecialization and regionalization of pediatric care
- Children at the greatest risk of perioperative cardiac arrest include higher ASA PS, young age (neonates and infants), presence of congenital heart disease, and the need for emergency procedures

Control of temperature

Physiology of temperature control

The management of temperature is critical in the care of pediatric patients. Much more so than adults, children are susceptible to changes in environmental temperature and the effects of anesthetics on thermoregulatory responses. As mammals, humans are homeothermic and therefore maintain their body temperature within a narrow range. Core temperatures in humans are generally maintained within 0.2°C around the thermal set point of 37°C. To achieve this precise temperature control, a complex array of thermoregulatory processes that are incompletely understood are required. From the earliest experiences in the use of general anesthesia, it has been recognized that general anesthetics impair normal thermoregulatory mechanisms and inevitably result in hypothermia in patients of all ages and sizes. Pickering [50], in a 1958 lecture to the Royal College of Physicians, discussed (among other things) the potential benefits of hypothermia and stated, "The practical difficulty in cooling men is to break through the defences of the body; the most effective means is to give an anaesthetic, which (as we have seen) has been shown to interrupt at some point or points the reflex arcs which protect against cooling, particularly shivering." Although perioperative hypothermia may have a benefit in selected patients and clinical settings, the effects of cold may have profound negative effects, including increased bleeding, infection, renal dysfunction, and alterations in the pharmacology of anesthetic agents and other medications [51–54]. Although relatively rare, severe hyperthermia is much less tolerated than hypothermia and will, in settings such as malignant hyperthermia (MH), result in death unless effectively treated. In this section, the physiology of thermoregulation is discussed along with temperature measurement and disturbances encountered in the perioperative setting.

Temperature regulation in homeotherms is highly complex and incompletely understood. Clearly, temperature regulation is among the most closely guarded of all physiological processes and involves interplay among peripheral and central receptors and controllers distributed widely throughout virtually the entire organism. Temperature control is not symmetrical; much greater control is exerted over increases in central temperature as opposed to central hypothermia. Temperatures higher than 44°C constitute the upper limit of survival in humans, whereas temperatures as low as 30°C are experienced in the operative setting without profound effect [55]. This asymmetry is, in all likelihood, related to the effect of high temperatures on the tertiary structure of proteins (Fig. 45.3).

The dominant control of temperature can be localized in the preoptic anterior thalamus (POAH); however, the dorsomedial nucleus, periaquaductal gray matter of the midbrain, and the nucleus raphe pallidus in the medulla also play an important role [56]. In the most commonly described model, the POAH is at the center of a negative feedback loop that involves afferent input from superficial and deep temperature receptors and efferent output to effectors in the sweat glands, blood vessels (dilation–constriction), muscles (shivering), brown fat deposits (non-shivering thermogenesis), and respiratory centers (hyperpnea). The thalamus functions much like a thermostat to closely maintain core temperature by reducing heat loss and activating heat production in response to cold afferent input and dissipating heat and decreasing thermogenesis in response to warm afferent input [57]. The interthreshold range, i.e. the range over which the thalamus senses temperature as normal, is between 36.8°C and 37.2°C although there are diurnal variations and differences between men and women associated with menstruation. Temperatures within the thalamus outside the normal range will initiate an effector response to return the central temperature to the normal set point.

The POAH contains warm-sensitive, cold-sensitive, and temperature-insensitive receptors; however, warm sensors vastly outnumber cold and insensitive receptors, emphasizing

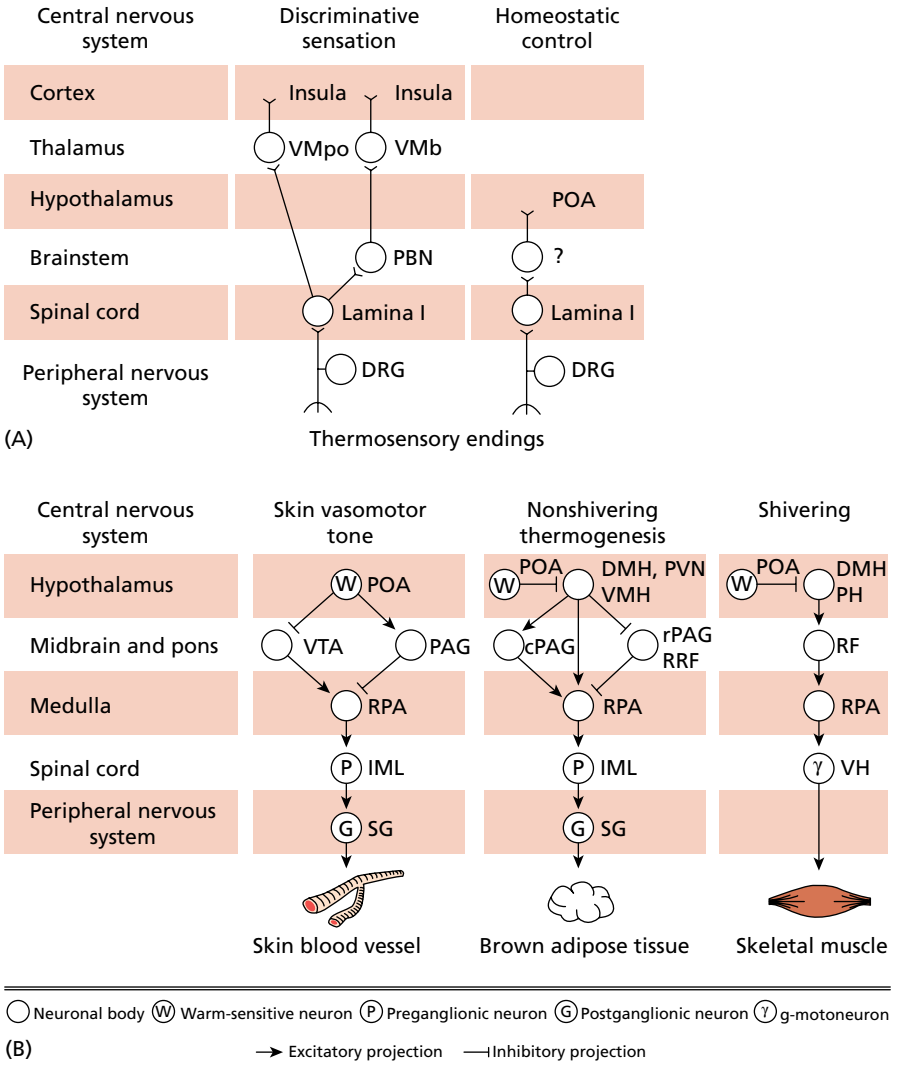

Figure 45.3 (A) Afferent neuronal pathways for discriminative sensation/localization of a thermal stimulus and for homeostatic control of body temperature. DRG, dorsal root ganglion; PBN, parabrachial nucleus; POA, preoptic anterior hypothalamus; VMb, basal part of the ventromedial nucleus of the thalamus (formerly known as the parvicellular part of the ventroposterior medial nucleus); VMpo, posterior part of the ventromedial nucleus of the thalamus; ?, unknown location(s) within the medulla, pons, and midbrain. (B) Efferent neuronal pathways for control of skin vasomotor tone, non-shivering thermogenesis in brown adipose tissue, and shivering in the rat. DMH, dorsomedial hypothalamus; IML, intermediolateral column; PAG, periaqueductal gray matter; cPAG, caudal PAG; rPAG, rostral PAG; PH, posterior hypothalamus; PVN, paraventricular nucleus; RF, reticular formation; RPA, raphé/peripyramidal area; RRF, retrorubral field; SG, sympathetic ganglia; VH, ventral horn; VMH, ventromedial hypothalamus; VTA, ventral tegmental area. *Source:* Reproduced from Romanovsky [55] with permission of The American Physiological Society.

the survival importance associated with guarding against hyperthermia. Warm sensors exert primary control over temperature by integrating thermal inputs from the periphery and by directly sensing thalamic temperature [58]. The dendrites of these warm-sensor neurons lie adjacent to the third ventricle and therefore directly sense cerebrospinal fluid temperatures [59]. As temperature rises, these sensors increase firing rates and initiate autonomic responses to reduce core temperature as well as provide tonic inhibition of cold sensors. Likewise, reduced input to warm sensors is the primary mechanism of initiating sympathetic responses to thermogenesis and thermal preservation. Cold-sensitive neurons are relatively few in number and are much less important in temperature control within the POAH. Temperature-insensitive sensors function to provide inhibition to warm sensors in response to afferent input from the periphery as well as to activate cold-sensor neurons. The integration of input to warm sensors, cold sensors, and insensitive neurons within the POAH establishes separate but highly integrated mechanisms for the response to cold and warm core temperatures. The response to cold relies predominantly on afferent input mostly from skin to inhibit warm-sensor activity rather than a reduction in firing of central cold sensors. At temperatures 0.5°C lower than normal, warm-sensor neurons essentially cease firing [60]. In contrast, a response to increasing core temperature relies primarily on the increased firing of warm-sensor neurons and does not depend on peripheral input.

Afferent input into the central thermoregulatory controllers is derived from receptors distributed throughout the body primarily in the skin and oral and urogenital mucosa. In contrast to the central sensors, peripheral receptors are predominantly cold sensors (a ratio of about 10:1) [60]. Traditionally, these sensors have been thought to provide input only to central sensors where these inputs are integrated

and result in an effector response. This theory of negative feedback has been challenged to the extent that an alternative model has been proposed that suggests that skin receptors may directly activate effectors in a feedforward rather than feedback loop [61]. Direct activation allows for pre-emptive control of temperature, primarily enabling defense against cold. This model of control suggests that the sensation of cold is a byproduct of control rather than an effector. Activation of cold sensors produces the sensation of cold and an effector response as a parallel process rather than a sequential one.

Regardless of the mechanism, input from peripheral sensors (primarily cold) located in the skin are sent to the brain via thin myelinated A δ-fibers through the spinoreticulothalamic tract to the thalamus and other brain regions involved in thermal control. These sensors' peak firing rate occurs at temperatures between 25°C and 30°C. Peripheral sensors in the skin are exquisitely sensitive and respond to temperature changes as small as 0.0003°C. They are most sensitive to rapid rather than gradual change in temperature and are the major source of peripheral thermal input [62].

Sensors (predominantly warm) are found in deep tissues of the core and send afferent signals via unmyelinated C fibers with peak firing rates at temperatures between 40°C and 50°C [63]. These sensors also respond primarily to change in temperature rather than to absolute temperature. Firing rates increase with increasing or decreasing temperature and subsequently accommodate to a new stable temperature [55]. This phenomenon explains both adaptation to temperature change and also the observation that responses to temperature change are most vigorous when change occurs rapidly.

Efferent output to temperature effectors occurs via autonomic and behavioral mechanisms. In humans, behavioral mechanisms predominate either directly, or in the case of a young child, indirectly through the actions of a caregiver. Behavioral control of temperatures allows humans to survive temperatures lower than −100°C and higher than 2000°C (temperature on the surface of the moon and surrounding the shuttle during re-entry) [55]. Behavioral control allows for the use of deep hypothermic circulatory arrest and survival from malignant hyperthermia. In caring for children in the perioperative setting, the pediatric anesthesiologist must provide indirect control of body temperature to avoid the negative consequences associated with both hypothermia and hyperthermia.

Autonomic control of temperature is achieved through thermoeffectors, including piloerection, sweating, cutaneous vasoconstriction or vasodilation, shivering, brown fat metabolism (non-shivering thermogenesis), and to at least a minimal extent, hyperpnea. These effectors function to either conserve or dissipate heat, depending on the specific need. Outputs to the effectors are integrated within the POAH as well as at the level of the spinal cord and potentially through even more direct mechanisms. Clearly, the most effective nonbehavioral means of both heat conservation and dissipation is vasodilation or vasoconstriction of cutaneous blood vessels. In adult humans, skin blood flow can be increased in response to hyperthermia to as high as 6–8 L/min and, when combined with sweating, is the most effective means of heat dissipation [57]. Given the large surface area to weight ratio of infants, heat loss and gain are much more rapid. The normal newborn has a surface area to volume ratio of approximately 1, whereas in the adult, the ratio is closer to 0.4. In the adult in a thermally neutral environment, cutaneous blood flow is approximately 250 mL/min, dissipating approximately 90 kcal/h. When core temperature rises, a gradient is created between the central and skin temperatures resulting in a reduction in peripheral cold sensor activity and subsequent cutaneous vasodilation with a severalfold increase in blood flow. Heat is then effectively transferred from the core to the periphery, and the thermal set point is re-established. In cold environments, blood flow is shunted away from cutaneous vessels by closing arteriovenous shunts that are maximally open in a thermally neutral environment. Reducing blood flow up to 10-fold may result in as much as a 50% reduction in heat loss [64].

Shivering increases heat production in adults by a factor of five for brief periods or by a smaller factor for sustained periods. It is involuntary muscular activity that is central in origin and can be reliably reproduced by cooling of the hypothalamus (POAH). In neonates and young infants, shivering is often believed not to occur; however, it is difficult to find a reference to that effect or to define the age at which shivering can be expected to occur. Darnall [65] has suggested that neonates can indeed shiver although shivering is a secondary mechanism of heat production much less efficient than non-shivering thermogenesis and therefore rarely observed. When β-blocking agents that inhibit non-shivering thermogenesis are given to guinea pigs, they demonstrate shivering at temperatures higher than normally observed [66]. Regardless, shivering, if it occurs in infancy, plays a relatively minor role in heat generation. Instead, neonates and infants are to a large extent dependent on non-shivering thermogenesis.

Non-shivering thermogenesis, resulting primarily from the metabolism of brown fat, is the most important means of thermal response to cold in hibernating animals as well as in neonates and infants. Once thought to occur only in infants, brown fat has been identified in adults and may be important in future research on weight management [67]. Brown fat is adipose tissue that is rich in mitochondria that have a unique capacity to uncouple oxidative phosphorylation, thereby generating large amounts of heat rather than adenosine triphosphate (ATP). The uncoupling of oxidative phosphorylation is dependent on uncoupling protein 1, a 33 kD protein found on the inner membrane of the mitochondria in brown fat [68]. This tissue comprises approximately 2–6% of bodyweight in a newborn and is found in the mediastinum, between the scapulae, around the adrenals, and in the axillae. Non-shivering thermogenesis is mediated by sympathetic stimulation in response to cold stress, and as previously stated, can be inhibited by β-blocking agents. In addition to norepinephrine and epinephrine, thyroxin and glucocorticoids may also stimulate lipolysis of brown fat. Lipolysis of brown fat, compared with that of white adipose tissue, results in oxidation of approximately three times the amount of fatty acid (30% versus 10%) within the lipocyte [69]. A considerable proportion of free fatty acids are released into the bloodstream to be oxidized elsewhere in the body. Ultimately, the metabolic result of maximum oxidation of brown fat is a near doubling of heat production with an increase in oxygen consumption from 5.4 to 9.3 mL/kg/min [70]. The capacity for substantial heat production through non-shivering thermogenesis is present at birth and persists through the 2nd year of life.

In animals, hyperpnea makes a major contribution to thermoregulation – especially of the brain. In humans, the role of panting is less pronounced; however, panting is nonetheless important. There are two phases of the panting response. The first phase, thermal tachypnea, is characterized by increased respiratory frequency with reduced tidal volume, resulting in heat loss but no change in carbon dioxide tension [71]. This pattern produces preferential ventilation of the anatomic dead space, including the nasopharynx, selectively cooling the brain. The second phase, thermal hyperpnea, produces a reduced respiratory rate coupled with an increased tidal volume resulting in alveolar hyperventilation, hypocapnia, and alkalosis. In humans, thermal hyperpnea predominates and can at times account for 46% of cephalic heat loss [72]. Given the relative size of the infant cranium, it could be assumed that this figure may be larger, although no data support this assumption.

An interesting theory is related to the role of yawning in thermoregulation, especially with regard to selective brain cooling [73]. In a study group of college students, contagious yawning was eliminated by selective cooling of the forehead [74]. In preterm and near-term infants, yawning begins at approximately 20 weeks and decreases in frequency between 31 and 40 weeks, coincident with the development of homeostatic control [75]. Also interesting is the role of opioids in yawning behavior. Opioids are known through κ-receptor activity to produce hypothermia in animals and also to inhibit yawning. Additionally, the administration of naloxone increases yawning in opiate-dependent humans [76]. Ultimately, the importance of yawning is uncertain in humans and especially in neonates and infants.

Mechanisms of heat loss

Unintentional hypothermia is the major concern that motivates inclusion of a discussion of thermoregulation in this and every text of pediatric anesthesia. Although heat is lost and gained from the body in similar ways, heat gain is a relatively rare concern, whereas avoiding heat loss is part of the anesthetic management of every child. A basic understanding of the mechanisms of heat loss is central to the prevention of unintentional hypothermia. Hypothermia has beneficial effects in a few select clinical situations such as hypoxic ischemic brain injury, CPB, and deep hypothermic circulatory arrest, but it has clear negative effects in most day-to-day perioperative situations. Hypothermia inhibits immune responses and is a source of renal dysfunction and coagulation abnormalities. It affects the action of various medications, including muscle relaxants, that are components of many anesthetics provided to adults and children.

Heat loss in the operating room environment occurs in order of importance through radiation, convection, evaporation, and conduction. Radiant heat loss is the heat loss that occurs between two objects in the environment. All objects in the operating room, whether animate or inanimate, gain or transfer heat to one another in a process that would in the absence of intervention lead to equilibrium. The heat of the sun and the heat generated by an infrared warming light are typical examples of radiant heat sources. Radiant heat loss is somewhat less easy to imagine but much more important in the operating environment. Radiant heat is transferred as electromagnetic waves in the infrared spectrum and is unaffected by air currents, air temperature, or distance between the radiating surfaces. Radiant heat loss becomes an increasingly important source of heat loss as the temperature of surrounding objects and surfaces decreases. In a neutral thermal environment, radiant heat loss accounts for about 39% of total heat loss, whereas at 22°C, radiant losses increase to nearly 80% of the total [69].

Radiant heat loss can be greatly reduced by the use of simple coverings such as clothing, sheets, or blankets. Even light clothing can dramatically reduce radiant heat losses. It may at times not be possible to cover the child. In this circumstance, the most effective means of maintaining temperature is increasing the temperature of objects within the environment (heating the operating room), or alternatively, providing a source of radiant heat energy such as an infrared heat lamp or other radiant heater. In this example, increasing the ambient temperature to 30°C would reduce radiant heat loss by almost 50%, keeping in mind that in order to achieve this the environment must be at equilibrium. Simply raising the air temperature briefly has little effect until all objects in the environment have had sufficient time to equilibrate.

Convective heat loss is second to radiation as a source of energy loss in the operating room environment. It accounts for approximately 34% of heat loss in a neutral thermal environment. Convection is the loss in heat that occurs as a result of mass motion of a fluid, typically either air or water. The amount of heat loss depends on the velocity of air (water) movement and the difference between the temperature of the object (person) and the surrounding fluid. For those living in northern latitudes, the concept of wind chill is a familiar example of the effects of convection on cooling or heat loss from one object to the surrounding air (termed *forced convection*). Although air currents in the indoor environment are minimal, it is important to keep in mind that a warm object heats the surrounding air (termed *natural convection*). The warmer air is less dense and rises away from the warm object, thus creating an air current that promotes convective heat loss. The addition of even a light covering inhibits this air current and reduces convective heat loss. The rate of convective heat transfer ($\dot{Q}$) is determined by the following formula: $\dot{Q} = hA(T_s - T_b)$, where h is the constant heat transfer coefficient of the fluid, in this case air; A is the surface area in meters squared; T_s is the surface temperature; and T_b is the temperature of the fluid (air). The transfer coefficient is situationally dependent and must be determined for each setting, making use of this formula problematic in the clinical setting.

Heat loss through conduction occurs whenever the body comes in direct contact with a cooler object that is not in motion (air or water are objects in motion) such as the operating table or other solid. Similar to convection, the transfer of heat is dependent on the temperature difference between the two objects, the densities of the objects, and the area of contact. The greater the area of contact and the greater the density of the cooler object, the more heat is transferred. A soft mattress transfers less heat than a solid surface such as an x-ray table. The mathematical expression of this relationship is identical to that for convection: $\dot{Q} = hA(T_s - T_b)$. However, in this case, heat transfer is related to h, the conductivity or thermal properties of the solid; A, the area in contact; and the temperature difference between the body (T_s) and object (T_b)

Table 45.2 Mechanisms of heat loss in anesthetized infants and children (see text for detailed explanation)

Mechanism	Relative % of heat loss	Causes	Prevention/treatments
Radiation	39% in NTE (80% at 22°C)	Cold room temperature	Warm room as high as 26°C; heating lamp; cover with clothing, sheets, blankets, caps; wrap extremities – plastic, cotton wadding
Convection	34% in NTE	Motion of air/fluid	Cover with clothing, sheets, blankets, caps; wrap extremities – plastic, cotton wadding; forced-air warming; warmed IV fluids
Evaporation	25% in NTE	Respiratory losses; drying of skin preparation fluids and other fluids on skin	Condenser humidifier or active warming/humidification of gases; warm skin prep solutions
Conduction	3% in NTE	Direct contact with cooler object not in motion: operating room table	Circulating water blankets; forced-air warming

IV, intravenous; NTE, neutral thermal environment.

in contact. Heat loss via conduction is typically small and accounts for about 3% of heat loss in a neutral thermal environment.

Evaporative heat losses are encountered whenever a fluid evaporates from the surface of an object such as a patient whose abdomen has been prepared with a solution such as povidone-iodine. Evaporation is an important means of cooling the body when the body temperature exceeds 37°C. Heat loss through sweating, evaporation of another liquid from the skin (skin preparation solutions), or insensible losses from an open abdominal wound or via the respiratory tract depend on the vapor pressure gradient between the skin and surrounding air and the velocity of air movement. The formula is familiar from the previous discussion; however, in the case of evaporation, the difference is not in temperature but rather vapor pressure between skin and surrounding air: $\dot{Q} = hA(P_s - P_a)$, where $\dot{Q}$ is heat transfer in watts; h is the coefficient of evaporation and accounts for the latent heat of vaporization of the liquid as well as the airflow velocity; A is the area covered by the liquid in meters squared; and P_s and P_a are the vapor pressures of the liquid at the skin surface and the surrounding air.

Evaporative heat loss accounts for approximately 25% of total heat loss, of which roughly half can be attributed to respiratory losses. In the infant, respiratory losses can be assumed to be greater given the increased minute ventilation per kilogram of bodyweight. The use of warm, humidified inspired gases eliminates this source of heat and free water loss. Table 45.2 summarizes the mechanisms of heat loss, prevention, and treatment in anesthetized children.

Anesthetics and thermoregulation

Anesthetic agents produce consistent effects on thermoregulation in infants, children, and adults. All agents act to increase the interthreshold range both by increasing the upper threshold and decreasing the lower threshold such that the range of temperatures within which thermoregulatory mechanisms are not initiated becomes much wider. Under normal circumstances, the poikilothermic range is limited to 0.2°C. Under anesthesia, that range increases to between 2°C and 4°C, depending on the agent. The interthreshold range is determined at the lower end by measuring the temperatures at which vasoconstriction and shivering are initiated and at the higher end by the initiation of sweating. Vasoconstriction and shivering track consistently at approximately 1°C difference, regardless of the effects of anesthesia, such that vasoconstriction is initiated at a 1°C higher temperature than shivering.

The effects of anesthetics on the interthreshold range are not symmetrical. The upper boundary of the range is increased only by 1.0–1.5°C, whereas the lower threshold is decreased by approximately 2.5°C. The effect is that hypothermia is much more likely to occur than hyperthermia, especially given the typical ambient temperature of most operating rooms. At this point, it is also important to recognize that the most effective responses to both hyperthermia and hypothermia are behavioral, and these responses are absent under general anesthesia. Although the range over which no response to temperature change occurs increases under anesthesia, the intensity of response does not. Cutaneous vasoconstriction under isoflurane anesthesia in healthy volunteers occurred at 34.6°C and was similar in intensity to that achieved in awake volunteers. Shivering can also be observed in anesthetized patients; although, it is much less common because it occurs at a temperature 1°C lower than vasoconstriction. Like vasoconstriction, the intensity of shivering observed is unchanged.

Non-shivering thermogenesis is the predominant means of heat generation in neonates and infants. It too is inhibited in the setting of general anesthesia. Halothane 1.5% inhibits non-shivering thermogenesis by 70% in rodents [77]. Human infants under propofol and fentanyl anesthesia fail to increase metabolic rate despite core temperatures 2°C below the vasoconstrictive threshold, suggesting that non-shivering thermogenesis is absent in this setting [78], although Ohlson et al [79] failed to demonstrate an inhibitory effect on non-shivering thermogenesis by propofol in hamsters.

Inhalational anesthetics affect the thermoregulatory threshold of infants and children in a manner similar to that observed in adults. Bissonnette and Sessler [80] showed that halothane and nitrous oxide reduce the thermoregulatory threshold in children to 35.7°C, whereas in a previous study [81], they found that under isoflurane the threshold was further reduced to levels similar to those observed in adults (34.4–35.3°C). In both studies children were stratified by weight, and in neither study did threshold response vary significantly with weight. Sevoflurane and desflurane have been found to produce similar changes in thermoregulatory responses; although, desflurane is unique in that it reduces the magnitude or gain of the vasoconstrictive response to hypothermia [82–85]. Xenon has been shown to have a greater inhibitory effect on thermoregulation than isoflurane, whereas nitrous oxide is less inhibitory [85]. In general, the thermoregulatory response to inhalational

anesthetic agents appears to be similar in adults and children and is not determined by weight or age. Inhalational anesthetics, with the exception of nitrous oxide, appear to inhibit non-shivering thermogenesis [79].

The effects of intravenous anesthetics on thermoregulation vary. Propofol produces a linear decrease in the threshold temperature for vasoconstriction and shivering, while only slightly increasing the threshold for sweating in humans, as demonstrated by Matsukawa, Kurz, and colleagues [86,87]. Unlike volatile anesthetics, propofol does not appear to inhibit non-shivering thermogenesis. Ohlson et al [79] compared the effects of various anesthetic agents on brown fat metabolism and found that propofol and ketamine did not inhibit non-shivering thermogenesis in hamsters. Midazolam appears to impair thermoregulatory control only minimally compared to the effects of propofol and narcotics [88].

The individual thermoregulatory effects of opioids have not been widely studied. Spencer et al [89] showed that, in rats, different opioid agonists had differing effects on thermoregulation depending on the type of receptor stimulated (μ, κ, δ) with the μ-agonist increasing the set point and κ- and δ-agonists reducing it. Kurz et al [90] examined the thermoregulatory effects of alfentanil in human volunteers and found a minimal increase in set point for sweating and a linear, serum concentration-dependent decrease in set point for vasoconstriction and shivering similar to those observed for other general anesthetics. Meperidine similarly reduces set point and also appears to diminish the threshold for non-shivering thermogenesis by its effects on the α_2-adrenergic receptor [91–93]. Clonidine and dexmedetomidine also act as α_2-agonists and reduce the threshold for vasoconstriction and shivering but have little or no effect on sweating [94].

Postoperative shivering is a problem that primarily affects older children and adults and occurs in two patterns termed *thermoregulatory* and *non-thermoregulatory*. Thermoregulatory shivering is related to hypothermia and appears similar to shivering that occurs in other settings. Non-thermoregulatory shivering seems to have an etiology separate from thermoregulation because it occurs in normothermic patients in the postoperative period and is also seen in patients such as laboring women who have not been exposed to an anesthetic and are not hypothermic. The exact mechanism of this type of shivering is not entirely clear; however, its appearance is distinct in that it is predominantly clonic, resembling the clonus seen in spinal cord-injured patients [95]. Postanesthetic shivering occurs in approximately 50% of patients allowed to become hypothermic and in 27% of non-hypothermic patients, 15% of whom display a primarily clonic pattern of shivering [96]. Pain appears to be a factor also; patients with lower pain scores are less likely to shiver postoperatively [97].

Shivering in children is not well studied; however, a few studies have been published that describe the problem. Akin et al [98] prospectively followed more than 1500 children in the postanesthetic care unit and found the incidence of shivering to be 3.5%. Older children, those undergoing long procedures, and those in whom anesthesia was induced with an intravenous agent appeared to be at greater risk, whereas those whose anesthetic was supplemented with a caudal block appeared to be at lower risk. Lyons et al [99] found a rate of almost 15% in a smaller study and found that anticholinergic use was also a risk factor.

The consequences of shivering are primarily confined to patients who do not have the cardiovascular reserve to tolerate as much as a 380% increase in oxygen consumption that may be associated with shivering [100]. Shivering may also increase intraocular and intracranial pressure and should certainly be treated in those settings. The majority of episodes in children, however, are brief and do not necessarily require treatment other than external warming. When pharmacological treatment is desired for comfort or safety, meperidine appears to be the most efficacious agent. Its usefulness may be the result of its activity as an α_2-adrenergic receptor agonist based on its opioid activity. In keeping with this, other α_2-agonists have been used successfully to treat shivering. Dexmedetomidine and clonidine have been used successfully, although clonidine appears to be most useful in preventing rather than treating this problem. Other opioids have been used but with mixed results and none with the efficacy of meperidine.

Thermoregulation and regional anesthesia

In children unlike adults, regional anesthesia is nearly always combined with a general anesthetic. The thermoregulatory effects of regional anesthesia are confined primarily to neuraxial techniques as the effects of extremity and other blocks tend not to involve a large enough area to greatly affect core temperature. The effects of neuraxial anesthesia on thermoregulation have been extensively studied by Sessler and others, mostly in adults [101–111]. Bissonnette and Sessler, in two studies [80,81], examined the effect of general anesthesia with regional block in children, a situation that has clear relevance to clinical pediatric practice. In the first study [81], in which isoflurane was used in combination with caudal blockade, the authors found that thermal responses in children were similar to those in adults and were independent of bodyweight and age. The use of combined neuraxial and general anesthesia was thought not to be an important factor in determining responses. In the second study [80], halothane was used in combination with either penile or caudal block. Thermal responses were not different between the two groups and were similar to those in adults and children under general anesthesia without regional anesthesia. It appears from these studies that the combination of regional with general anesthesia has little impact on thermoregulation in children.

Temperature monitoring

The ASA requires that temperature monitoring be available for all patients under anesthesia. Accurate measurement of temperature in the operative period is primarily directed at the detection of hypothermia. Less common but no less important are instances of notable fever, especially those related to MH. Temperature is measured using various technologies at multiple sites with accuracy that varies widely. The appropriate unit of measure is degrees Celsius as the Fahrenheit scale is cumbersome, outmoded, and like most aspects of the US customary system ("English units"), should be abandoned in clinical practice.

The measurement of temperature has a rich and fascinating history that cannot be covered in this text. One of the first thermometers, invented by Rhomer at the turn of the 18th century, used red wine as an indicator. Fahrenheit invented the mercury thermometer in 1714 and later the Fahrenheit scale, which remains in use in the United States and a few other countries. The Celsius scale originally designated 0° as the boiling point and 100° as the freezing point of water. Linnaeus inverted the scale to its present format in the middle of the 18th century, and the scale became widely popular as the centigrade scale, later designated the Celsius scale in 1948. The official metric unit of temperature is the Kelvin after its inventor Lord Kelvin in 1848. The Kelvin scale is based on absolute zero and uses the triple point of water (273.16°K) as a reference. The triple point of a substance is the temperature at which all three phases coexist in equilibrium.

Monitoring temperature requires that an accurate instrument be used at an appropriate site that reflects the temperature of interest. Modern thermometers use thermistors, thermocouples, infrared, and liquid crystal technologies. All are sufficiently accurate for most applications, although thermistors are probably the most accurate and liquid crystal thermometers the least accurate.

Typically, in the operative setting, the temperature of interest is an estimation of core temperature; however, the ability to measure core temperature is often limited by the availability of appropriate sites and instruments. Core temperature is undefined but represent the major input into thermoregulation and therefore is of the greatest importance in terms of measurement. Sites such as the tympanic membrane, bladder, esophagus, nasopharynx, and rectum are typically considered to represent core temperature – each has limitations, however. It has been suggested that the core temperature is the temperature of the thalamus; however, the core temperature can more appropriately be described as the temperature at which the thalamus responds rather than its own intrinsic temperature. Since the thalamus receives input from throughout the body, core and thalamic temperatures may differ.

Peripheral temperature varies widely over time and by location and therefore is much more limited as a measure of thermoregulatory input or status. Skin temperature, including axillary measurement, is often the simplest and most accessible site for monitoring. When the sensor has been placed properly, axillary temperature correlates well with measures of core temperature in infants, making it useful for brief procedures during which marked temperature change is not anticipated [112]. Skin temperature measurement over the carotid artery has also been described as a viable non-invasive estimate of core temperature in infants and young children [113]. Placement of skin temperature probes elsewhere on the skin surface are much less likely to reflect core temperature and should be used with that caveat in mind. Figure 45.4 shows the correlation of various temperature measurement sites as measured in children weighing between 5 and 30 kg. Nasopharyngeal, esophageal, and rectal temperature measurements are similar, but forearm and fingertip temperatures are much lower and clearly do not reflect core temperature [112]. The optimal depth of the nasopharyngeal probes is important as misplaced probes will be affected by both ambient air and ventilation gases [114,115].

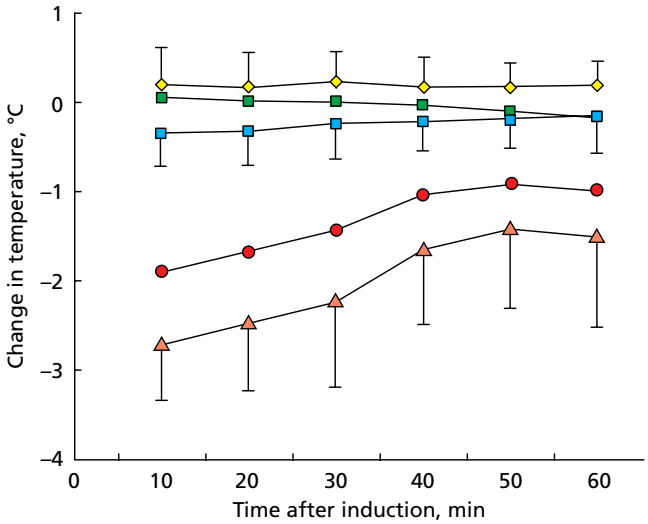

Figure 45.4 The average difference between temperatures at five different measurement sites and tympanic membrane temperature in 20 children weighing between 5 and 30 kg. The central sites (esophagus (◇), rectum (■), and nasopharyngeal (■)) did not differ significantly, whereas the temperatures of the peripheral skin surface (forearm (●) and fingertip (▲)) were significantly lower than the central temperatures. Vertical bars illustrate the standard deviation. Standard deviations of the rectal temperatures (omitted for clarity) were similar to those of the esophageal and axillary temperatures. Standard deviations of fingertip temperatures were similar to those of the forearm temperatures. *Source:* Reproduced from Bissonnette et al [112] with permission of The American Physiological Society.

Hypothermia, hyperthermia, and internal heat transfer

Heat loss or gain in the operative setting results in the transfer of heat either to or from the core. Redistribution hypothermia results from the transfer of heat from the core to the periphery caused by vasodilation that is usually induced by anesthetic agents. This heat transfer is responsible for the initial drop in temperature of 1.0°C to 1.5°C typically observed in the 1st hour under anesthesia. Once initiated, the process is difficult to reverse; it can be prevented, however, through the use of prewarming and active warming immediately after the induction of anesthesia [116–120]. The use of active warming through the use of heated gases, heated forced air, heat lamps, heating pads, or heated intravenous fluids can be effective in slowing or eliminating heat loss during the intraoperative period, but the most effective means of limiting heat loss is increasing the ambient temperature of the operating room.

Warming intravenous fluids is a relatively ineffective means of treating or preventing hypothermia except in situations such as rapid blood loss or CPB in which large volumes of blood are transferred to the patient in a very short time. The ineffectiveness of warming fluids is otherwise true for several reasons. Intravenous fluids can be warmed safely to temperatures only slightly above core temperature to prevent hemolysis, typical procedures require relatively small amounts of fluids, and, finally, fluids warmed in an intravenous bag are often significantly cooler by the time they reach the patient. This is particularly true in small children, infants, and neonates with low intravenous flow rates and when warmed fluids are likely to cool prior to reaching the child. Whereas warm fluids are not an effective means of restoring normothermia, cold fluids are a much more effective means of

cooling, primarily because cold or cool fluids have a much larger temperature gradient (15°C below core temperature for room temperature fluids) than warmed fluids (1–2°C above core temperature). Therefore, it is important to warm fluids when severe hypothermia can be anticipated, but warmed fluids are not an effective means of treating even mild hypothermia.

The use of a heated and humidified breathing circuit is also only modestly effective in either preventing or treating intraoperative hypothermia because heat loss through the respiratory tract accounts for only about 10% of total heat loss. Of that 10%, roughly two-thirds is accounted for in the process of humidifying inspired gases, suggesting that the use of a passive heat and moisture exchanger (artificial nose) is probably sufficient for most situations. In children, especially infants, the role of respiratory heat loss may be greater, given that minute ventilation is much higher than in adults. Insertion of a heat and moisture exchanger increases both the humidity and temperature of inhaled gases, and when coupled with low fresh gas flow in the circuit, is an efficient way to conserve both heat and moisture when anesthetizing infants and young children [121]. Bissonnette and Sessler [122], in a study in infants that compared active heating and humidification with either no intervention or passive humidification, found a marked difference in rectal temperature 2 h after induction. This difference suggests that, at least in infants and neonates, active heating and humidification may be useful, at least for longer or more extensive procedures. For shorter procedures that do not involve major body cavities, the use of an artificial nose (condenser humidifier) maintains sufficient airway humidity above the 50% needed for mucociliary function.

Surface warming using warm, fluid-filled mattresses effectively reduces conductive heat losses, but these losses are a minor contributor to overall heat loss. As with heated airway gases and intravenous fluids, a major limitation of surface warming is the small increment between the temperature of the warming device and that of the patient. The use of high temperatures to warm externally creates an unacceptable risk of thermal injury. Therefore, the use of traditional hot water blankets has limited value in the management of hypothermia in the pediatric operative suite. Newer circulating-water devices have been developed that are more effective than either older systems or current forced-air systems [123]. This is due to the increased capacity of fluids to transfer heat and the increased surface area in contact with the skin. Skube et al [124] recently reported 10 pediatric noncranial surgical patients who maintained ideal core body temperature via the application of a liquid-warming garment applied to the head.

The most widely used and effective means of external warming are forced-air (convective) warming devices [125,126]. They have been in use for more than a decade and have an excellent safety record, despite reports of burns in children [127]. When a sufficient area of the body surface is covered, these systems can eliminate heat losses from the skin. A 2016 Cochrane Database Systematic Review [128] assessing active body surface warming systems to prevent unintended hypothermia in adults found forced-air warming to be benefical in terms of lower surgical site infections and improved patient comfort compared with not applying any active warming device.

Despite the development of new technologies, the most effective means of preventing intraoperative hypothermia remain the maintenance of high ambient temperatures and the use of simple insulators such as plastic sheeting or cloth coverings. Few data suggest that one type of covering is superior, but all are highly effective means of reducing surface heat loss and are of minimal cost. Ultimately, however, to maintain normothermia in infants, an ambient temperature of 29°C is required, which is uncomfortable, especially for the surgical team [129]. For longer or more invasive procedures in which major body cavities are exposed, active warming may be necessary and can be most comfortably and effectively achieved with the use of forced-air convective systems.

Hyperthermia in the operative setting is relatively rare compared with hypothermia. Temperatures exceeding 38°C may result from intrinsic processes such as infection, drug fever, transfusion reaction, or MH, or may be the result of excessive warming. Children – especially infants and neonates – are most susceptible to hyperthermia induced by overly aggressive warming. It is important to investigate and eliminate the cause of the hyperthermia rather than to simply treat with antipyretics. Clearly, the most concerning cause of hyperthermia in the operative setting is MH; however, pyrexia is also associated with worse outcomes in septic shock, acute respiratory distress syndrome, heart failure, acute brain injury, and out-of-hospital cardiac arrest, so continued vigilance to avoid hyperthermia in patients presenting to the operating theatre with these morbidities is warranted [130–132].

KEY POINTS: CONTROL OF TEMPERATURE

- General anesthetics impair normal thermoregulatory mechanisms and result in hypothermia in patients of all ages and sizes
- Non-shivering thermogenesis is the predominant means of heat generation in neonates and infants and is inhibited in the setting of general anesthesia
- Heat loss in the operating room environment occurs in order of importance through radiation, convection, evaporation, and conduction
- Hypothermia inhibits immune responses and is a source of renal dysfunction and coagulation abnormalities
- Despite the development of new technologies, the most effective means of preventing intraoperative hypothermia remain the maintenance of high ambient temperatures and the use of simple insulators such as plastic sheeting or cloth coverings

Malignant hyperthermia

History

Malignant hyperthermia is a pharmacogenetic syndrome characterized by a hypermetabolic state of skeletal muscle typically induced by exposure to specific anesthetic agents, including all halogenated volatile anesthetics as well as the depolarizing neuromuscular relaxant succinylcholine. Patients with MH typically present with hypercapnea (elevated end-tidal CO_2) and tachycardia followed by muscle

rigidity, hyperthermia, rhabdomyolysis, profound acidosis, and if untreated – death [133,134].

Malignant hyperthermia was first described in 1960 in a letter to the editor of *Lancet* and subsequently in an article in the *British Journal of Anaesthesia* entitled "Anaesthetic deaths in a family," reported by Denborough et al [135]. In that paper, the authors described the MH symptoms in a young man and several of his family members who had previously experienced unexplained anesthetic deaths. The young man survived a halothane anesthetic but displayed what are now known to be classic signs and symptoms of what later became known as MH. The term "malignant hyperthermia" was first used in a 1966 paper by Wilson et al [136] describing phosphorylation defects as a possible mechanism for MH. A subsequent 1972 report identified a characteristic phenotype for some affected individuals [137]; this entity was termed King–Denborough syndrome, and Britt et al [138] confirmed the heritability of the syndrome in a 1969 paper. Key to the understanding of MH was the early recognition of the pale, soft, exudative pork or porcine stress syndrome as an animal model for the human disorder.

Genetics and pathophysiology

Both contraction and relaxation of skeletal muscle are energy-requiring processes that depend on the coupling of excitation to contraction through acetylcholine-mediated depolarization of the muscle membrane and sarcoplasmic reticulum (Fig. 45.5). Depolarization results in the release of calcium stored within the sarcoplasmic reticulum. The released calcium binds to actin thin filament proteins, allowing activation of myosin thick filaments, and ultimately initiating muscle contraction. The sequestration of Ca^{2+} is active and required for relaxation of the motor unit. In MH, high levels of intracellular calcium persist, resulting in sustained contraction and continued consumption of ATP in a cellular attempt to restore Ca^{2+} homeostasis. This consumption of ATP leads to the production of heat and ultimately muscle breakdown that is characteristic of MH. Therapy with dantrolene, an inhibitor of Ca^{2+} release from the sarcoplasmic reticulum, is directed at reducing intracellular calcium, thereby allowing for muscle relaxation and elimination of uncontrolled ATP metabolism.

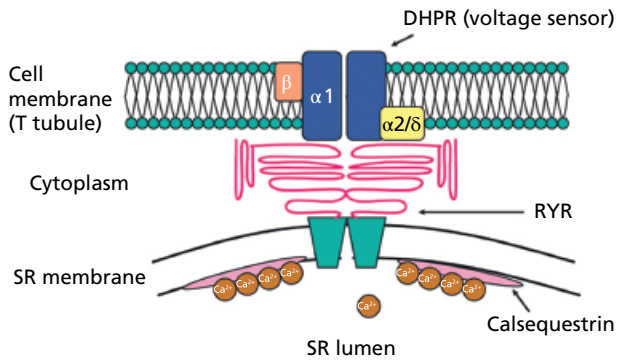

Figure 45.5 A schematic representation of the key structures involved in excitation–contraction coupling, including the ryanodine receptor (RYR) located on the sarcoplasmic reticulum (SR) membrane. DHPR indicates dyhydropyridine receptor. *Source:* Reproduced from Hopkins [256] with permission of Oxford University Press.

Without prompt reversal of this hyperdynamic condition with dantrolene, MH is almost always fatal [134].

Over the generations since its original description, the pharmogenetic origins of MH have has been increasingly described in the extant literature. Mutations in two genes, the ryanodine receptor type 1 (*RYR1*) gene and the voltage-dependent L-type calcium channel alpha 1S subunit (*CACNA1S*) gene, are causally linked to the majority of reported MH cases, with the *RYR1* gene accounting for 70% and *CACNA1S* gene accounting for only 1% of the known cases [139]. Recently, mutations in *STAC3* have been reported in an isolated population of Lumbee Indians in the southeastern United States with myopathy and increased MH susceptibility [139,140]. The remaining cases have not been characterized genetically and may or may not have a genetic basis [134].

Both the *RYR1* gene and *CACNA1S* gene products control intracellular calcium metabolism through the skeletal muscle excitation–contraction coupling complex. The *RYR1* gene encodes the sarcoplasmic reticulum membrane-localized Ca^{2+} channel ryanodine receptor. The *CACNA1S* gene encodes the Ca^{2+} channel-forming voltage-sensing α1-subunit on the T-tubule-localized L-type Ca^{2+} channel (dyhydropyridine receptor or DHPR) [134]. Excitation–contraction coupling occurs through the physical interaction of the voltage-sensing α1-subunit of DHPR with the RyR Ca^{2+} channel (Fig. 45.6). Genetic varaiations in *RYR1* and *CACNA1S* can cause channelopathies, which in the presence of halogenated volatile anesthetics or succinylcholine, can lead to dysregualted Ca^{2+} release from the sarcoplasmic reticulum, uncrontrolled skeletal muscle contraction, and a hypermetabolic state characteristic of MH (Fig. 45.7) [134]. In MH patients, volatile

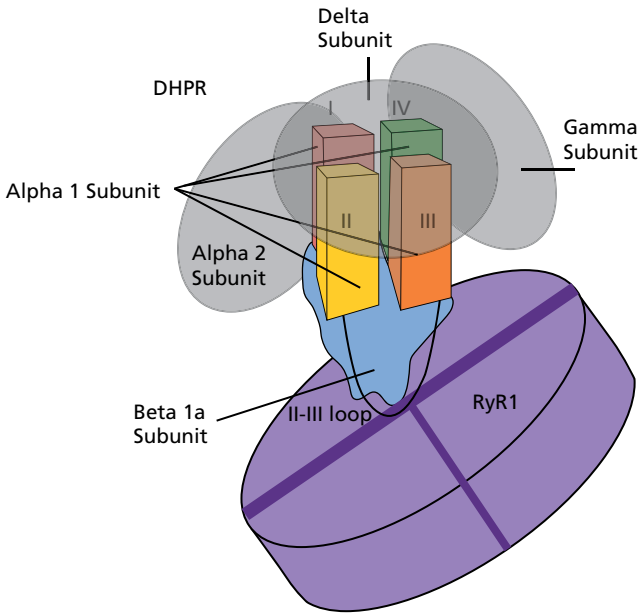

Figure 45.6 Subunit architecture and II–III loop coupling of the voltage-gated calcium channel alpha 1S subunit (CACNA1S) (rainbow blocks) of the dyhydropyridine receptor (DHPR) to the ryanodine receptor type 1 (RyR1) channel (purple). Voltage-induced conformational changes in the α1 subunit are transmitted through the II–III loop–β1a subunit complex, and through direct interactions with RyR1 promote excitation–contraction coupling. *Source:* Reproduced from Beam et al [134] with permission of The American Physiological Society.

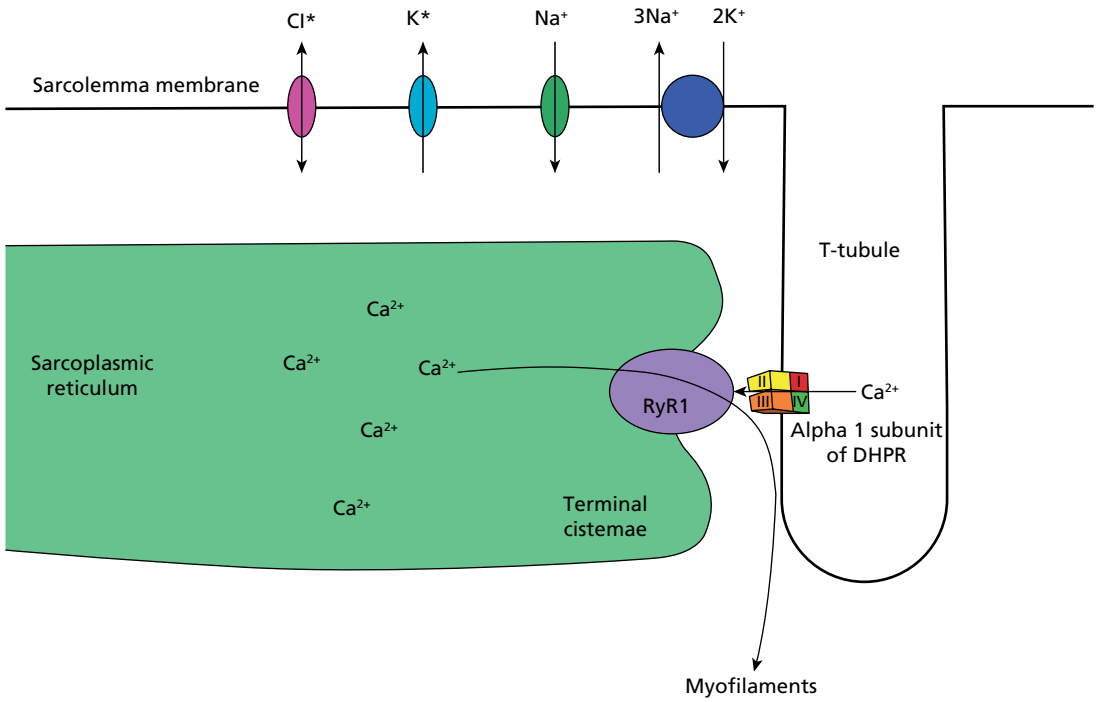

Figure 45.7 Channelopathies of Ca^{2+} channels, dyhydropyridine receptor (DHPR) and ryanodine receptor type 1 (RyR1), confer susceptibility to malignant hyperthermia. The CACNA1S alpha 1S subunit (rainbow cube) of DHPR is the voltage sensor that interacts with RyR1 (purple) to allow excitation–contraction coupling. *Source:* Reproduced from Beam et al [134] with permission of The American Physiological Society.

halogenated anesthetics remove the Mg^{2+} inhibition of the RYR Ca^{2+} channel and have been shown to activate Ca^{2+}-dependent ATPases in the sarcoplasmic reticulum [134]. Succinylcholine targets acetylcholine receptor Na^{2+} channels, and when co-adminsitered with volatile halogenated anesthetics, can worsen clinical MH [134]. As of publication of the text, there are at least 34 known causative *RYR1* mutaitons and two *CACNA1A* mutations diagnostic for MH.

The pattern of inheritance in MH is autosomal dominant although a considerable proportion of affected individuals appear to follow a recessive pattern or no identifiable inheritance pattern. This is likely the result of variable expression or reduced penetrance within or among affected families. The gold standard diagnostic test for MH in North America is still the caffeine–halothane contracture test (CHCT) [133]. In Europe, the diagnostic test is called the *in vitro* contracture test (ICVT) [141]. The CHCT was first developed nearly 40 years ago and requires a muscle biopsy to obtain fresh muscle that can be exposed under controlled conditions to halothane and caffeine [142,143]. Strict criteria are used to define positive, negative, or equivocal tests [144–147]. The sensitivity and specificity is approximately 100% and 80%, respectively. A video of the CHCT can be found at the following link: http://www.mhaus.org/videos [133]. Testing is restricted to a few centers (four in the United States) and can only be accurately performed using fresh muscle from adults and children older than about age 6 years [148]. The European Malignant Hyperthermia Group has recently revised their guidelines for IVCT investigation of MH susceptibility in children to include a minimum age of 4 years; although, the guidelines specify that laboratories testing children younger than 10 years of age must have relevant control data [141]. Because of the invasive nature of this testing and significant cost, including travel for the patient, genetic testing is becoming increasingly popular and an option for first-line testing in place of muscle biopsy in some cases. The indications for CHCT and genetic testing from the Malignant Hyperthermia Assocation of the United States are summarized in Boxes 45.1 and 45.2, respectively. Of note, a single-center recent analysis of the histomorphology in MH-susceptible patients did not reveal any consistent histological abnormalities; however, some MH-suscepitble patients were found to have evidence of other myopathies [149].

Box 45.1: Indications for the caffeine–halothane contracture test (CHCT)

Patient with known MHS* relative (as determined by positive muscle contracture test)

- Patient with MHS family member (as determined by past suspicious MH episode, but *without* a known *RYR1* causative genetic mutation)
- Patient with past suspected MH event (wait 3–6 months after event, depending upon the degree of rhabdomyolysis)
- Patient with *severe* MMR during anesthesia with a triggering agent
- Patient with *moderate to mild* MMR with evidence of rhabdomyolysis
- Patient with unexplained rhabdomyolysis during or after surgery (may present as sudden cardiac arrest due to hyperkalemia)
- Patient with exercise-induced rhabdomyolysis after a negative rhabdomyolysis work-up
- Signs suggestive of but not definitive for MH
- If military service is desired, patients with suspicion of MHS are required to undergo CHCT

*Malignant hyperthermia susceptible: suspicious MH event and predisposing factors to MH in patient/family.
MH, malignant hyperthermia; MHS, malignant hyperthermia susceptibility; MMR, masseter muscle rigidity.

Source: Reproduced from http://www.mhaus.org with permission of MHAUS.

Box 45.2: Indications for genetic testing in United States

- Patient with a confirmed or highly suspicious clinical episode of MH
- Patient with positive CHCT
- Patient with MHS relative as determined by positive CHCT
- Patient with MHS relative as determined by a confirmed or highly suspicious clinical episode of MH
- Patients with relatives with known causal *RYR1* mutation*

*Proband or index case should always be tested first if possible.
CHCT, caffeine–halothane contracture test; MH, malignant hyperthermia; MHS, malignant hyperthermia susceptibility; MMR, masseter muscle rigidity.
Source: Reproduced from http://www.mhaus.org with permission of MHAUS.

Epidemiology

Malignant hyperthermia is a rare disorder affecting fewer than 1:50,000 adults and as many as 1:3000 children [150], representing approximately 13 cases per million hospital discharges in the United States [151] or one per 100,000 in New York State in 2005 [152]. Although large epidemiological studies have not been performed recently, it appears that the frequency of MH has declined with increased awareness and a greater degree of certainty as to the agents that are and are not associated with the syndrome. MH may occur at any age, although it is most common in children and young adults. It has been reported rarely in infants and among the elderly [153,154]. Concentrations of cases can be found among large extended families or among members of closed or relatively closed communities. In a recent review of data compiled by the Malignant Hyperthermia Association of the United States, Larach and colleagues [155] found that of 286 cases reported between 1987 and 2006, 75% were male, most were young (median age, 22 years), a disproportionately large number were of muscular build (29%), and most were white (70%). In a recent study of data obtrained from existing reports in the North American Malignant Hyperthermia Registry, muscular body build and male sex were independently associated with malignant hyperthermia susceptibility [156].

Acute presentation

In the past, agents known to trigger MH included halothane and enflurane. Currently, sevoflurane, isoflurane, desflurane, and succinylcholine have been known to trigger an episode of MH. Desflurane and sevoflurane are weak triggers for MH and therefore may be associated with episodes that are less fulminant than those seen in association with older agents and succinylcholine [157,158]. The rate of triggering may also be slowed or even eliminated by other factors, including the use of non-depolarizing muscle relaxants, barbiturates, and hypothermia [159]. Nevertheless, specific pharmacological triggering agents are not necessary to initiate a reaction among susceptible individuals. Carr et al [160], in a series of more than 2000 biopsy-proven MH patients, observed a rate of triggering of 0.46% despite the use of a non-triggering anesthetic.

The clinical presentation for MH is highly variable and may at times be confused with other conditions such as rhabdomyolysis. The classic features of the disorder are non-specific and can be found in association with many other conditions. The combination of a highly variable presentation with non-specific signs and symptoms in a rare disorder explains the continued association of MH with poor outcomes, including death. This also explains the frequency with which MH is confused with other conditions. To assist in the clinical diagnosis of MH, Larach and colleagues [161] developed a clinical grading scale.

The presentation of MH relates to the underlying hypermetabolic state after exposure to a triggering agent such as a volatile anesthetic or succinylcholine. Hypermetabolism of skeletal muscle produces tachycardia, tachypnea, fever, muscle rigidity, acidosis (both respiratory and metabolic), hyperkalemia secondary to rhabdomyolysis with associated dysrhythmia, and ultimately cardiovascular collapse and death. Each of the symptoms can be traced to the calcium-induced hypermetabolic state within the skeletal muscle. Rigidity, occurring in approximately 40% of patients in the series described by Larach et al [155], is a function of sustained contraction that may lead to muscle breakdown and release of large amounts of potassium. The release of potassium in the setting of profound acidosis is often the proximate cause of ventricular dysrhythmia, cardiac arrest, and mortality unless resuscitation efforts are successful. It must be kept in mind that acute hyperkalemia, fever, acidosis, and other manifestations of MH are associated with other conditions and may be confused with MH, although regardless of the etiology, treatment may be the same. Table 45.3 lists the order of appearance of clinical signs of MH in a series of 255 patients reported by Larach et al [155].

Laboratory evidence of MH reflects the underlying pathology. Thus, along with the aforementioned hyperkalemia and metabolic and respiratory acidosis, a rapid rise in creatine kinase (CK) and myoglobinuria reflect muscle destruction. Coagulopathy is common along with pulmonary edema and cardiac and hepatic dysfunction. Survivors of the acute phase may have evolving evidence of acute renal failure, with increasing serum creatinine, oliguria, or anuria [155].

The onset of symptoms of MH is variable and may occur within minutes or may at times be delayed for hours [162–164]. Many patients with MH have had uneventful anesthetics in the past, with 30% having had as many as three previous exposures without triggering. Tachycardia and, in the spontaneously breathing patient, tachypnea are usually the first signs and are virtually always present, and the absence of tachycardia should cast doubt on the diagnosis of MH. In general, the more rapid the onset, the more severe the presentation; however, fulminant cases of MH have been described in patients whose first symptoms did not appear until after admission to the postanesthesia care unit or even many hours later [163,164]. Accurate and timely recognition requires a high degree of clinical suspicion and vigilance. As many as 20% of patients experience a recrudescence of symptoms an average of 13 h after the initial reaction. Those at greatest risk for recrudescence are those with delayed onset and muscular build [165].

Patients at risk

Recognition of MH must begin with an appreciation of the patient populations at greatest risk. Susceptibility to MH has been a subject of controversy since its original description.

Table 45.3 Order of appearance of clinical signs[a] during 255[b] malignant hyperthermia events

Clinical sign	Medial (first, third quartile) appearance number[c]	Range of appearance number[c]	No. (%) of patients with sign
Masseter spasm	1.00 (1.00, 1.00)	1.00–4.00	68 (26.7)
Hypercarbia	2.00 (1.00, 2.00)	1.00–8.00	235 (92.2)
Sinus tachycardia	2.00 (1.00, 2.00)	1.00–7.00	186 (72.9)
Generalized muscular rigidity	2.00 (1.00, 3.50)	1.00–6.00	104 (40.8)
Tachypnea	2.00 (1.00, 3.00)	1.00–6.00	69 (27.1)
Other	2.00 (1.00, 4.00)	1.00–7.00	43 (16.9)
Cyanosis	2.00 (2.00, 4.00)	1.00–7.00	24 (9.4)
Skin mottling	2.00 (1.00, 3.50)	1.00–7.00	16 (6.3)
Rapidly increasing temperature	3.00 (3.00, 4.00)	1.00–7.00	165 (64.7)
Elevated temperature[d]	3.00 (2.00, 4.00)	1.00–8.00	133 (52.2)
Sweating	4.00 (3.00, 5.00)	1.00–8.00	45 (17.6)
Ventricular tachycardia[d]	4.00 (2.00, 5.00)	1.00–7.00	9 (3.5)
Cola-colored urine	5.00 (3.00, 5.00)	2.00–9.00	35 (13.7)
Ventricular fibrillation[d]	5.50 (4.00, 8.00)	1.00–8.00	6 (2.4)
Excessive bleeding	6.00 (5.00, 6.00)	4.00–8.00	7 (2.7)

[a] Table lists the abnormal clinical sign and appearance order (judged to be inappropriate by the attending anesthesiologist or other physician) during malignant hyperthermia (MH) events. Clinical signs are listed in order of occurrence with the earliest signs listed first and the latest signs listed last. (No points on the clinical grading score are accumulated for the presence of the following adverse signs: cyanosis, skin mottling, sweating, excessive bleeding, and other.)

[b] For 31 cases, clinical sign appearance order was not known. (Appearance order is not required to calculate clinical grading scale score, and no additional points accrue for early appearance.)

[c] Appearance number is the numerical order in which a clinical sign appeared, e.g. the first clinical sign that appeared during an MH event would be assigned the appearance number of 1, the second clinical sign that appeared during an MH event would be assigned the appearance number of 2, and so on.

[d] An early version of the AMRA (*a*dverse *m*etabolic/*m*usculoskeletal *r*eaction to *a*nesthesia) report form did not request these signs in one fatal case in which the maximum temperature was 41°C, but these findings were noted elsewhere in the AMRA report and have been counted in this table.

Source: Reproduced from Larach et al [155] with permission of Wolters Kluwer.

In a 1985 paper, Britt [166] described a series of features that suggest the potential for MH: "While some are perfectly healthy, others complain of: ptosis and strabismus in childhood; kyphoscoliosis or lumbar lordosis; club foot, various kinds of hernias …; joint hypermobility …; … undescended testicle; calcium stones …; poor dental enamel …" [166]. The author's extensive list reflected the lack of knowledge available at the time regarding the disorder. Currently, it is believed that MH is associated with only a few conditions, including King–Denborough syndrome, Evans myopathy, central core disease, multi-minicore disease, congenital-fiber type disproportion, core–rod myopathy, and centronuclear myopathy [13,139,167,168]. The presence of strabismus, scoliosis, or other non-specific findings cannot be considered helpful in identification of those at risk.

Clearly succinylcholine-induced masseter spasm and susceptibility to MH are associated. The combination of halothane and succinylcholine produces masseter spasm in approximately 1% of children anesthetized for otolaryngological procedures [169]. Larach et al [155] noted that, among subjects with probable or certain MH in their database, 20% had masseter spasm as a finding during their MH event. Among those exhibiting masseter spasm, the association with MH depends to a large extent on the presentation. Those with mild jaw stiffness appear to have only a slight increase in susceptibility to MH, whereas those exhibiting what has been termed "jaws of steel" are thought to have as high as an 80% concordance with MH. Patients having masseter spasm and an associated elevation of CK to more than 20,000 units/L have been demonstrated to have a 100% concordance with MH susceptibility [170]. As the use of succinylcholine has declined, especially in children, so has the frequency of masseter spasm; however, succinylcholine is still widely used and can be life saving for emergency airway management [171].

For the clinician, a decision must be made about whether to proceed with a procedure after a patient experiences masseter spasm. Some advocate for canceling the planned procedure [170] and others recommend conversion to a non-triggering anesthetic and then proceeding, provided no further evidence of MH is seen [170,172]. Although clear guidance is unavailable, the decision should probably be based on the severity of the masseter spasm, the urgency of the procedure, the environment, and the resources available to provide care should the event progress to fulminant MH despite a change to a non-triggering anesthetic. A child experiencing masseter spasm should almost certainly be admitted for observation and a serum CK level determined, preferably before any surgical incision to assist in determining risk for MH in the future. Weglinski and colleagues [173] demonstrated that among children with idiopathic elevations of CK and no history of masseter spasm, 49% were found to be susceptible after biopsy and a CHCT. As noted previously, the combination of masseter spasm and CK higher than 20,000 units/L is virtually diagnostic. Follow-up of the child who has experienced masseter spasm should probably include counseling with regard to the risk of MH, diagnostic testing, avoidance of triggering agents in the future for the child and first-degree relatives, and referral to pediatric neurology to evaluate for other potential causes of masseter spasm (e.g. congenital myotonia).

The association between various myopathies and MH continues to remain an area of controversy. Specifically, are children with undiagnosed myopathies at increased risk? And are

Table 45.4 Descriptive risk of malignant hyperthermia (MH)*

Disease	Risk of MH
Duchenne muscular dystrophy	No increased risk over general population. Weak evidence for MH
Becker dystrophy	No increased risk over general population. Weak evidence for MH
Noonan syndrome	Weak evidence for MH. But closer to zero than dystrophinopathies
Osteogenesis imperfecta	Weak evidence for MH. But closer to zero than dystrophinopathies
Arthrogryposis	Weak evidence for MH. But closer to zero than dystrophinopathies
King–Denborough	MHS
Carnitine palmitoyltransferase II deficiency	MHS plausible but unproven. Increased risk of rhabdomyolysis but less risk of MH than in dystrophinopathies. Weak evidence
Myophosphorylase B deficiency (McArdle syndrome)	Weak evidence for MH. Increased risk of rhabdomyolysis but less risk of MH than in dystrophinopathies
Myoadenylate deaminase deficiency	Weak evidence for MH. Increased risk of rhabdomyolysis but less risk of MH than in dystrophinopathies
Brody disease	Weak not zero but treat patients for MH because intracellular Ca^{2+} is abnormal. Less risk of MH than in dystrophinopathies
Asymptomatic hyperkalemia	Weak evidence for MH. Increased risk of rhabdomyolysis but less risk of MH than in dystrophinopathies
Myotonia congenita	No increased risk over general population
Paramyotonia congenita	No increased risk over general population
Potassium aggravated myotonia	No increased risk over general population
Myotonia fluctuans	No increased risk over general population
Myotonia permanens	No increased risk over general population
Aceta/olamide-responsive myotonia	No increased risk over general population
Hyperkalemic periodic paralysis ± myotonia	No increased risk over general population
Myotonic dystrophy type I (Steinert disease)	No increased risk over general population
Myotonic dystrophy type 11	No increased risk over general population
Hypokalemic periodic paralysis	Unclear, may be greater risk than in general population but less risk of MH than in dystrophinopathies
Central core myopathy	MHS
Multi-minicore disease with *RYR1* mutation	MHS
Multi-minicore disease without *RYK1* mutation	MHS less risk of MH than in dystrophinopathies
Nemaline rod myopathy without *RYR1* mutation	No increased risk over general population
Nemaline rod myopathy with *RYR1* mutation	MHS risk of MH not yet determined

* Described in [1,3–5,7].
MHS, malignant hyperthermia susceptibility.
Source: Reproduced from Davis and Brandom [174] with permission of Wolters Kluwer.

those patients with Duchenne-type muscular dystrophy at increased risk? As previously stated, only a few myopathic conditions can be clearly associated with MH; other myopathies have been associated with MH in the past but have not been clearly linked. Table 45.4 gives a descriptive risk of MH in unusual diseases [174].

Reports have described sudden CA and death in children known to have a muscular dystrophy and attributed those events to fulminant MH. It has become clear, however, that these events are more likely to be the result of rhabdomyolysis and subsequent hyperkalemic CA rather than true MH. The question remains as to whether volatile anesthetics are the cause of the rhabdomyolysis and consequently should be avoided in these patients. Succinylcholine is associated with this phenomenon and should never be used in a patient with a known or suspected dystrophy (or myopathy). In the young boy with Duchenne-type muscular dystrophy, the decision to avoid both succinylcholine and a volatile agent is relatively straightforward, as there are obvious alternatives; however, it is less clear how to approach the child with an undiagnosed myopathy because the alternative, typically propofol, may be contraindicated in children with mitochondrial disorders [13,168,175,176].

Acute management

Successful management of an acute MH episode depends on early recognition and swift application of a treatment protocol that has been well thought out in advance. Figure 45.8 is a poster from the Malignant Hyperthermia Association of the United States that describes the management of fulminant MH [133].

Specific management includes discontinuation of triggering agents and institution of therapy with dantrolene. Non-specific therapy is aimed at the effects of acidosis, fever, rhabdomyolysis, and consequent hyperkalemia, including correction of acidosis with hyperventilation and sodium bicarbonate; and active cooling, maintenance of urine output, and management of hyperkalemia with bicarbonate, glucose, and insulin. Additional antiarrythmic therapies directed against dysrhythmia may be useful; however, rhythm disturbance is almost certainly secondary to hyperkalemia, and therapy should be primarily directed at reducing serum potassium.

First available in the late 1960s as an oral muscle relaxant for use in patients with spasticity, dantrolene was recognized as an effective therapy for MH in pigs by Harrison in 1975 [177] and 2 years later in humans by Austin and Denborough [178]. The drug was of limited value for acute management

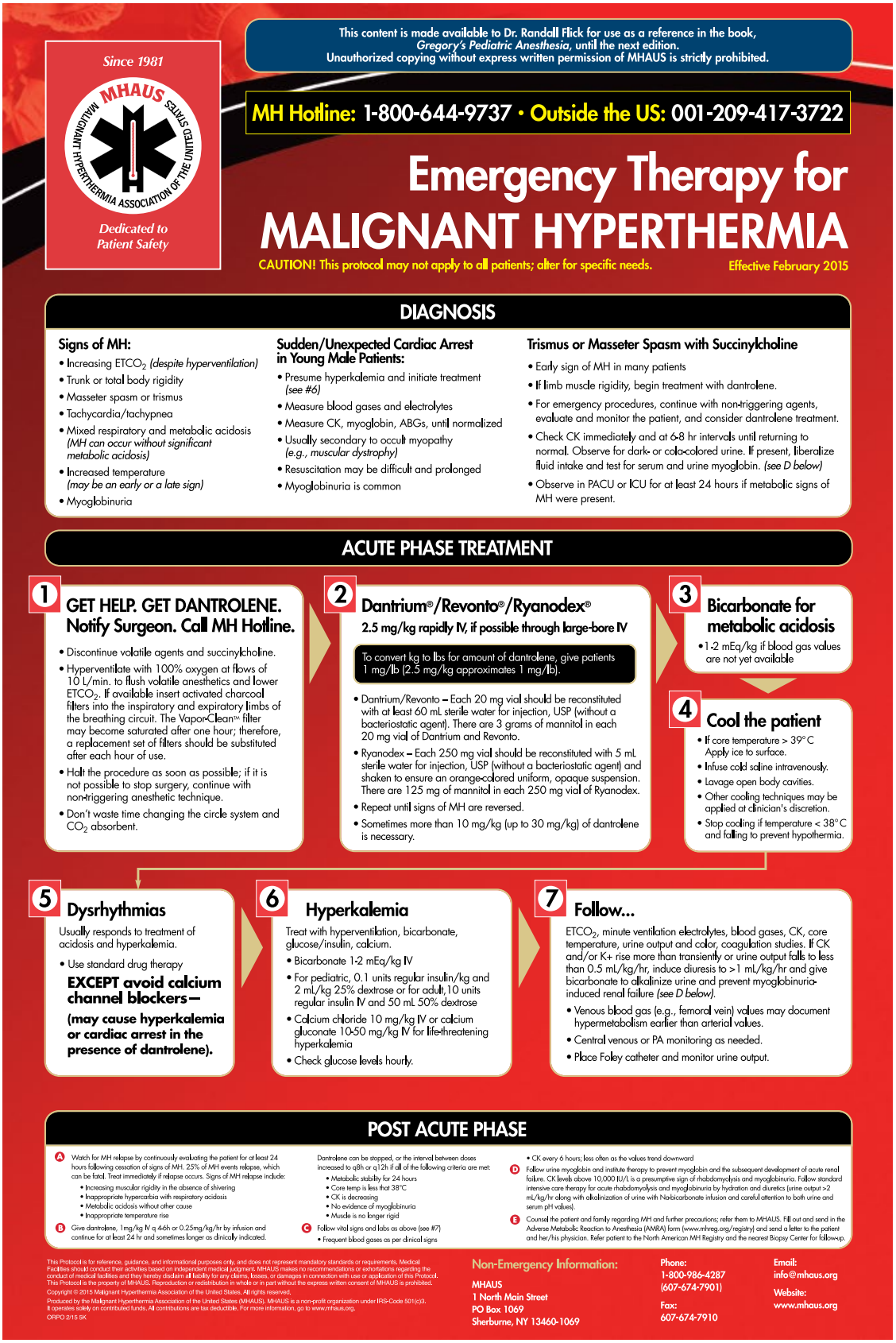

Figure 45.8 Poster prepared by the Malignant Hyperthermia Association of the United States (MHAUS) to provide the clinician with essential information for the care of the malignant hyperthermia patient. *Source:* Reproduced from http://medical.mhaus.org with permission of The American Physiological Society.

given the need to deliver it orally. When solubility problems were resolved, it became available for intravenous use in 1979. Dantrolene acts to inhibit EC coupling in skeletal muscle by inhibiting calcium release at the level of the sarcoplasmic reticulum. It depresses twitch height by more than 70% in humans when given intravenously in a dose of 2.5 mg/kg. Bioavailability of the oral form, once an issue of concern, is very similar to that of the intravenous form [179]. Elimination is by hepatic conversion to an active 5-hydroxy metabolite that is excreted in the urine, with a half-life of approximately 9 h for the parent form and 15 h for the metabolite [180]. Newer formulations are more concentrated and less time intensive to administer rapidly, which is crucial given the importance and proven efficacy of prompt treatment [133]. Dantrolene is highly effective, and when used in sufficient doses early in the course of acute MH, is virtually 100% effective in preventing mortality. The trend in mortality associated with acute MH up to 1993 was described by Strazis and Fox [181]. Mortality declined dramatically in the years immediately after the introduction of dantrolene from more than 60% to less than 10%. Currently, mortality has further declined to less than 5%.

The older preparations of dantrolene contain 20 mg of lyophilized dantrolene and 3000 mg mannitol. Reconstitution with 60 mL sterile water is necessary for each vial. A 2.5 mg/kg initial dantrolene dose requires nine vials for a 70 kg patient; and the drug must be completely dissolved before administration. Anyone who has participated in the preparation of this drug, either for a real MH case, or for a simulation, can attest to how difficult this is to accomplish quickly, and how many team members are required. A new preparation, Ryanodex® (Eagle Pharmaceuticals, Inc., Woodcliff Lake, NJ, USA), is supplied in 20 mL vials containing 250 mg dantrolene sodium and is reconstituted with 5 mL sterile water, dissolving in less than 1 min. The novel formulation includes 125 mg mannitol, 25 mg polysorbate 80, and 4 mg povidone K12 per vial. One provider can reconstitute a 2.5 mg/kg loading dose for a patient weighing up to 100 kg with one vial. Given the emergent nature of treatment of this rapidly evolving hypermetabolic process, it would seem intuitive to utilize the newer preparation when possible.

Preparation and care of the susceptible patient

Identification of the patient at risk and the provision of a safe, non-triggering anesthetic environment are the primary goals for those providing care to people at risk for MH. Patients at risk have been discussed previously and should be managed as if they are known to have MH, regardless of whether they have been tested.

For the patient determined to be at risk, a non-triggering anesthetic should be provided, avoiding the use of volatile anesthetic agents and succinylcholine. The use of regional anesthesia is an excellent option because concerns regarding the safety of amide-type local anesthetics have not been found to carry risk either in animal models or in clinical practice. The anesthesia machine should be prepared per specific manufacturer guidelines, the absorbant changed, and the agent and vaporizers either removed or otherwise rendered inoperable. Activated charcoal filters have decreased the time required to prepare some anesthesia machines; however, preparation time at some sites may require that a clean machine be kept available or that MH-susceptible cases be cared for as the first case on the surgery schedule to avoid delays.

Summary

In summary, MH is a rare pharmacogenetic disorder that is likely to become increasingly rare, given its increased recognition, more frequent use of weak triggering agents, and less frequent use of succinylcholine. Prompt recognition and early treatment with dantrolene should make severe morbidity or mortality extremely rare. As genetic diagnosis becomes increasingly available and sensitive, optimism exists that the disorder will be more easily identified, prevented, and effectively managed in the future.

KEY POINTS: MALIGNANT HYPERTHERMIA

- Malignant hyperthermia is a pharmacogenetic syndrome characterized by a hypermetabolic state of skeletal muscle typically induced by exposure to specific anesthetic agents, including all halogenated volatile anesthetics as well as the depolarizing neuromuscular relaxant succinylcholine
- Treatment of MH includes specific management through discontinuation of triggering agents and administration of dantrolene and non-specific therapy aimed at the reversal of acidosis, fever, rhabdomyolysis, and hyperkalemia, and providing cardiopulmonary support
- Only a few myopathic conditions can be clearly associated with MH: King–Denborough syndrome, Evans myopathy, central core disease, multi-minicore disease, congenital fiber-type disproportion, core–rod myopathy, and centronuclear myopathy
- A new preparation of dantrolene is available that requires only 5 mL sterile water and 1 min to prepare a 2.5 mg/kg loading dose for a patient weighing up to 100 kg

Propofol infusion syndrome

Propofol is an intravenous anesthetic agent used for the induction and maintenance of general anesthesia in children and adults. Because of its rapid onset and offset of action, it is an ideal agent for sedation of mechanically ventilated patients. Developed in 1980, it had been used for a number of years in both adults and children without report of severe adverse events. In 1992, Parke et al [182] reported on the deaths of five children in whom metabolic acidosis and myocardial failure developed after propofol infusion. All these children had upper respiratory tract infections, ranged in age from 4 weeks to 6 years, and were sedated with propofol at a rate ranging between 66 and 178 μg/kg/min (4–10.7 mg/kg/h) for between 66 and 115 h. The constellation of metabolic acidosis, bradyarrhythmia, and heart failure was typical for these patients. The dose range was within those recommended by the British Medical Association at that time: 150–2500 μg/kg/min (9–150 mg/kg/h). Parke was the first to suggest that

propofol infusion, although safe in adults, perhaps should not be used for sedation for children.

In 1998, Bray [183] further characterized this constellation of symptoms as propofol infusion syndrome (PRIS) by the review of information collected from the literature on 18 children who received propofol and had similar adverse effects. The majority of affected patients had respiratory tract infections, although other associations have been reported subsequently by other providers [184]. These other situations were found to occur in young, healthy patients who had sustained head trauma and had received intravenous steroids as well as vasopressors. In Bray's series, the terminal event was myocardial failure, ventricular dysrhythmia, or in some instances, a resistant and progressive bradycardia, which has further been identified as the Brugada syndrome [184]. Postmortem examination commonly reveals a fatty liver and myocardial fiber necrosis, metabolic acidosis is common, and plasma is lipemic. According to Bray [183], there appeared to be a definite association between PRIS and propofol infusions higher than a mean dose of 67 μg/kg/min (4 mg/kg/h) and lasting 48 h or longer.

Although the dose limits suggested by Bray [183] provide guidance, the rapid development of tolerance requires an increased rate of propofol infusion to maintain adequate sedation, and the relatively low dose suggested by Bray is often quickly exceeded. The catecholamine surge, present in acute neurological conditions or produced in various other stress models, may result in sympathetic overactivity with secondary endogenous catecholamine toxicity that may be responsible for decreasing the anesthetic effect of propofol as well as contributing to the direct myocytolytic effects of catecholamines [185].

The mechanism of the myocytotoxic effect of propofol given in prolonged doses has not yet been entirely elucidated. It is known that propofol uncouples oxidative phosphorylation and energy production in the mitochondria, impairs oxygen utilization, and inhibits electron flow along the mitochondrial electron transport chain [186,187]. These cellular effects result in a clinically apparent decrease in ventricular performance. Additionally, in this setting propofol may directly antagonize β-adrenoceptor binding and act directly on calcium channel proteins resulting in diminished cardiac contractility [185].

Cardiac and peripheral muscle necrosis is often evident on postmortem examination. This may be the result of an imbalance of energy supply and demand [185]. Free fatty acids derived from lipolysis of adipose tissues are the most important fuel for both the myocardium and skeletal muscle under fasting conditions [185]. Oxidation within the mitochondria is the key process generating electrons, which are subsequently transferred to the respiratory chain. As propofol can impair the movement of electrons through this chain, the subsequent accumulation of free fatty acids can eventually lead to various grades of myocytolysis. Furthermore, the accumulation of unused free fatty acids has proarrhythmogenic properties that contribute to the overall clinical picture of dysrhythmia and myocardial failure observed in PRIS (Fig. 45.9) [185]. Current experimental data suggest that the respiratory chain inhibition may result in the early, dose-dependent signs of PRIS (cardiac failure, metabolic acidosis, fever, hypotension) while the later, time-dependent signs may be secondary to inhibition of fatty acid oxidation (rhabdomyolusis, hypertriglyceridemia, arrhythmia) [187].

Although PRIS is most commonly observed after a prolonged propofol infusion, there have been some reports of the development of this syndrome after just a few hours of continued propofol infusion in pediatric patients (Table 45.5). Koch et al in 2004 [188] reported the first case of suspected PRIS after short-term infusion of propofol in a child. The patient was a 5-year-old girl admitted to the hospital after endovascular coil embolization of a high-output arteriovenous malformation. Propofol infusion was started at 250 μg/kg/min (15 mg/kg/h). A progressive elevation in serum lactate developed within 6 h of admission, and a diagnosis of PRIS was considered. The lactic acidosis rapidly resolved after propofol infusion was tapered and discontinued, and the child subsequently recovered.

It has been proposed that in patients receiving propofol infusion, frequent monitoring of acid–base status and lactate levels may alert the clinician to early development of PRIS [189]. Veldhoen and colleagues [189] described a 17-year-old boy who sustained multiple skull fractures in a motor vehicle accident. A propofol infusion was initiated to allow continued endotracheal intubation, and over the ensuing hours escalating doses were required to maintain adequate depth of sedation. A maximum of 8 mg/kg/h was administered for 14 h early in the hospital course. On the 4th day, propofol was discontinued as a progressive lactic acidosis was noted. Despite serial measurement of acid–base status and lactate and eventual discontinuation of propofol after lactate was noted to increase, albeit modestly, the child subsequently had CA and eventually died as a result of profound myocardial failure. This was the first report of mortality due to PRIS despite careful monitoring of metabolic parameters and prompt discontinuation of propofol with increased lactate. It should be noted, however, that the child received a continuous infusion of propofol at a dose exceeding the recommended dose of 67 μg/kg/min or 4 mg/kg/h for a duration of no longer than 48 h [189]. Figure 45.10 details this patient's hospital course. It is important to note that PRIS may occur even with moderate doses of propofol (<4 mg/kg/h) or short infusion duration [187].

Some predictors have been identified for mortality in patients with suspected PRIS [190]. Patients with suspected PRIS who died were more likely to be younger than 18 years old, be male, have received propofol for more than 48 h, and have been concomitantly treated with catecholamine therapy. The presence of cardiac symptoms, hypotension, rhabdomyolysis, renal involvement, metabolic acidosis, or dyslipidemia also heralded increased mortality in these patients.

Pediatric patients should not receive infusions of propofol that exceed the recommended dose for more than 48 h [191]. A retrospective study of 142 critically ill children sedated with propfol infusion at doses less than 3 mg/kg/h for less than 24 h found no evidence of PRIS [192]. A retrospective study of more than 200 critically ill children sedated with propofol in the intensive care unit (median average infusion rate 2.7 mg/kg/h (interquartile range, 1.9–3.6 mg/kg/h) and mean infusion duration of 10.3 h (standard deviation, 6.7 h)) did not identify any cases of PRIS and concluded that the use of propofol infusions consistent with current guidelines appears safe although monitoring for adverse effects is still warrented [193]. For those individuals with mitochondrial myopathies or known mitochondrial defects, it is probably prudent to

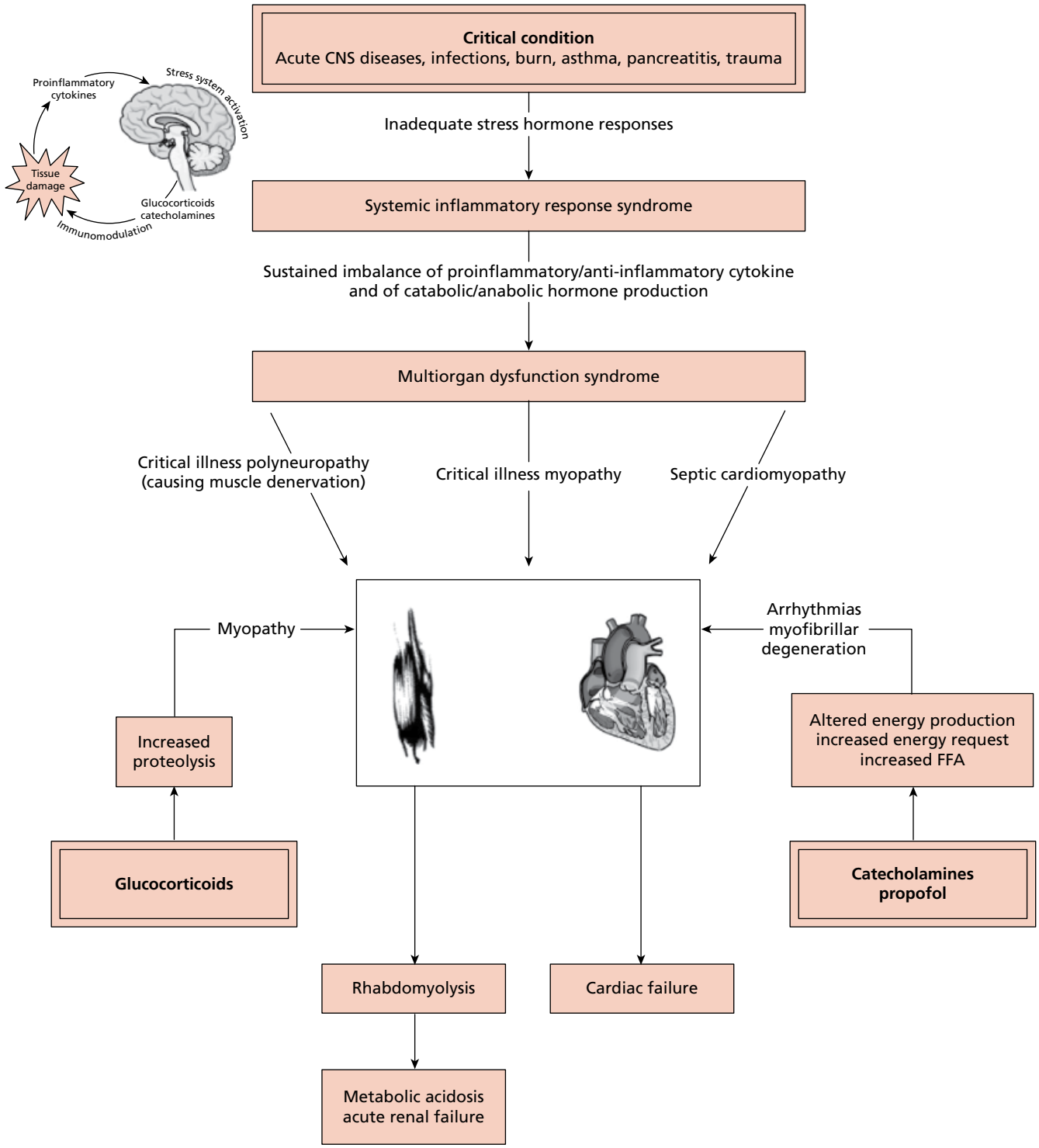

Figure 45.9 Propofol infusion syndrome is a critical illness; cardiac failure and rhabdomyolysis are associated with high-dose propofol, catecholamines, or steroids. CNS, central nervous system; FFA, free fatty acid. *Source:* Reproduced from Vasile et al [185] with permission of Springer Nature.

Table 45.5 Evolution of propofol dose and acid–base status (hours after admission)

		Time after admission (h)						
Dose and status	**Admission**	**2**	**4**	**6**	**8**	**10**	**18**	**24**
Propofol (μg/kg/h)	15	15	15	15	6	6	0	0
pH	7.45	7.38	7.31	7.34	7.33	7.36	7.39	7.37
$PaCO_2$ (mmHg)	33	36	42	36	41	41	40	39
Bicarbonate (mmol/L)	22.8	20.9	20.7	19.1	21	23.1	23.7	22.1
Lactate (mmol/L)	1.8	3.4	4.6	5.3	3.9	1.9	1.4	1.3
Base excess (mmol/L)	–0.7	–3.4	–4.5	–5.6	–4	–1.6	–0.6	–2.4

Source: Reproduced from Koch et al [188] with permission of Springer Nature.

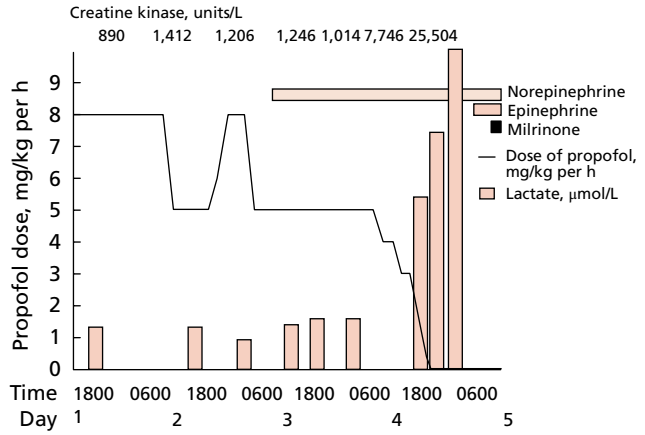

Figure 45.10 Time overview of propofol dose and laboratory results. See text for detailed explanation. *Source:* Reproduced from Veldhoen et al [189] with permission of Wolters Kluwer.

avoid propofol infusions altogether unless there is no viable alternative or to use adjunctive medications to facilitate sedation and allow a lower dose of propofol as infusion. Regardless, it would certainly be recommended to monitor acid–base status as well as lactate level on a regular basis (every 6 h) to minimize the chance for development of PRIS. The development of a metabolic acidosis or rise in lactate without another cause would warrant discontinuation of propofol infusion and administration of an alternative sedating medication. Patients who develop PRIS should be screened for mitochondrial disorder [194].

KEY POINTS: PROPOFOL INFUSION SYNDROME

- PRIS is characterized by dose-related morbidity (cardiac failure, metabolic acidosis, fever, hypotension) and time-dependent morbidity (rhabdomyolusis, hypertriglyceridemia, arrhythmia)
- Propofol uncouples oxidative phosphorylation and energy production in the mitochondria, impairs oxygen utilization, and inhibits electron flow along the mitochondrial electron transport chain
- Predictors of mortality in patients with suspected PRIS include age less than 18 years, male sex, propofol infusion for more than 48 h, and concomitant treatment with catecholamine therapy

Local anesthetic toxicity and intralipid administration

Thousands of doses of local anesthetic medications are administered to pediatric patients every day in hospitals and outpatient surgical centers throughout the world. Local anesthetic medications may act not only as the sole agent for analgesia but also as an important component of an anesthetic technique that uses a combination of both regional and general anesthesia.

Cocaine was the first local anesthetic isolated from coca leaves in the 1860s by Albert Niemann, a German chemist. Cocaine was initially used by Sigmund Freud in 1884 to assist a patient in weaning from morphine. The first clinical use of cocaine for nerve block occurred in 1884 by William Stewart Halsted to create surgical anesthesia. The first modern local anesthetic developed was lidocaine, in the 1940s [195].

Local anesthetics prevent neural transmission through inhibition of fast sodium channels as well as via inhibition of γ-aminobutyric acid in pathways located in the cerebral cortex [196]. Local anesthetics are of either the amide or the ester type and are metabolized via different mechanisms. Local ester anesthetics are metabolized via plasma pseudocholinesterase; local amide anesthetics are metabolized via the liver. It is important to understand that the toxicities of local anesthetics are additive. Therefore, when two local anesthetics are combined, the maximum dose of the local anesthetics must be carefully determined, keeping in mind the overall ratio of each of these medications.

Ever since the first use of cocaine for medicinal purposes, there have been reports of its adverse reactions on the nervous, respiratory, and cardiac systems. In 1885, four publications dealt with serious adverse events, including death. A report by Mayer [197] in 1924 raised medical awareness of the toxic reactions to these medications with a report of 40 fatalities related to local anesthesia.

In pediatric patients, local anesthetic toxicity is relatively rare. Among the largest series that have reviewed complications of regional anesthetics in the pediatric population, Giaufre et al [198] reported a complication rate of four per 10,000 systemic toxic reactions after the performance of epidural injection of local anesthetic. In this series, no systemic toxicity was associated with peripheral nerve blocks.

When neurotoxicity occurs, it typically precedes the more severe cardiotoxicity. In awake patients, tinnitus, a metallic taste in the mouth, and circumoral tingling are frequent initial symptoms. As the blood level of local anesthetics increases, there is progression to motor twitching followed in some by seizures. In those who progress to cardiotoxicity, the manifestations include cardiac arrhythmia and hypotension, with eventual cardiovascular collapse [199]. McClenahan [200] reported the first pediatric death in 1955 after local anesthetic toxicity after the child consumed a dibucaine troche. He described a wide-complex bradycardia unresponsive to conventional treatment with sodium bicarbonate and other medications.

In 2006, Rosenblatt et al [201] reported the first successful use of a 20% lipid emulsion in a human patient during resuscitation after a presumed bupivacaine-related CA. The rationale for the use of lipid emulsion had been introduced by Weinberg et al in 1998 [202] with initial studies in rats and subsequently dogs, demonstrating that lipid infusions both raise the threshold for cardiotoxicity and increase the likehood of survival in rodents receiving a large single intravenous dose of bupivacaine. Ludot et al [203] presented the first case report of successful resuscitation after presumed local anesthetic toxicity in a child. A 13-year-old child received a lumbar plexus block under general anesthetia and subsequently experienced ventricular tachycardia 15 min after the injection of lidocaine and ropivacaine with epinephrine. Plasma levels of local anesthetics were obtained during early resuscitation and indicated local anesthetic toxicity. Within 2 min of intralipid administration, normal sinus rhythm was

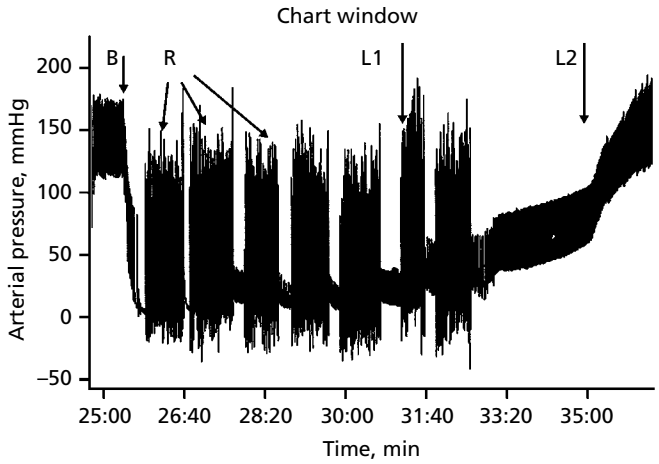

Figure 45.11 Hemodynamic response to lipid infusion. The arterial pressure trace of a rat is shown over approximately 12 min. The arrow at B indicates intravenous injection of bupivacaine 20 mg/kg over 20 s. The arrows at R indicate resuscitation by closed chest compression. The L1 arrow indicates infusion of 30% soybean oil emulsion 5 mL/kg over 10 s. The recovery of the hemodynamic profile occurs after the second lipid bolus, L2 (arrow). *Source:* Reproduced from Weinberg [205] with permission of Wolters Kluwer.

achieved [203]. Experience in animals and humans suggests that intravenous lipid emulsion increases the lethal threshold and decreases mortality after systemic overdose of local anesthetics [204]. This finding represents an important advance in the care of both adults and children, given that CPB has traditionally been the therapy of last resort in adults and children with CA secondary to local anesthetic overdose [205].

Mechanism of action of lipid emulsion

The "lipid sink" theory described by Weinberg suggests that local anesthetic is sequestered in the plasma lipid fraction, thereby isolating tissue from the toxic effect [205]. Lipid may also have a direct inotropic effect on the heart and that effect may contribute positively to its ability to reverse bupivacaine-induced cardiac depression (Fig. 45.11) [205].

Clearly, evidence supports the early use of lipid emulsion in the treatment of local anesthetic toxicity. Rather than wait for progression to a non-productive or unstable rhythm, treatment with lipid emulsion should be initiated as soon as possible. Weinberg suggested that lipid emulsion should be used at the earliest signs of local anesthetic toxicity, for example when the neurological signs and symptoms appear and before the onset of more serious cardiac manifestations [205]. Subsequently, Shah et al [206] reported the successful use of a lipid emulsion in a 40-day-old infant with presumed local anesthetic toxicity after caudal injection.

In 2010, the American Society of Regional Anesthesia and Pain Medicine published guidelines for the prevention and treatment of local anesthetic toxicity. According to Weinberg's recommendations [205], a dose of 1.5 mL/kg of lipid emulsion 20% can be repeated to a maximum dose of 10 mL/kg over the first 30 min [207]. At the point of conversion to sinus rhythm, infusion of lipid emulsion 20%, at a rate of 0.25 mL/kg/min should be continued until hemodynamic recovery. The initiation of intralipid infusion is often needed because the sequelae of local anesthetic systemic toxicity can potentially persist or recur even hours after the initial exposure. Given this potential, monitoring of patients should continue for at least 12 h, particularly if there has been evidence of severe cardiovascular compromise.

While life saving, adverse effects from intravenous lipid emulsion administration have been reported. A recent systematic review identified over 100 studies and found adverse effects associated with intravenous lipid emulsion administration to include acute kidney injury, cardiac arrest, ventilation/perfusion mismatch, acute lung injury, venous thromboembolism, hypersensitivity, fat embolism, fat overload syndrome, pancreatitis, extracorporeal circulation machine circuit obstruction, allergic reaction, and increased susceptibility to infection [208]. Adverse effects appear proportional to total dose received and rate of infusion [208].

The role of more conventional medications used during resuscitation from local anesthetic overdose has been investigated. There is evidence for impairment of lipid-based resuscitation with a single dose of epinephrine of 10 μg/kg or greater. Dose–response trials suggest small epinephrine doses (1–2.5 μg/kg) may be advantageous in terms of rapid recovery; however, higher doses of epinephrine appear to adversely affect both metabolic and hemodynamic recovery profiles. Although experimental animals treated with high-dose epinephrine had earlier return of circulation than the saline-treated or lipid-treated controls, this earlier return of circulation did not translate to sustained hemodynamic stability and, in fact, contributed to their mortality [209]. Likewise, studies in swine that included the use of vasopressin and epinephrine along with lipid administration demonstrated that survival was not improved with this practice [210]. Despite the fact that propofol is formulated in a 10% lipid emulsion, it should not be used as a substitute for lipid administration because a fatal dose of propofol would have to be administered to achieve a therapeutic level of lipid. Propofol also may cause dose-related bradycardia and hypotension and can potentially further impair myocardial contractility in the setting of local anesthetic toxicity [196].

The prevention of local anesthetic systemic toxicity is of utmost importance and is possible via careful choice and dosing of local anesthetics, aspiration prior to injection, dose fractionation, and the use of ultrasound to prevent intravascular injection [211].

Summary

Local anesthetic systemic toxicity, although a rare event, can have devastating consequences. It has been suggested that every facility that administers local anesthetics to patients should assure the rapid availability of lipid emulsion for the treatment of toxicity [201]. Lipid emulsion should be used early in treatment, even before the devastating effects of cardiotoxicity have occurred. As previously described, the initial dose of lipid emulsion 20% is 1.5 mL/kg. This dose could be repeated to a maximum dose of 10 mL/kg in the first 30 min – which has been made easier by new, more concentrated formulations. At the point of return of hemodynamic stability, consideration should be made for initiation of an infusion at the rate of 0.25 mL/kg/min. Because local anesthetic toxicity may recur even after hemodynamic stability, patients should be monitored for at least 12 h if there has been evidence of cardiovascular compromise. In addition, during

resuscitative efforts, attention must be paid to standard cardiopulmonary resuscitation and include provision of adequate oxygenation and ventilation, seizure termination, and maintenance of circulation which may include early initiation of extracorporeal mechanical support. The use of epinephrine in doses higher than 10 μg/kg, administered along with lipid emulsion therapy, may not translate to improved survival and may even contribute to higher mortality. Smaller doses of epinephrine limited to 1–2.5 μg/kg may be tolerated well during resuscitation. Similarly, the addition of vasopressin to this regimen is not recommended, although additional research may be necessary to fully elucidate the effects of more traditional therapy when combined with lipid emulsion therapy.

KEY POINTS: LOCAL ANESTHETIC TOXICITY AND INTRALIPID ADMINISTRATION

- Local anesthetics prevent neural transmission through inhibition of fast sodium channels as well as via inhibition of γ-aminobutyric acid in pathways located in the cerebral cortex
- Lipid emulsion should be used early in treatment, even before the devastating effects of cardiotoxicity have occurred
- Prevention of local anesthetic systemic toxicity is of utmost importance and possible via careful choice and dosing of local anesthetics, aspiration prior to injection, dose fractionation, and use of ultrasound to prevent intravascular injection

Nerve and positioning injuries

The anesthesiologist is primarily responsible for the safe and comfortable positioning of the surgical patient during the operative period. Despite great care and attention, nerve injuries do occur and can lead to temporary, or rarely, permanent disability. Perioperative peripheral neuropathy refers to postoperative signs and symptoms related to peripheral nerve injury (e.g. brachial plexus, sciatic, femoral), manifested by paresthesias, muscle weakness, tingling, or pain.

Few data directly address positioning injuries in children. Clinical practice is therefore primarily dependent on data extrapolated from adult studies to the pediatric population. The incidence of peripheral nerve injuries in pediatric patients appears to be much lower than that among adults although data are limited to a handful of case reports. Morray et al [17], using the ASA Closed Claims database, found that the rate of peripheral nerve injuries in children was only 1% of claims, whereas in adults the figure was 16%. Given that pediatrics represents about 10% of all anesthetics performed, these data tend to confirm the sense that positioning injury is recognized less frequently in children than in adults.

In an adult population, Welch et al [212] evaluated a total of 380,680 anesthetics administered over a 10-year period; only 112 were associated with a nerve injury (0.03%). In that study, nerve injury was defined as a new sensory and/or motor deficit. Nerve injuries from the surgical procedure itself were excluded. This series represents the largest number of consecutive patients ever reviewed for all types of perioperative peripheral nerve injuries. In this study [212], as in others, it was difficult to define nerve injury related to positioning because existing deficits, injuries occurring in the postoperative period, and predisposing conditions make case finding challenging. In that study, by far the most common of the positioning-related injuries was that affecting the ulnar nerve [212]. Table 45.6 is a simplified guide to the recognition of various nerve injuries [213].

Table 45.6 Simplified clinical identification of major peripheral nerve injuries

Nerve	Injury
Arm	
Median nerve	Numbness over the index finger; weakness of abduction of the thumb
Ulnar nerve	Numbness over the little finger; weakness of abduction and/or adduction of the fingers; weakness of flexion at the distal interphalangeal joints of the little and ring fingers if the lesion is at the elbow
Radial nerve	Weakness of extension at the distal interplanalgeal joint of the thumb and of the wrist and finger extensors
Musculocutaneous nerve	Weakness of flexion of the elbow
Circumflex nerve	Weakness of abduction of the shoulder
Brachial plexus	Various combinations of lesions within the median, ulnar, radial, musculocutaneous, and circumflex nerve territories
Leg	
Femoral nerve	Weakness of flexion of the hip; numbness over the thigh
Obturator nerve	Weakness of adduction of the hip
Sciatic nerve	Weakness of ankle dorsiflexion and plantar flexion; weakness of knee flexion, if the lesion is proximal; numbness below the knee
Common peroneal nerve	Weakness of dorsiflexion of the ankle and toes
Tibial nerve	Weakness of plantar flexion of the ankle and toes

Source: Reproduced from Sawyer et al [213] with permission of John Wiley and Sons.

The updated practice advisory for the prevention of perioperative peripheral neuropathies published by the ASA in 2011 provides guidance that, although directed primarily at adult patients, can be useful for children as well [214]. Even when the ASA guidelines are followed, injury may not be preventable in all patients secondary to predisposing conditions. Welch et al [212] demonstrated that certain populations may be more likely to have perioperative positioning injuries due to co-morbid conditions. This study reported associations with the following surgical specialties: neurosurgery, cardiac surgery, general surgery, and orthopedic surgery. Medical co-morbid conditions such as hypertension, tobacco use, and diabetes mellitus were also associated with peripheral nerve injuries in the perioperative setting. It is interesting to note that this study [212] did not demonstrate an increased frequency in peripheral nerve injuries in patients maintained in

a prolonged lithotomy position, although it has been shown in previous studies [215] that the lithotomy position for more than 2 h has been a major risk factor for injury. Upper extremity nerve injuries were more common than lower extremity injuries. During this study, three different databases were examined [212]. Sensory deficits were slightly more frequent in one database, whereas motor deficits were more frequent in another, and, not surprisingly, patients with a motor component to their injury were more likely to pursue legal measures.

Ischemia and infarct are mechanisms of localized injury to the peripheral nerves of an anesthetized patient. Winfree and Kline [216] indicated that the disruption of blood supply to the nerves is integral to the mechanism of injury. Thus, it is reasonable to consider that patients with disease states that affect blood flow might have a higher frequency of positioning injuries. Pediatric patients, who are less likely to have some of the above co-morbid conditions, may have a lower frequency of peripheral nerve injuries due to positioning.

Although rare, the potential for nerve injury in children should not be ignored. Careful positioning, special attention to those at greatest risk, and awareness of nerve injury as a cause of postoperative pain and limited mobility, even in the non-verbal or preverbal child, should be maintained.

KEY POINTS: NERVE AND POSITIONING INJURIES

- The anesthesiologist is primarily responsible for safe and comfortable positioning of the surgical patient during the operative period
- Perioperative peripheral neuropathy refers to postoperative signs and symptoms related to peripheral nerve injury manifested by paresthesias, muscle weakness, tingling, or pain
- Although uncommon, the potential for nerve injury in children is present and mostly preventable through careful positioning and care towards those at greatest risk

Perioperative vision loss

In addition to peripheral neuropathy and subsequent neurological deficits, the occurrence of postoperative vision loss (POVL) is of particular concern during the performance of certain procedures. POVL is a devastating but fortunately rare complication most prevalent after cardiac, spine, head and neck, certain orthopedic procedures, and cases performed in the steep Trendelenburg position. POVL can occur after injury at any site in the visual pathway from the cornea to the occipital lobe. POVL can range from transient blurring or loss of vision to permanent bilateral blindness. The exact incidence of POVL is unknown. Estimates of the rate of POVL in the USA by type of surgery ranges between 0.12 for appendectomy to 8.64 for cardiac surgery per 10,000 [217]. The causes of POVL are threefold: ischemic optic neuropathy (including anterior and posterior types), central retinal occlusion, and cortical blindness [218]. A number of factors which may be under the control of the anesthesiologist have been identified as being associated with POVL, including patient positioning, intraoperative hypotension, and blood loss. Patients who had ischemic optic neuropathy had longer periods in the prone position with a larger estimated blood loss compared with those patients with central retinal artery occlusion. The majority of patients with ischemic optic neuropathy had both eyes affected whereas central retinal artery occlusion is almost always unilateral. Recovery of vision is more likely in ischemic optic neuropathy, with 44% of patients recovering their vision compared with 0% recovery in the central retinal artery occlusion group [219]. Etiology of ischemic optic neuropathy is unknown and possibly multifactorial; it is more commonly associated with large blood loss, hypotension, anemia, the prone position, and/or vaso-occlusive disease, although specific etiologies for anterior and posterior ischemic optic neuropathy may differ [220,221]. Conversely, the etiology of central retinal artery occlusion is thought to be caused by direct pressure on the globe from facemasks or cushions when the patient is in the prone position, by emboli, or by low perfusion pressure in the retina [220].

POVL requires urgent ophthalmological consultation for diagnosis and treatment of potentially reversible causes of visual loss. Immediate evaluation should include an assessment of pain, visual deficits, and pupillary light reflex. The best strategy to manage POVL is to make every effort to prevent it. Maintenance of stable hemodynamics, utilization of invasive monitoring (intra-arterial catheter), positioning the head in a neutral or slightly above the level of the heart position, with frequent eye checks should be the goal of an anesthesiologist.

No proven beneficial treatment for POVL related to ischemic optic neuropathy has been identified. It usually consists of attempts to normalize hemodynamics and hemoglobin. Head elevation is of theoretical benefit in cases with significant facial edema such as after prone spinal fusion surgery. High-dose steroids, hyperbaric oxygen, and mannitol have been used without consistent results [222]. Similarly, some conservative measures of uncertain efficacy for central retinal artery occlusion have been tried, including the inhalation of a mixture of 95% oxygen and 5% carbon dioxide (carbogen), anterior chamber paracentesis, and administration of acetazolamide. Intra-arterial thrombolysis is controversial and carries significant risk [223]. POVL is often thought of as being associated with spinal surgery; however, other surgical procedures may be complicated by problems similar to those encountered during prolonged spinal procedures and might also be associated with this complication. Indeed, Lee et al [224] reported on the first case of POVL caused by anterior ischemic optic neuropathy in a pediatric patient who underwent cranial vault reconstruction (Fig. 45.12). Since cranial vault reconstruction is often associated with the possibility of a large volume of blood loss and prolonged surgery often in the prone position, and occasionally the need for controlled hypotension, these conditions increase the chance for ischemic optic neuropathy. The child described by Lee et al [224] had an uneventful anesthetic and immediate postsurgical recovery but was readmitted on postoperative day 6 with bilateral blindness.

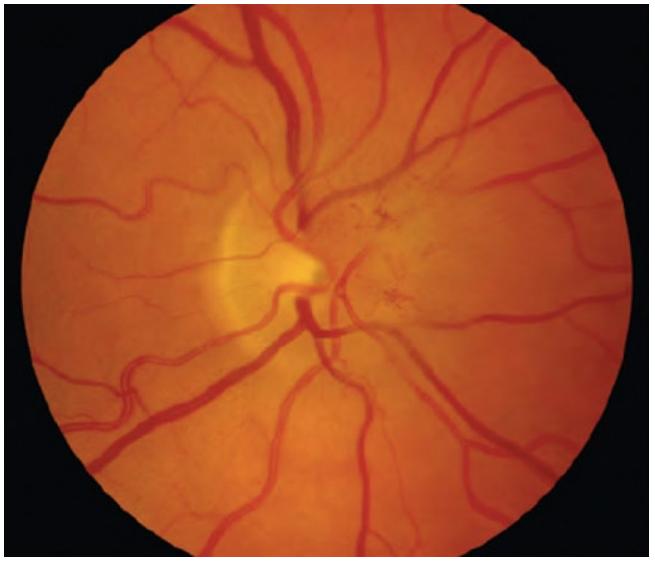

Figure 45.12 Acute (non-arteritic) anterior ischemic optic neuropathy. Blurring of the optic disk margin is from edema. Peripheral hemorrhage is noted superiorly and to the right of the disk. *Source:* Reproduced from Lee [257] with permission of Wolters Kluwer.

KEY POINTS: PERIOPERATIVE VISION LOSS

- POVL is a devastating but fortunately rare complication most prevalent after cardiac, spine, head and neck, certain orthopediac procedures, and cases performed in the steep Trendelenburg position
- POVL can occur after injury at any site in the visual pathway from the cornea to the occipital lobe
- The best strategy to manage POVL is to make every effort to prevent it. Maintenance of stable hemodynamics, utilization of invasive monitoring when indicated, positioning the head in a neutral or slightly above the level of the heart position, with frequent eye checks should be the goal of an anesthesiologist

Anaphylaxis and its treatment

Anaphylactic reactions are immediate, hypersensitivity reactions that are potentially life threatening and are classified according to the World Health Organization as allergic anaphylaxis (immune) rather than non-allergic (anaphylactoid), and that result in the release of mediators from mast cells and basophils [225]. Anaphylaxis is a progressive, potentially fatal, immunoglobulin E (IgE)-mediated reaction associated with histamine release into the systemic circulation. Upon histamine release, hypotension, edema, and hypoxia, even circulatory arrest and death, may occur. To improve survival and outcome, rapid diagnosis and treatment are important. Multiple factors may lead to anaphylaxis (e.g. food allergies, insect stings, drugs); however, up to 20% of patients treated for anaphylaxis have no identifiable cause [226]. This section focuses on drug-induced anaphylaxis in the perioperative period.

Definition

In 2006, the Second Symposium on the Definition and Management of Anaphylaxis recommended the following definition: "Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death" [227]. Due to the powerful sequelae of histamine release into the systemic circulation, immediate diagnosis and treatment are of utmost importance. Anaphylaxis is due to an IgE-mediated, immediate hypersensitivity reaction, resulting in the immediate release of potent chemical mediators from mast cells and basophils. Histamine is the predominant mediator released, followed by prostaglandin D2, leukotrienes, platelet-activating factor, tryptase, and eosinophil and neutrophil chemotactic factors. In contrast, anaphylactoid reactions are not IgE mediated, do not require previous contact with a substance, and cannot be distinguished clinically from anaphylaxis [225]. The most important organ systems affected by anaphylactic reactions are the cutaneous, respiratory, cardiovascular, and gastrointestinal systems [228].

Epidemiology

The incidence of anaphylactic reactions in the perioperative period ranges from one in 10,000 cases to one in 20,000 cases [229]. Unfortunately, incidence data are often underestimated because of under-reporting. Interestingly, 90% of anaphylactic reactions appear at anesthesia induction. Mortality rates are reported to be between 3% and 9%. Most of the deaths related to anaphylaxis are drug induced, followed by food- and insect sting-related causes. Data regarding pediatric anaphylaxis in the United States vary because of insufficient reporting in the pediatric population and discrepancies in the definition of anaphylaxis. Data from 2004 estimated the incidence of anaphylaxis among children and adolescents to be 10.5 episodes per 100,000 person-years [230], lower than the incidence in the general population.

Overall, in the United States, the lifetime prevalence of anaphylaxis is reported to be 1.6%, while in other industrialized countries it ranges between 0.05% and 2% [231]. The population of the United States seems to have a higher incidence of anaphylaxis compared with that in other countries. Factors such as expansion of diet and increasing use of peanut products in foods have been attributed to this finding. Children and adolescents with atopic conditions are at an increased risk of anaphylaxis. Genetics and racial differences do not seem to play a role; however, any patient who has had an anaphylactic reaction is at increased risk of recurrence. The severity of the previous anaphylactic reaction does not predict the severity of the recurring reaction [228].

In regard to anaphylactic reactions within the perioperative period, non-depolarizing neuromuscular blocking agents (NMBAs) and antibiotics are at the top of the list of offending agents. The incidence of anaphylactic reactions during anesthesia varies widely between counties, ranging from 1:1,200 to 1:20,000 per procedure with substantial geographical variability in different drugs or substances reported [225,232]. While once a common offender of perioperative anaphylaxis, reactions to latex are decreasing as a result of increased awareness and prevention strategies [232].

Death from anaphylaxis is rare, yet lack of reporting and difficulty diagnosing anaphylaxis posthumously with any

specific test contribute to inaccurate numbers related to morbidity and mortality.

Etiology

Although this section is focused on drug-induced anaphylaxis in the perioperative period, there is some relationship between food allergies and drug-induced anaphylaxis. The incidence of anaphylaxis, in particular food-induced anaphylaxis, continues to rise in developed countries, with the greatest impact on those under 5 years [233]. Food is actually the most common cause of anaphylaxis in children, followed by medications, insect stings, blood products, latex, vaccines, and contrast dye [230,234]. While children can outgrow many food allergies (e.g. milk, eggs, soybeans), certain food allergies persist. Foods causing persistent sensitivity include peanuts, tree nuts, and shellfish. These foods are responsible for more severe and near-fatal and fatal anaphylactic reactions [235].

Among drug-induced anaphylactic reactions, allergy to penicillin is the most common [230]. Among individuals with penicillin allergy, 4–10% have cross-reactivity to other penicillin-related drugs [234]. Some medications contain food-related substances to which food-allergic individuals may react. Propofol, marketed as Diprivan (AstraZeneca, Wilmington, DE, USA), is used for sedation and general anesthesia in children and is contraindicated in patients with egg or soy allergy because it contains egg lecithin and soybean oil [236]. While this egg and soy-based lipid solvent is not thought to be allergenic, there may be cross-contamination with egg or soy protein and case reports implicate propofol in some IgE-mediated reactions in some patients with egg and soy allergy; however, confirmatory evidence in many of these case reports is lacking [236]. On the contrary, several studies have shown propofol to be safely used in egg and soy allergic patients [237]. A recent single-center, retrospective, observational analysis of over 1300 esophagogastroduodenoscopies in patients with a clinical history of egg or soy allergy or eosinophlic esophagitis found no difference in compliation rates [236].

Pathophysiology

The IgE-mediated hypersensitivity reaction has been classically used to describe anaphylaxis (Fig. 45.13). The body is introduced to different allergens via different routes like ingestion, skin contact, or intravenous injections or infusions. Only a small amount of allergen exposure is sufficient for cells to react. On initial exposure to an allergen, IgE isotype antibodies are produced and bind to high-affinity FcεRI receptors located in the plasma membrane of tissue mast cells and blood basophils. Lymphocytes, eosinophils, and platelets bind IgE antibodies via low-affinity FcεRII receptors. This initial antigen sensitization is clinically silent.

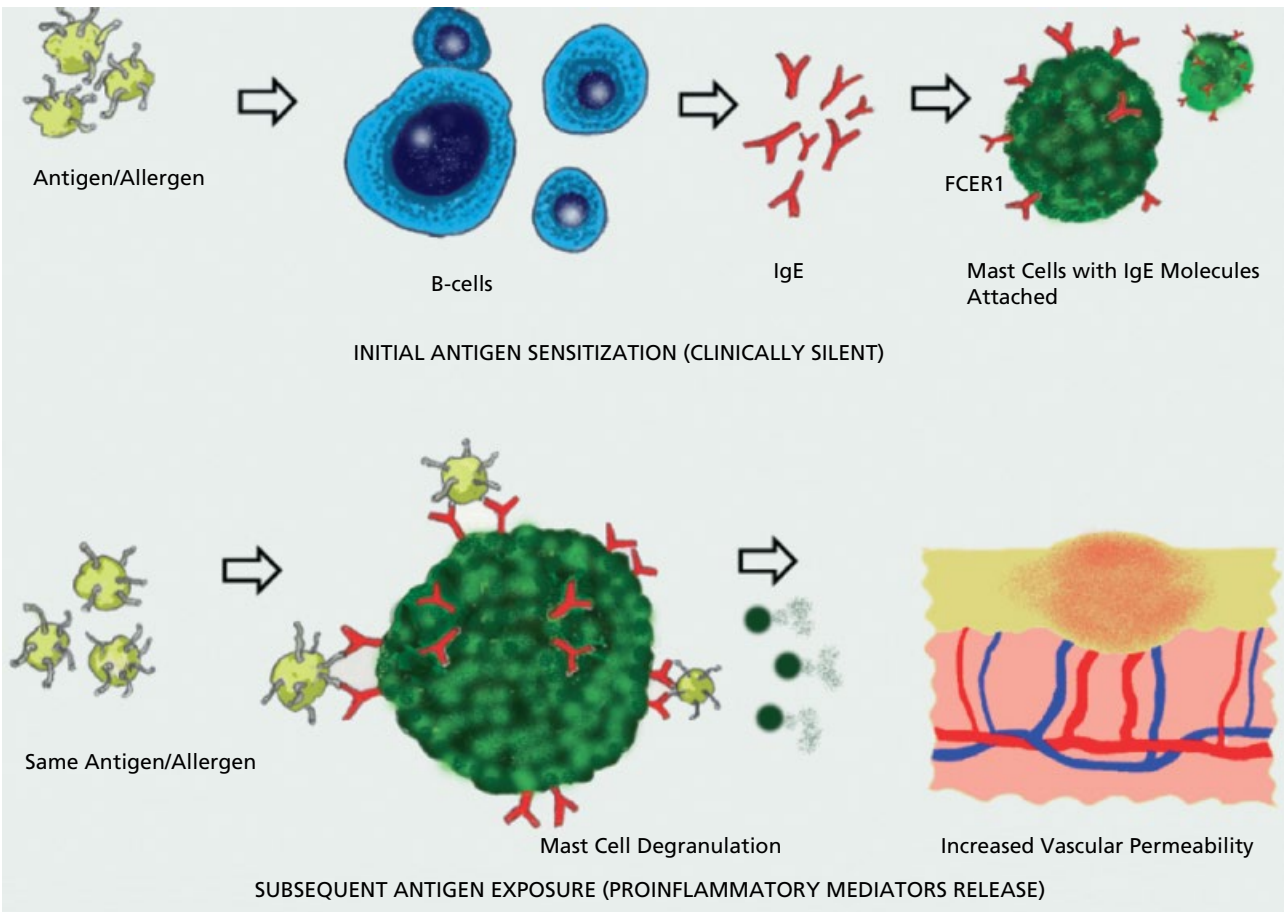

Figure 45.13 Initial antigen sensitization and subsequent antigen exposure in immunoglobulin E (IgE)-mediated allergic reactions. *Source:* Illustration by John Swan II.

On re-exposure, epithelial and endothelial barriers break down. This allows the antigen to come into contact with its specific IgE antibodies. The multimeric allergen cross-links two specific IgE receptors, thereby creating a bridge between two IgEs. The two IgE receptors aggregate and induce a signal transduction cascade releasing systemically preformed biochemical mediators. Histamine is released predominantly from intracellular granules in cells within tissues and blood, followed by neutral proteases (tryptase, chymase) and proteoglycans (heparin). Proinflammatory phospholipid-derived mediators, including prostaglandin D2, leukotrienes, thromboxane A2, and platelet-activating factor, are released soon after. Mast cells then release numerous chemokines and cytokines that initiate recruitment and activation of additional inflammatory cells.

The release of these mediators induces the symptoms of anaphylaxis, i.e. increased vascular permeability with erythema, edema, and pruritus, vasodilation, bronchospasm, and increased smooth muscle tone. Mast cell and basophil activation with subsequent chemical mediator release can also be triggered via activation of the complement system and direct actions on mast cells and basophils; however, the symptoms are indistinguishable from those triggered via IgE.

Timing of reactions

While most anaphylactic reactions occur within minutes of exposure to the offending agent, an additional delayed response is also possible. Delayed reactions may occur up to 72 h after the initial reaction. In addition, inadequate treatment of the initial reaction may predispose individuals to delayed reactions [238]. Route, quantity, and type of antigen do not seem to play a role in delayed reactions. Severity of the initial reaction does not predict the occurrence of a delayed reaction.

Causes of anaphylaxis in the perioperative period

The most common cause of anaphylaxis in the perioperative period is due to NMBAs, with approximately 40–70% of anesthesia-related anaphylaxis thought to be due to NMBAs [226–230,234,235,238–241], followed by antibiotics [242]. Usually, anaphylactic reactions occur shortly after induction, which is especially true for NMBAs and antibiotics, but may occur at any time with all potentially allergenic agents [242]. Latex allergy, which once contributed to a high number of anaphylactic reactions in the perioperative period, is discussed separately in this chapter.

In NMBAs, the quarternary ammonium groups (NH_4^+) on the NMBAs are responsible for the anaphylactic reactions. Quarternary ammonium groups also exist in foods, cosmetics, and drugs. Prior contact with quarternary ammonium groups contained in foods, cosmetics, and drugs may lead to anaphylaxis on subsequent exposure to NMBAs. In addition, NMBAs may trigger mast cell degranulation through activation of nicotinic acetylcholine receptors on cell surfaces [226]. Cross-reactivity between NMBAs occurs in approximately 60–70% of those tested [242].

Antibiotics are also known to cause anaphylaxis, especially in the perioperative period. Specifically β-lactam antibiotics (e.g. penicillins and cephalosporins) and vancomycin seem to trigger anaphylaxis [243]. In regard to vancomycin, direct mast cell activation seems to be the cause. The specificity of skin testing with β-lactams is between 97% and 99%, whereas the sensitivity is about 50% [229].

Anaphylaxis in response to propofol is reported infrequently, whereas anaphylaxis to etomidate and ketamine is extremely rare [240,242]. Anaphylaxis to opioids is very rare as well [240,242].

Anaphylaxis to local anesthetics is uncommon and has decreased in frequency as a result of the reduced use of the ester group of local anesthetics. Most allergic reactions are attributable to the common metabolic product of the ester local anesthetic, para-amino benzoic acid [240,242], which also leads to cross-reactivity among all local anesthetics belonging to the ester group. Allergic reactions to amide local anesthetics remain anecdotal. Ingredients included in local anesthetic solutions such as antioxidants or preservatives, including metabisulfite or parabens, may also elicit allergic or adverse reactions [243]. Cross-reactivity among esters is common, whereas it is rarely seen in the amide group and is absent between esters and amides.

Diagnosis

Because anaphylaxis may progress within minutes to a life-threatening condition, immediate diagnosis is essential. The first line of evidence for the diagnosis of anaphylaxis includes the features and severity of clinical signs as well as the timing between the introduction of a suspected allergen and the onset of symptoms. The amount of resuscitative agents required to treat the occurrence gives insight into the severity of the reaction [242].

Dewachter et al [244] adapted a clinical severity scale from Ring and Messmer [245] to describe perioperative immediate hypersensitivity reactions. Although this scale does not take into account the pathophysiological mechanisms, it is appropriate for grading the clinical severity and guiding the clinical care of immediate reactions [242]. Grades I and II describe cutaneous and cutaneous–mucous signs. Although cutaneous symptoms such as flushing, pruritus, or urticaria may be the first indication of an anaphylactic reaction, these are often missed in the operating room where patients are covered with drapes and blankets. In addition, anesthetized patients cannot verbalize complaints regarding pruritus or nausea. Bronchospasm has been reported to be the first sign of anaphylaxis in the operating room followed by hypotension, hypoxemia, and angioedema, which relates to a grade III reaction [226], followed by CA, which is grade IV. Grades I and II are usually not life-threatening conditions, whereas grades III and IV are emergency situations necessitating prompt resuscitation.

In cases of suspected anaphylaxis, the time of occurrence is important. Appearance of symptoms within minutes of anesthetic induction implicates an intravenous agent. Reactions 15 min or more after induction suggest skin or mucous membrane contact of the offending compounds. Biphasic reactions, with an initial event followed by a second delayed reaction, have been described to occur in 6–23% of patients with

Box 45.3: Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any *one* of the following three criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips–tongue–uvula) *and at least one of the following:*
   a. Respiratory compromise (e.g. dyspnea, wheeze–bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g. hypotonia (collapse), syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin–mucosal tissue (e.g. generalized hives, itch–flush, swollen lips–-tongue–uvula)
   b. Respiratory compromise (e.g. dyspnea, wheeze–bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g. hypotonia (collapse), syncope, incontinence)
   d. Persistent gastrointestinal tract symptoms (e.g. crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline

* Low systolic BP for children is defined as less than 70 mmHg from 1 month to 1 year; less than (70 mmHg + [2 × age]) from 1 to 10 years; and less than 90 mmHg from 11 to 17 years.

BP, blood pressure; PEF, peak expiratory flow.

Source: Reproduced from Sampson et al [227] with permission of Elsevier.

anaphylaxis [228]. Delayed reactions can occur up to 72 h after the initial reaction. Insufficient treatment with epinephrine during the initial reaction increases the risk of a delayed reaction.

Box 45.3 shows the clinical criteria for diagnosing anaphylaxis. This table was developed by the participants of the Second Symposium on the Definition and Management of Anaphylaxis, which was thought to capture at least 95% of the cases of anaphylaxis [227]. It is important to notice that the criteria listed refer to patients not undergoing anesthesia at the same time as there is suspicion for an anaphylactic reaction.

The manifestations of anaphylaxis during anesthesia can be different from anaphylaxis not associated with anesthesia, making the diagnosis of perioperative anaphylaxis more challenging. For example, symptoms such as malaise, pruritus, dizziness, and dyspnea can be difficult to ascertain in an unconscious patient. The most commonly reported objective features include pulselessness, ventilation difficulty, decreased end-tidal CO_2, and desaturation [246].

Laboratory tests

During acute management of anaphylaxis, no test is needed to confirm the diagnosis; however, if the diagnosis is uncertain, elevated levels of histamine, serum tryptase, or both may be helpful [228]. Histamine and tryptase are the major components released during mast cell degranulation. While histamine is the major compound released during anaphylaxis, its detection is difficult because of its short plasma half-life of 15–20 min. After a grade I or II reaction, blood samples for histamine measurement should be drawn within 30 min. After severe reactions (grades III and IV), histamine may still be increased 2 h after the reaction. Saturation of the enzymatic metabolism of histamine is the suggested mechanism that allows detection of increased histamine levels for this prolonged period after the reaction [247].

Tryptase is a mast cell neutral serine protease and a preformed enzyme. Two major forms – α-tryptase and β-tryptase – have been identified [240]. While α-tryptase is increased in mastocytosis, pro-β-tryptase serves as a measure of mast cell mass. Mature β-tryptase is preferentially stored in mast cell granules, and when systemically released, reflects mast cell activation with mediator release. Serum tryptase concentrations reach a peak between 15 and 60 min, with a half-life of approximately 2 h [240,242]. In grade I or II reactions, blood samples may be drawn within 15 and 60 min, and within 30 min and 2 h in grade III or IV reactions [242]. An increase of total tryptase concentrations (i.e. the sum of α-tryptase and β-tryptase) is highly suggestive of mast cell activation as seen in anaphylaxis, but its absence does not exclude the diagnosis. Some studies have demonstrated low sensitivity of tryptase levels in the diagnosis of anaphylaxis [240].

As a result of an immediate non-allergic reaction (e.g. histamine release), histamine may be increased, whereas tryptase remains normal. Because histamine and tryptase concentrations correlate with the severity of the allergic reaction, combined histamine and tryptase measurements have been recommended for the diagnosis of immediate reactions, whereas others recommend only tryptase [240,242].

More specific testing should be done in patients who have more than just cutaneous symptoms. Specific IgE testing can be done 2–3 weeks after an anaphylactic reaction. Skin testing is more sensitive than measuring IgE-specific antibodies and remains the gold standard for the detection of IgE-mediated reactions by exposing the mast cells of the skin to the suspected allergen in patients who have had anaphylaxis [229].

Premedication with H1- or H2-receptor antagonists, with corticosteroids, or with a combination of these agents have not been proven to prevent anaphylaxis [242]. Therefore, skin tests allow identification of the offending agent and demonstrate the pathophysiological mechanism of the reaction (allergic versus non-allergic). A 4–6-week delay after the reaction is required to avoid a false-negative test result because of mast cell depletion [242]. After the final test results, patients should be given a detailed report to provide to caregivers prior to future anesthetic exposures.

Management and treatment

The management of patients in whom anaphylaxis develops in the perioperative period is challenging. Most of these patients will have received multiple medications and present with more advanced symptoms, and their

condition progresses faster than in other settings. Anaphylaxis during anesthesia is especially challenging since most of the time the initial symptoms of urticaria or erythema are not observed because the patients are covered by drapes. It is important for all people involved in the care of these patients to help identify the cause so that future exposures can be avoided [226].

Due to its severity, the diagnosis and treatment of anaphylaxis must occur simultaneously. Treatment is directed toward managing the most severe symptoms, including cardiovascular collapse, bronchospasm, and airway edema. Initiation of intravenous epinephrine and other therapies and expeditious interruption of suspected causative agents must go hand in hand. In addition to ventilation with 100% oxygen, volume support and definitive airway managment are required [226]. Patients should be placed supine in the Trendelenburg position, and the surgical procedure abbreviated if possible when anaphylaxis occurs intraoperatively.

The administration of intravenous epinephrine and expansion of intravascular volume are essential to the perioperative management of anaphylaxis [240,242]. Epinephrine's α-agonistic effects reverse vasodilation, while its β-agonist effects treat bronchospasm and the release of inflammatory mediators. Because epinephrine has a short half-life, repeated doses or a continuous infusion may be necessary. There is no absolute contraindication during anaphylaxis for the use of epinephrine, and early administration should be the rule [240,242].

Due to the increased vascular permeability, fluid therapy with crystalloid or colloid solutions should be initiated immediately. Bronchospasm is treated with an inhaled β_2-agonist (albuterol) [240,242]. Given that cardiovascular collapse and bronchospasm occur together, epinephrine remains the first-line therapy as it corrects both cardiovascular disturbances as well as bronchoconstriction through its β_2-adrenergic effects. Intravenous corticosteroids early in the course of therapy are recommended because of their anti-inflammatory effects, although the beneficial effects are delayed at least 4–6 h [242]. Corticosteroids, H1-receptor antagonists, or both are often recommended, with varying success, in the management of anaphylaxis [240,242].

Affected patients are sometimes unresponsive to catecholamines, possibly because of desensitization of adrenergic receptors. The use of arginine vasopressin may be an alternative as its vasoconstrictive effects are mediated by non-adrenergic vascular arginine vasopressin V1 receptors [248].

Summary

Perioperative anaphylaxis is a severe and rapid clinical condition that can lead to mortality even in previously healthy patients. Because of its infrequent presentation and variable clinical presentation, perioperative anaphylaxis may not be diagnosed immediately. The severity of symptoms as well as the rapidity of symptom progression demands prompt and aggressive treatment. The combination of clinical, biochemical, and skin test evidence will identify the responsible agent and allow the patient to avoid these agents in the future.

KEY POINTS: ANAPHYLAXIS AND ITS TREATMENT

- Anaphylactic reactions are immediate, hypersensitivity reactions that are potentially life threatening and are classified according to the World Health Organization as allergic anaphylaxis (immune) rather than non-allergic (anaphylactoid), and thatresult in the release of mediators from mast cells and basophils
- The most common causes of anaphylaxis in the perioperative period are NMBAs
- The clinical manifestation of anaphylaxis during anesthesia can be challenging because initial symptoms of malaise, pruritus, dizziness, and dyspnea can be difficult to ascertain in an unconscious patient. The most commonly reported objective features include pulselessness, ventilation difficulty, decreased end-tidal CO_2, and oxygen desaturation

Latex allergy

Natural rubber latex (NRL) is derived from the rubber tree, *Hevea brasiliensis*, one of over 200 lactifer-type plants belonging to the family Euphorbiaceae [249]. Among numerous compounds released by NRL, the heat-stable proteins retained in NRL are responsible for the adverse events. Although the risks of hypersensitivity as well as anaphylactic reactions to latex are well recognized, the frequency of events have been reduced in the past few years by increased awareness and prevention measures [225,232]. In addition to healthcare workers, children with atopy and spina bifida and those undergoing frequent procedures requiring surgical instrumentation are at increased risk. Among all the products containing NRL in the healthcare environment, surgical gloves made from NRL have the highest prevalence for latex sensitization. Overall, the continued use of latex and the resulting sequelae of allergic reactions impose a high cost in terms of patient risk as well as provider risk and a financial burden to the healthcare system [250].

History

The use of latex items can be tracked back to 1600 BCE in ancient Mesoamerica; however, surgical gloves came into common use in the early 20th century. Descriptions of allergic reactions to NRL appeared in the medical literature by 1927, but the description of an immediate allergic reaction to NRL was not published until 1979. Since 1980, the allergic potential of NRL has been more widely recognized, and different approaches have been taken to study latex sensitivity [251].

Epidemiology

Due to differences in populations studied and methods used to verify sensitization, the reported prevalence of latex allergy in the general population varies widely, ranging from

less than 1% to 6.7% [250]. A French survey obtained between 1989 and 2001 reported that latex was the second highest cause of perioperative accidents, at a rate of 27%. The healthcare environment has the highest incidence of latex sensitivity, ranging form 3% to 17% [252]. Anesthesiologists themselves have a high prevalence of latex senitization [253]. As mentioned above, gloves made from NRL have been associated with the greatest prevalence of sensitization in the hospital setting.

Mechanism of sensitization

Frequent exposure remains the main cause of sensitization. This finding resulted in the recommendation that children undergoing frequent surgical procedures, for example children with spina bifida, should be handled latex-free from the very beginning of their management. As a result of this initiative, these children are automatically listed as being latex sensitive. In addition, children with atopy are at increased risk, especially children with food allergies to tropical fruits such as avocado, kiwi, and banana. Some evidence suggests that genetic profiles may potentiate latex reactions to hevein (HLA-DR phenotypes) [250]. The route of exposure may also play a role. In the case of NRL, skin exposure and inhalation exposure are more common. Skin exposure is of particular importance because it may result in airway hyper-reactivity leading to allergen-induced asthma [254]. Independent of the exposure, patients with latex sensitivity develop increased levels of IgE-specific latex protein. Increased IgE levels are responsible for the symptoms, and IgE levels may increase with increased exposure frequency.

Identification of patients at risk

The identification of patients at risk relies primarily on the history but may be aided by the use of questionnaires developed specifically to aid in identification of these patients. Although some patients initially present with only cutaneous symptoms, cardiovascular symptoms as well as bronchospasm are common clinical features. Cutaneous manifestations are often inapparent as patients in the operating room are typically covered by drapes. As a consequence, the initial manifestation may be increased airway resistance manifested by high airway pressures and wheezing rapidly followed by cardiovascular collapse. Typically, these events occur within 30–60 min after induction [240].

Diagnostic methods

While obtaining a thorough patient history may suggest the diagnosis of latex allergy, specific laboratory tests are needed to confirm the diagnosis. Currently two tests are available: the skin prick test and detection of IgE specific to latex protein (radioallergosorbent test). Skin prick tests are inexpensive, sensitive, and specific; however, they must be performed in the physician's office with appropriate precautions because of the real risk of anaphylaxis. The sensitivity of the measurement of latex-specific IgE is lower than that for the skin prick test, being positive in only 60–90% of sensitized patients [250]. With first exposure, patients produce latex-specific IgE, and the levels increase with each subsequent exposure. Sensitivity of the measurement of latex-specific IgE depends on the number of prior exposures.

Box 45.4: Recommendations for primary prevention of latex allergy (reducing exposure to latex protein to prevent sensitization for latex)

- Bring a latex-free cart into the room
- Use a latex-free reservoir bag, airways, and endotracheal tubes, and laryngeal mask airways
- Use a non-latex breathing circuit with plastic mask and bag
- Ventilator must have non-latex bellows
- Use IV tubing without latex ports; utilize stopcocks if available
- Cover all rubber injection ports on IV bags with tape and label in the following way:
  Do not inject or withdraw fluid through the latex port. Note: pulmonary artery catheters (especially the balloon), central venous catheters, and arterial lines may all contain latex components
- Use non-latex gloves
- Use non-latex tourniquets, electrodes, and examination gloves
- Draw medication directly from opened multidose vials (remove stoppers) if medications are not available in ampoules
- Utilize latex-free syringes, bladder catheter, and nasogastric tubes
- Use stopcocks to inject drugs rather than latex ports
- Minimize mixing/agitating lyophilized drugs in multidose vials with rubber stoppers

IV, intravenous.

Source: Reproduced from De Queiroz et al [250] with permission of John Wiley and Sons.

Prevention in patients at risk

The first line of prevention is identification of children at risk. Creation of a latex-free or latex-sensitive environment within the perioperative area is desirable and encouraged. Complete avoidance of latex products prevents severe anaphylactic reactions. Indeed, De Queiroz et al [250] reported that since the creation in one institution of a latex-free environment in all operating rooms and perioperative areas in 2002, no latex anaphylactic reactions have occurred after more than 25,000 procedures over a period of 5 years.

A latex-free protocol should include a checklist on how to manage children with latex allergy in every department involved in the care of children. Arrangements for a latex-free environment need to be made not only for the operating room but also for the recovery room and postoperative period. Communication between the different care teams (anesthesiologist, surgeon, nurses) is crucial. In the operating room, there should be a cart with latex-free equipment readily available to be used in these patients. Box 45.4 summarizes the recommendations for the prevention of latex allergy [250].

Aerosolized latex allergen from previous cases requires at least 90 min to clear. The recommendation is to schedule elective procedures as first cases since levels of aerosolized latex allergens are at the lowest level then. Otherwise, a time gap of 90 min should be allowed to lower latex allergen levels between patients [250].

Pre-emptive use of medication to reduce allergic reactions is controversial. Although there have been recommendations to use medications such as diphenhydramine, cimetidine, and prednisone prophylactically, the current opinion is not to do so. In addition, premedication is not necessarily successful in preventing latex anaphylaxis and might even mask the initial immune response [250].

In children where latex exposure can not be completely avoided, desensitization may be an option. Sublingual, subcutaneous, or percutaneous desensitization may improve cutaneous reactions as well as improve rhinitis and asthma.

Prevention: complete avoidance

Complete avoidance of latex in the perioperative care areas is the most effective way to prevent sensitization to latex. The American College of Allergy, Asthma, and Immunology released recommendations to avoid latex material in healthcare institutions [255]. Indeed, since children at risk are better identified, the incidence of latex allergy has markedly decreased. There are numerous reports of reduction of latex sensitization with the implementation of a latex-free perioperative environment. In addition, avoidance of latex can reduce latex-specific IgE in these patients and the progression of symptoms.

Although latex is ubiquitous in medical equipment and devices, manufacturing of single-use latex-free items has improved tremendously. In addition, there is more emphasis by manufacturers on labeling items to identify potential latex content. To maintain a latex-free perioperative environment requires continuous meticulous effort by all healthcare workers involved as well as continuous education among healthcare staff. After all, anaphylactic reactions to latex are most commonly encountered in the perioperative period.

KEY POINTS: LATEX ALLERGY

- The risks of anaphylactic reactions to latex are well recognized; however, the frequency of events have been reduced in the past few years by increased awareness and prevention measures
- Complete avoidance of latex in the perioperative care areas is the most effective way to prevent sensitization to latex
- Children undergoing frequent surgical procedures (spina bifida, bladder exstrophy) should be handled latex free from the very beginning of their management

CASE STUDY

An otherwise healthy, 6-month-old, 7.5 kg male underwent combined general and caudal anesthesia for a distal hypospadias repair. After placement of standard monitors, an inhalation induction was accomplished with sevoflurane and oxygen, a 22 G peripheral IV was inserted, and tracheal intubation was accomplished with a 3.5 mm cuffed endotracheal tube, without muscle relaxants after a 1.5 mg/kg bolus of propofol. The patient was turned to the right lateral decubitus position, and after confirming normal anatomy of the sacral region by inspection and palpation, the area was prepped with 2% chlorhexidine solution. Using sterile technique, a 22 G angiocatheter was placed in the caudal space on the second attempt without ultrasound, using palpation technique. A noticeable loss of resistance was encountered when the needle pierced the sacrococcygeal ligament. The catheter was advanced to its hub, and 7.5 mL of 0.25% plain bupivacaine was injected in divided doses of 1–2 mL each. After gentle aspiration there was no blood or cerebrospinal fluid in the tubing of the T-piece.

Approximately 5 minutes after the caudal injection and during surgical preparation of the operative field, the electrocardiogram (ECG) changed to a wide-complex bradycardia, the end-tidal CO2 decreased from 35 to 6 mmHg, and the noninvasive blood pressure reading was not obtainable. Pulses were not palpable. There were no cutaneous changes, and ventilation volumes and pressures were unchanged. The anesthesiologist suspected local anesthetic systemic toxicity (LAST), and directed the anesthesia fellow to begin chest compressions, and the circulating nurse to call for additional help. Sevoflurane was discontinued, FiO2 increased to 1.0, and the anesthesiologist directed the circulating nurse to bring the 20% intralipid and the resuscitation cart just outside the operating room. She also consulted the cognitive aid cards attached to the anesthesia machine to ensure that no treatment strategies were omitted (Society for Pediatric Anesthesia; https://www.pedsanesthesia.org/critical-events-checklist/).

Subsequently 20% intralipid, 1.5 mL/kg, was injected into the peripheral IV over 1 minute, and repeated every 3 minutes, four times for a total of 7.5 mL/kg. High-quality chest compressions, with a firm backboard underneath the patient, were continued, and epinephrine, 7.5 µg IV, was injected every 5 minutes for a total of three doses. Because there was no return of spontaneous circulation after 5 minutes, the extracorporeal membrane oxygenation (ECMO) team and surgeon were called stat to the operating room.

After the fifth dose of intralipid and 15 minutes of chest compressions, the cardiac rhythm improved to sinus rhythm at 100 bpm, the end-tidal CO2 increased to 24 mmHg, pulses became palpable, and the noninvasive blood pressure registered at 55/42 mmHg. Point-of-care ultrasound was used to image the heart via the subcostal four-chamber view and revealed a poorly contracting left ventricle with no pericardial effusion. A low-dose infusion of epinephrine was started at 0.02 µg/kg/min via a second peripheral IV. A 22 G right radial arterial line was placed with ultrasound guidance, and revealed an arterial pressure of 60/43 mmHg; arterial blood gas was pH 7.15, PaCO2 35 mmHg, PaO2 325 mmHg on FiO2 1.0, and base deficit was −15. Electrolytes, ionized calcium, and glucose were normal, and lactate was 10.5 mmol/L. Sodium bicarbonate 15 mEq was infused over 10 minutes.

An infusion of 20% intralipid was started at 0.25 mL/kg/min, and a 4 Fr double-lumen 8 cm right internal jugular central catheter was inserted using ultrasound guidance. Initial central venous pressure was 14 mmHg, and the infusions were changed to the central line. Blood pressure improved to 84/52 mmHg, heart rate increased to 125 bpm with normal sinus rhythm, and a normal pattern on multilead ECG was recorded from the physiologic monitor. Left ventricular contractility improved on repeat ultrasound examination. A urinary catheter was placed, and when the patient exhibited some spontaneous movement of the extremities (without evidence of clinical seizures), midazolam 0.05 mg IV was administered for sedation, and repeated twice. The patient was transported to the pediatric ICU and a full comprehensive report was given to the ICU team. Mechanical ventilation, intralipid, and epinephrine infusions were continued for 12 hours, and, with no indication of the signs of LAST recurring, the infusions were discontinued. The patient was extubated 2 hours later. He was neurologically intact and was discharged to the surgical ward the next day, and discharged home 48 hours later, with no neurologic or cardiac symptoms, and a normal echocardiogram and ECG on the day of discharge. The anesthesiologist met with the patient's parents each day to explain the LAST event, answer their questions and address their concerns. The patient was scheduled for elective hypospadias repair in 6 weeks, after follow-up with his pediatrician.

This case illustrates the rapid diagnosis and treatment of a rare event, LAST, including the fact that an intravascular injection was not suspected, during divided injections of the local anesthetic. An epinephrine-containing test dose was not used in this case; this practice is often ineffective in infants. Ultrasound guidance for caudal anesthetic placement was also not used; ultrasound can visualize the local anesthetic solution being deposited in the sacral canal and theoretically could determine that this injection was not in the correct location (see Chapter 20). After ruling out anaphylaxis, LAST was quickly diagnosed and high-quality CPR was initiated (see Chapter 13). Defibrillation was not used because the cardiac rhythm was not ventricular fibrillation or pulseless ventricular tachycardia. 20% intralipid, which was available immediately with the resuscitation cart in the operating room, was quickly obtained and injected, and repeated every 3 minutes until return of sinus rhythm and spontaneous circulation; an infusion started and maintained for 12 hours to prevent recurrence of LAST. A lower dose of epinephrine, 1 µg/kg instead of the standard 10 µg/kg, was used during resuscitation because of evidence that the latter may be harmful in LAST. Cognitive aids were readily available in the operating room and consulted so that proper treatment for this rare but potentially devastating complication could be given. The ECMO team was called early in the resuscitation, although not needed. Point-of-care ultrasound was used to image the heart and rapidly obtain invasive vascular access. The patient was transferred to pediatric ICU for ongoing care and monitoring and made a complete recovery. The anesthesiologist kept in close touch with the parents and was able to thoroughly explain the adverse event experienced by their child.

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A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 46

Impact of Pediatric Surgery and Anesthesia on Brain Development

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Introduction

The ability to pharmacologically render patients insensible to noxious stimulation using general anesthetics and sedatives represents one of the greatest discoveries in medicine. Undoubtedly, life-threatening conditions are mitigated every day by surgical interventions that can only be performed due to the meticulous administration of modern anesthetic drugs and advanced physiological monitoring. While the exact molecular mechanisms by which general anesthetics provide immobility, analgesia, and amnesia remain under investigation, most are thought to provide their physiological effects in the central nervous system by either potentiating neuronal activity at γ-aminobutyrate acid (GABA) receptors, by inhibiting N-methyl-D-aspartate (NMDA) glutamate receptors, or by a combination of the two.

Worldwide, every year, millions of children are exposed to $GABA_A$-agonists or NMDA-antagonists to ablate the stress response to noxious stimulation and to mitigate potential, stress-related morbidity during painful procedures and imaging studies. However, recent findings in laboratory animals have demonstrated structural brain abnormalities, such as widespread brain cell death and alterations in dendritic architecture immediately following exposure to these drugs early in life. Moreover, several animal studies have also observed lasting neurocognitive impairment into adulthood. These preclinical findings have led to significant concerns among pediatric anesthesiologists, government agencies, and the public. Given the potentially serious consequences of long-term neurological sequelae following an otherwise uneventful surgical procedure early in life, this chapter presents the pediatric anesthesiologist with an overview of this rapidly emerging field of research by summarizing the currently available data from animal models as well as human clinical studies. These findings will be moderated by a review of the neuroprotective effects of anesthetic drugs. Moreover, the impact of other perioperative events, such as pain, stress, inflammation, hypoxia-ischemia, co-morbidities, and genetic predisposition, on long-term neurological function will be discussed. Finally, the reader will be introduced to the phenomenon's putative mechanisms and to the currently proposed ameliorating strategies.

Historical perspective

General anesthetics have been widely used for more than 170 years and are administered to millions of children every year [1]. Prior to the 1980s, general anesthetics were routinely withheld from hemodynamically unstable premature and term neonates. The rationale for this practice was to avoid further hemodynamic deterioration in surgical neonates who were perceived to be unable to tolerate the myocardial depressant effects of the then utilized anesthetic drugs. However, the denial of adequate doses of anesthetics or analgesics in these patients ignored the fact that the neonatal central nervous system is capable of sensing pain and mounting a stress response during surgical stimulation, even in premature infants [2]. Studies by Robinson and Anand demonstrated that opioid administration was able to blunt physiological responses to surgical stress without compromising hemodynamic stability and substantially reduced perioperative morbidity in critically ill neonates [3–5]. These developments, along with technological advances in hemodynamic monitoring and mechanical ventilation, have resulted in the current humane practice of administering anesthetics and analgesics even to the most critically ill neonates during and after surgery.

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

Nociception and stress in the neonate

Neonatal animal models testing the effects of stressful conditions and exposure to recurrent painful stimulation have demonstrated widespread neuronal cell death and adverse neurological outcomes as a result from these deleterious conditions [6]. Both somatic as well as visceral noxious stimulation of the developing brain appear to alter processing of nociceptive inputs in adulthood. Thus, neonatal injury can subsequently be associated with either hyperalgesia or hypoalgesia, depending upon the type and severity of injury and the sensory modality tested [7]. In addition to altered pain processing, repetitive or persistent pain in the neonatal period may result in changes in brain development, widespread alterations in animal behavior, cognitive function, and in subsequent increased vulnerability to stress and anxiety disorders or chronic pain syndromes [6,8,9]. Specifically, inflammatory pain associated with repeated injection of complete Freund's adjuvant in rat pups resulted in hyperalgesia and lasting changes in nociceptive circuitry of the adult dorsal horn [10]. Rat pups receiving repeated formalin injections into the paw developed subsequent generalized thermal hypoalgesia [7]. Moreover, early adverse emotional experiences induced long-lasting age-, brain region-, and neuronal subgroup-specific imbalances of the inhibitory nervous system [11], disrupted development of the nociceptive system, and caused long-term behavioral changes [12] as well as leading to persistent learning impairment [13]. Repetitive painful stimulation in neonatal animals has also been shown to lead to decreased pain thresholds and increased anxiety later in life [8,14,15]. In addition to alterations of the central nervous system, repetitive painful skin lacerations have also been found to lead to long-term, local sensory hyperinnervation [16]. Therefore, fetuses and neonates subjected to pain and stresses associated with painful procedures may be at risk for long-term adverse outcomes.

The pre-emptive administration of analgesics and sedatives, such as morphine or ketamine, in this context, has been found to ameliorate the deleterious effects of neonatal pain in animals [6,13,15]. Importantly, painful stimulation in turn obviated adult behavioral impairment due to neonatally administered morphine [13].

Similar to these animal studies, clinical reports have demonstrated that neonates and infants respond to perioperative stress and painful stimulation with increases in catecholamines, cortisol, β-endorphins, insulin, glucagon, and growth hormone [17–19]. Some of these markers, such as cortisol, can remain elevated for more than a year, potentially due to cumulative stress related to multiple painful procedures early in life [20]. The administration of potent anesthetics, opioid analgesics, and regional anesthesia has been shown to inhibit intraoperative stress and to improve postoperative outcome [4,18,21] by reducing the incidence of sepsis, disseminated intravascular coagulation, and overall mortality [5]. Even less invasive procedures, such as circumcisions, when performed without analgesia, can exaggerate pain responses later in life [22]. In contrast, topical or regional anesthesia for circumcision not only blunted the immediate humoral stress response [23], but also obviated long-term hyperalgesia [22].

In premature neonates, an association has been observed between painful stimulations early in life and subsequent diminished cognition and motor function [24]. Cognitive and motor development was compared after 1 year of age between children born at less than 32 weeks' gestational age, without significant neonatal brain injury or major sensorineural impairment, and full-term controls. Results demonstrated that the number of skin-breaking procedures from birth to term (including heel sticks, intramuscular injections, chest tube placements, and central line insertions) predicted lower subsequent cognitive and motor development, as assessed using the Bayley Scales of Infant Development II. Importantly, after controlling for severity of illness and days on intravenous morphine or dexamethasone, gestational age at birth was not significantly associated with cognitive or motor outcome. These findings suggest that repetitive, pain-related stressful experiences and not prematurity per se were responsible for poor neurodevelopmental outcome [24]. While this study did not examine the effects of anesthetic or analgesic administration during painful stimulation on subsequent outcome, a small, retrospective study suggested improved outcome following anesthetic exposure during painful stimulation. In that study, painful stimulation during the reduction of herniated bowel without anesthesia in infants suffering from gastroschisis tended to more frequently lead to serious adverse events, such as bowel ischemia, need for total parenteral nutrition, and unplanned reoperation than in infants undergoing the same procedure with general anesthesia [25]. However, despite the fact that large numbers of painful and stressful procedures are being performed in vulnerable neonates, available data indicate that the majority of these are still not accompanied by analgesia [26].

KEY POINTS: NOCICEPTION AND STRESS IN THE NEONATE

- Data from animal and human studies suggest that pain-related stress early in life, especially when experienced repeatedly, is deleterious to the developing nervous system
- Sedatives and analgesics may alleviate many of the degenerative effects
- Pain in children still remains undertreated

Developmental anesthetic-induced neurotoxicity

Concerns regarding potentially deleterious effects of general anesthetics on neurological function were first raised after more than a century of their routine clinical use. Prolonged personality changes, such as night terrors, bed wetting, and increased fear responses, were observed in young children following the administration of vinyl ether, cyclopropane, or ethylchloride for otolaryngological surgery [27]. However, these symptoms were interpreted as psychological sequelae resulting from patients' anxiety during anesthesia induction and hospitalization. Approximately two decades later the focus of research into potentially deleterious effects of anesthetics shifted to prolonged occupational exposure of female healthcare workers [28–31]. Chronic exposure of pregnant rats to subanesthetic doses of halothane during their entire

pregnancy led to delayed synapse formation and behavioral abnormalities in their offspring. It took almost another two decades until initial studies were carried out examining anesthetic exposure early in postnatal life, more closely representing pediatric anesthesia practice. In these groundbreaking studies, widespread neuronal degeneration was observed following prolonged ketamine exposure in neonatal rat pups [32]. The researchers likened this phenomenon to abnormalities observed in children suffering from fetal alcohol syndrome caused by maternal ingestion of ethanol, a combined $GABA_A$-agonist/NMDA-antagonist [33–35]. Accordingly, these findings were followed up by using a combination of the $GABA_A$-agonist midazolam, the combined $GABA_A$-agonist and NMDA-antagonist isoflurane, and the NMDA-antagonist nitrous oxide. A 6 h exposure to this drug combination triggered widespread immediate brain cell death in newborn rodents as well as a long-term diminution in neuronal density, altered synaptic function, and impaired neurocognitive function in adult animals exposed as neonates [36,37]. Dramatic acute alterations in brain architecture as well as long-term cognitive impairment have now been confirmed for all routinely used general anesthetics by numerous laboratories in several immature animal models (reviewed in [38]).

However, a causative link between any immediate structural abnormalities and long-term cognitive impairment has yet to be made. The potentially serious implications of potential long-term cognitive deficits following exposure to sedatives or anesthetic early in life compelled the United States Food and Drug Administration (FDA) to issue a warning in December of 2016 (updated in April 2017), stating that exposure to anesthetics "for lengthy periods of time or over multiple surgeries or procedures may negatively affect brain development in children younger than 3 years". At the same time, the FDA acknowledged that "general anesthetic and sedation drugs are necessary for patients, including young children and pregnant women, who require surgery or other painful and stressful procedures" (https://www.fda.gov/Drugs/DrugSafety/ucm554634.htm; accessed May 2019).

Experimental evidence for anesthetic neurotoxicity

To date, more than 500 animal studies have investigated the effects of all clinically utilized sedatives and anesthetics on brain structure and function in immature animal species, including chicks, mice, rats, guinea pigs, swine, sheep, and rhesus monkeys (Fig. 46.1). The repeatedly observed structural abnormalities and/or functional impairment have been termed "anesthetic neurotoxicity" and resulted in an exponential rise in published scientific reports and reviews [38]. While the exact molecular mechanisms by which anesthetics provide their therapeutic effects remain incompletely delineated, two main putative targets include the glutamatergic NMDA and GABA receptors, which also have become the focus of research into this phenomenon. Table 46.1 presents published studies of non-human primates, and human neuronal cultures, after anesthetic exposure.

NMDA-antagonists

Glutamate represents the most ubiquitous excitatory neurotransmitter in the mammalian central nervous system. Clinically utilized anesthetics and sedatives that provide their hypnotic effects predominantly by inhibition of the NMDA-type glutamate receptor include ketamine and nitrous oxide [39], as well as the less frequently clinically utilized noble gas xenon [40]. Pioneering animal studies carried out 20 years ago demonstrated widespread degeneration of brain cells in newborn rat pups following the repeated administration of ketamine [32]. These findings have subsequently been replicated and expanded upon by several other laboratories [38,41].

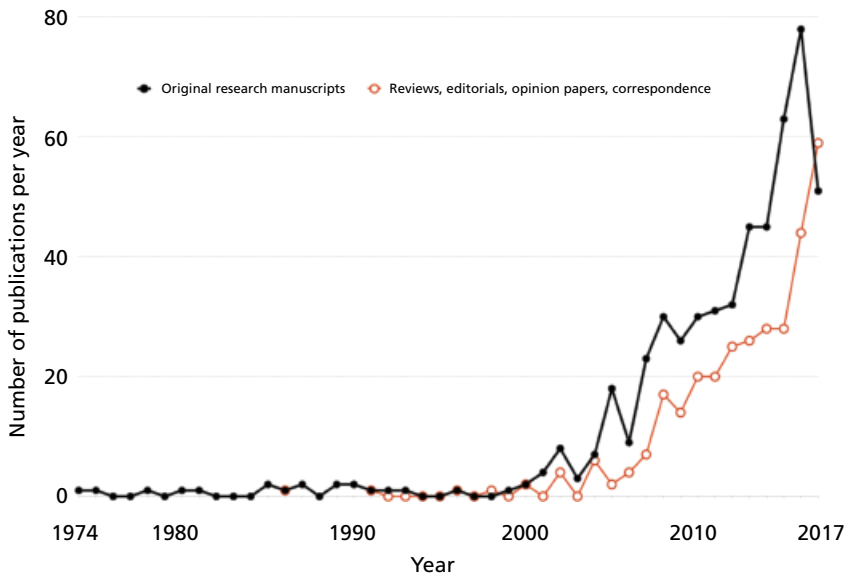

Figure 46.1 Increase in number of animal research articles investigating the effects of anesthetic exposure on the developing brain and commentaries over the past 43 years. The number of annually published original *in vivo* and *in vitro* animal studies (black filled circles) as well as review articles, editorial views, commentaries, opinion papers, and correspondence on this topic (open red circles) are shown from 1974 until October 2017, as identified in a literature search using PubMed and Scopus databases, as well as personal records. The body of literature has expanded into one of the most intensely researched fields in anesthesiology, increasing from two articles published in 2000 to approximately 80 articles in 2016. *Source*: Reproduced from Lin et al [38] with permission of Elsevier.

Table 46.1 Preclinical studies in non-human primates and human neuronal cultures into brain structural and functional effects of anesthetic exposure

Anesthetic agent	Dose and duration	Species, age	Pathology	Reference
Dexmedetomidine or ketamine	3 or 30 μg/kg dexmedetomidine followed by 3 or 30 μg/kg/h for 2 h, or 20 mg/kg ketamine IM, followed by 20–50 mg/kg/h for 12 h	*Macaca fascicularis*, E120	Marked neurode generation in frontal cortex following ketamine, but not after either low- or high-dose dexmedetomidine	Koo et al [294]
Isoflurane	1.6% for 5 h	*Macaca mulatta*, P5	Increase in neocortical apoptotic cell death	Brambrink et al [67]
Isoflurane, N_2O or isoflurane + N_2O	1%, 70%, or 1% + 70% for 8 h	*Macaca mulatta*, P5	Significant neuronal cell death in frontal cortex, temporal gyrus, and hippocampus following anesthetic combination, but not after isoflurane or N_2O alone	Zou et al [295]
Isoflurane	0.7–1% for 5 h	*Macaca mulatta*, P5–6	Widespread apoptotic cell death of neurons and oligodendrocytes	Brambrink et al [68]
Isoflurane	Propofol 2 mg/kg followed by isoflurane for 5 h to provide intermediate surgical plane of anesthesia to dam	*Macaca mulatta*, E120	Neuroapoptosis, most prominent in cerebellum, caudate, putamen, amygdala, and cortex; diffuse distribution of oligodendrocyte death across white matter	Creeley et al [118]
Isoflurane + lithium	1.5–3% for 5 h to maintain surgical plane of anesthesia	*Macaca mulatta*, P5–7	Increased neuronal and oligodendrocyte degeneration, ameliorated by lithium co-administration	Noguchi et al [139]
Isoflurane	Titrated to maintain a surgical plane of anesthesia for 5 h once, or three times 3 days apart	*Macaca mulatta*, P6 or P6, P9, and P12	No abnormalities following single exposure, but following triple exposure deficits are observed in motor reflexes at 1 month and increased anxiety at 12 months	Coleman et al [69]
Isoflurane	Surgical plane of anesthesia for 3 h	*Macaca mulatta*, P6	Widespread oligodendrocyte and neuronal apoptosis in white matter and in cortex, caudate, putamen, and thalamus, respectively	Noguchi et al [66]
Isoflurane	1.3–2.5% to maintain surgical plane of anesthesia for 5 h	*Macaca mulatta*, P20 or P40	Diffuse neuronal and oligodendrocyte cell death	Schenning et al [70]
Isoflurane	2% for 3 or 6 h	Human neuroglioma cells	Caspase-3 activation, ROS accumulation, reduction in cellular ATP, attenuated by hydrogen-rich saline	Li et al [296]
Ketamine	1–20 μM for 2–24 h	*Macaca mulatta* forebrain neuron culture	Increased DNA fragmentation and decreased mitochondrial function after higher doses for longer periods of time	Wang et al [52]
Ketamine	20–50 mg/kg/h for 24 h	*Macaca mulatta*, E122, P5, or P35	Increased neurodegeneration in two younger age groups, ketamine plasma levels higher than in humans	Slikker et al [43]
Ketamine	20–50 mg/kg/h for 24 h	*Macaca mulatta*, P5–6	Impairment in motivation and cognitive performance in Operant Test Battery starting at 10 months and continuing until 3.5 years of age	Paule et al [45]
Ketamine	20–50 mg/kg/h for 3–25 h	*Macaca mulatta*, P5 or P6	Neuronal degeneration only in neocortex following 9 h exposure or longer, no degeneration in deeper brain areas	Zou et al [44]
Ketamine	10 mg/kg followed by 10–85 mg/kg/h for 5 h (fetus), or 20 mg/kg followed by 20–50 mg/kg/h for 5 h (neonate)	*Macaca mulatta*, E120 or P6	Neuronal cell death following exposure; 2.2 times greater during fetal versus neonatal exposure	Brambrink et al [297]
Ketamine	100 μM for 24 h	Human neurons derived from stem cells	Increased apoptosis and caspase-3 expression	Bai et al [298]
Morphine	1–100 μM for 5 days	Human fetal microglial, astrocyte, and neuronal cultures	Progressive increase in apoptosis in neurons after 2-day exposure, or microglia after 3 days, but not in astrocytes	Hu et al [299]
Propofol	7–10 mg/kg followed by 350–450 μg/kg/min for 5 h (fetus), or 3 mg/kg followed by 300–400 μg/kg/min for 5 h (neonate)	*Macaca mulatta*, E120 or P6	Widespread neuronal and oligodendrocyte cell death, particularly subcortical and caudal in fetus and neocortical and caudal brain regions in neonates	Creeley et al [74]
Sevoflurane	Dose adjusted according to calibrated pain stimulus for three 4 h exposures	*Macaca mulatta*, P6–10, P20–24, and P34–38	Starting at 6 months of age, increased anxiety in human intruder test	Raper et al [63]
Sevoflurane	Dose adjusted between 2% and 2.6% to provide surgical plane of anesthesia for 5 h	*Macaca fascicularis*, P6	No abnormalities in behavioral (3–7 months) and cognitive assessment (7 months), or brain protein analysis (10 months)	Zhou et al [300]

Table 46.1 (Continued)

Anesthetic agent	Dose and duration	Species, age	Pathology	Reference
Sevoflurane + L-carnitine	2.5% for 8 h	*Macaca mulatta*, P5-6	Increased neuronal degeneration in frontal cortex. Temporary increased uptake of ^{18}F-FEPPA tracer on PET in frontal and temporal lobes, attenuated by co-administration of L-carnitine	Zhang et al [301]
Sevoflurane	Dose adjusted according to calibrated pain stimulus for three 4 h exposures	*Macaca mulatta*, P6–10, P20–24, and P34–38	No difference in visual recognition memory tested at 6–10 months of age, but deficit observed at 12–18 and 24–30 months old	Alvarado et al [65]

ATP, adenosine triphosphate; E, embryic age in days; IM, intramuscular; P, postnatal day; PET, positron emission tomography; ROS, reactive oxygen species

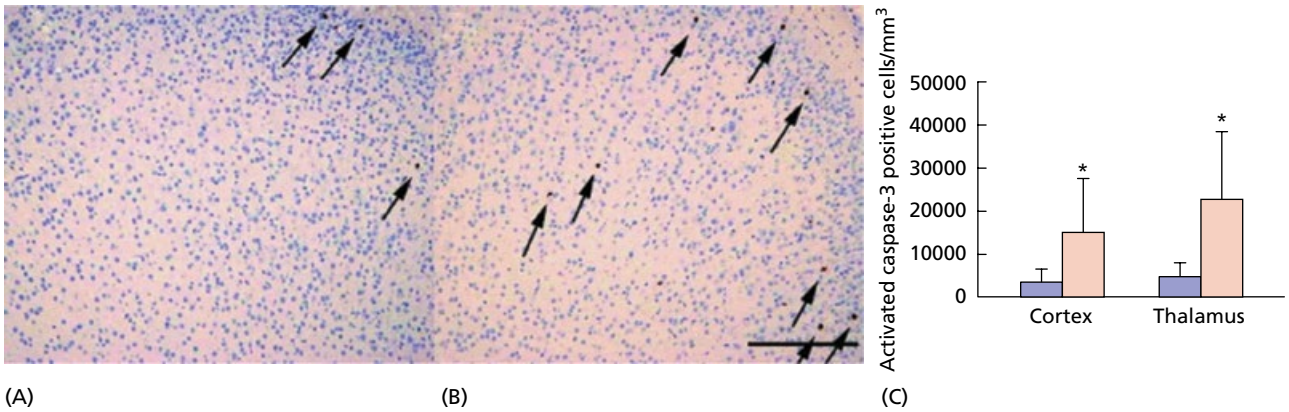

Figure 46.2 Ketamine induces caspase-3 activation *in vivo*. Immunohistochemistry with antibody to cleaved caspase-3 on cortical sections from P7 rat pups receiving either saline (A) or ketamine 20 mg/kg every 90 min for 6 h (B) (scale bar = 200 μm). (C) Quantitation of activated caspase-3-immunoreactive cells in P7 cortex and thalamus. Data are presented as mean ± standard deviation; * $p < 0.05$ compared to saline. *Source*: Courtesy of the Soriano laboratory.

Most studies have demonstrated an increase in cleaved caspase-3 expression, leading to apoptotic cell death. While this was not observed following a single ketamine dose of up to 75 mg/kg in young rodents, multiple doses of up to 75 mg/kg of ketamine led to widespread neuronal cell death [42]. Disturbingly, a similar dose-dependent increase in ketamine-induced neurodegeneration also occurs in non-human primates [43,44]. In these studies, a ketamine infusion (20–50 mg/kg/h for 24 h) significantly increased neuronal cell death in the superficial cortex of prenatal (gestational age 122 days when administered to the mother) or neonatal (5-day-old) rhesus monkeys. A 3 h exposure did not lead to increased neurodegeneration in neonates and even the 24 h infusion failed to cause cortical neuronal degeneration in older, 35-day-old animals. Alarmingly, however, newborn monkeys exposed to the 24 h ketamine infusion and tested with an operant test battery (OTB) starting at 7 months of age, exhibited lasting cognitive and motivational deficits, compared with unexposed peers [45]. In small rodents, a single ketamine exposure of 50 mg/kg in newborn mice led to subsequent abnormal behavior as well as impaired learning and memory acquisition in adolescence [46]; however, in another study, no gross neurobehavioral abnormalities were observed 7 days after neonatal administration of up to 40 mg/kg, albeit formal tests of learning were not performed [47]. Moreover, adult rats that were injected as neonates with relatively small doses of ketamine (5 mg/kg) once a day for 4 days performed as well as their unexposed peers in subsequent learning and memory tasks [6]. Concomitant administration of GABA-mimetic drugs, such as midazolam, thiopental, or propofol, a common practice during clinical anesthesia and sedation, significantly exacerbated the deleterious effects of ketamine [48,49].

In order to better understand the underlying mechanisms, ketamine neurotoxicity has also been studied using several *in vitro* preparations from neonatal rodents and rhesus monkeys [50–52]. When cultured in ketamine for 6 h or longer, primary cortical cells from both species underwent neurodegeneration, whereas shorter exposure times did not cause this effect. However, lower concentrations of ketamine have been shown to decrease dendritic arborization in differentiated neurons in culture [53]. Microscopic images of primary neurons exposed to ketamine demonstrate a reduction in neurite length and the number of branching points (Fig. 46.2). It currently remains unclear whether the large doses of all injectable anesthetics, including ketamine, required in small animals can be directly compared with the lower doses used in clinical practice (further discussed later as part of interspecies comparison). It should further be noted that studies in small rodents suggest differential susceptibility among species, as neonatal mice are vulnerable to lower doses of ketamine and propofol than those found to be deleterious in rats [48,54].

Less information is available regarding the effects of the NMDA-antagonists nitrous oxide or xenon on brain development. Whereas nitrous oxide by itself, even under hyperbaric

conditions, did not seem to increase neuronal cell death [36,55], xenon showed differential effects, being deleterious in one study [56] and not in another [55]. The two compounds, however, differed in their effects when co-administered with isoflurane; nitrous oxide exacerbated isoflurane-induced neurotoxicity [36,37,55,57], whereas xenon alleviated some of isoflurane's cytotoxic effects [55,56].

$GABA_A$-agonists

Gamma-aminobutyrate acid represents the main inhibitory neurotransmitter in the adult central nervous system, while it has excitatory properties in the developing brain [58]. To date, the exact impact of this developmental switch on the deleterious effects of anesthetics observed in the immature brain remains unresolved. Several positive modulators of the $GABA_A$ receptor are commonly used as anesthetics or sedatives in young children, and animal studies have demonstrated the brain structure-altering effects of exposure to all of these compounds during early brain development, including propofol, clonazepam, diazepam, midazolam, thiopental, pentobarbital, chloral hydrate, isoflurane, sevoflurane, halothane, and enflurane (Table 46.1).

Several studies have originated in the Jevtovic-Todorovic laboratory, examining the combined administration of the $GABA_A$-agonist midazolam, the mixed $GABA_A$-agonist and NMDA-antagonist isoflurane, and the NMDA-antagonist nitrous oxide. A 6 h exposure to this drug combination caused a widespread, dramatic increase in the rate of brain cell degeneration in newborn animals shortly following the exposure [36,59–61]. In addition to the immediate deleterious effects on brain structure, long-term abnormalities in spatial learning tasks, altered hippocampal synaptic function, and decreased neuronal cell density were observed in adult rats exposed to the anesthetic combination as neonates [36,37]. The most frequently utilized inhaled anesthetic in pediatric anesthesia, sevoflurane, has also repeatedly been shown to induce neuroapoptosis in neonatal animals and to lead to learning deficits, emotional abnormalities, and altered social behavior [62–65]. The most extensively studied inhalational anesthetic is isoflurane, which has been found to lead to widespread neuronal cell death immediately following prolonged exposures in immature small rodents (Fig. 46.3) and to subsequent cognitive abnormalities in young adulthood. Neuronal or oligodendrocyte death have also been reported in neonatal rhesus monkeys immediately following exposure to clinically relevant doses (0.75–1.5%) of isoflurane for as little as 3 h [66], and have also been found to impair long-term motor and behavioral development [67–70]. While initial studies focused on the very immature rodent brain in the 1st week of life, more recent work has demonstrated isoflurane-induced neuroapoptosis even during prolonged exposure in young animals, specifically in brain regions with ongoing neurogenesis [71]. Moreover, disruption of dendritic architecture has also been observed in small rodents that were older than 2 weeks during exposures to inhaled anesthetics and propofol [72,73]. Propofol, which represents a relatively specific $GABA_A$-agonist, has been shown to induce neuroapoptosis in small rodents and non-human primates [74–77].

Other anesthetics and sedatives

Recently, the α2-agonist dexmedetomidine has gained more prominence in pediatric sedation practice. The Sanders group has examined dexmedetomidine's effects on the developing brain and has found it to be devoid of neurotoxic effects and to ameliorate isoflurane's deleterious consequences on neonatal brain structure and adult learning [57]. More recent data in newborn rats supported the notion that dexmedetomidine caused significantly less neuronal injury than sevoflurane [78,79], while providing a lighter plane of anesthesia compared with the inhaled anesthetic. Another rodent study suggested that dexmedetomidine may induce apoptotic cell death in different brain regions than those affected by ketamine [80]. A dose-ranging study of dexmedetomidine reported that only at cumulative doses likely to be supratherapeutic was neuroapoptosis increased in rat pups; at doses approximating clinical doses in humans there was not an increased level of neurodegeneration [81].

Opioid analgesics

Opioid analgesics are another class of drugs commonly administered to young children before, during, and after surgery, often in conjunction with anesthetics and sedatives [81,82]. Since opioids can reduce dose requirements for anesthetics and sedatives, their co-administration could lead to lower anesthetic requirements and thereby potentially mitigate anesthesia-induced cytotoxicity. However, several animal studies have suggested that opioid exposure may also have harmful effects in the developing brain (Table 46.1). Moreover, opioid co-administration can enhance cell death of

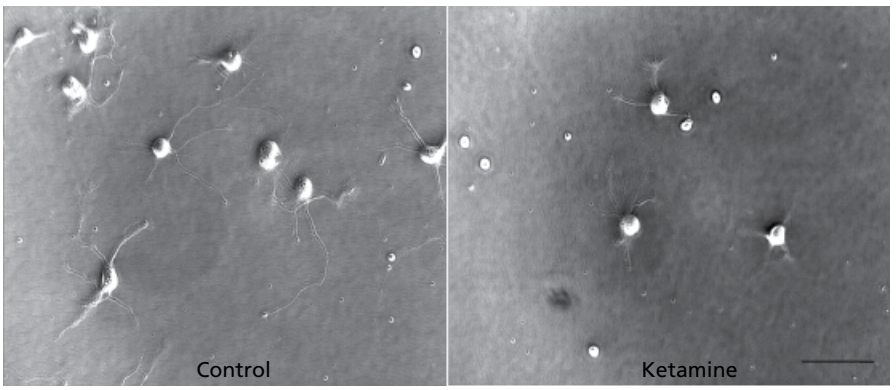

Figure 46.3 Ketamine stunted neurite arborization and branching points in primary neurons (scale bar = 100 μM). *Source*: Courtesy of the Soriano laboratory.

immature brain cells triggered by other apoptosis-inducing drugs [83]. Specifically, chronic perinatal exposure to morphine, fentanyl, or methadone has been shown to induce acute neuronal degeneration in the neonatal animal brain [84], to alter brain opioid receptor density [85–87], and to disrupt nerve growth factor expression as well as dopaminergic, noradrenergic, serotonergic, and cholinergic activity [88,89]. Conversely, Vutskits et al demonstrated that single morphine injections of 1 or 10 mg/kg at 7 or 15 days of age did not induce neuronal cell death in the cerebral cortex of rat pups and that nine daily administrations starting at either of these time points did not impair dendritic arbor differentiation or excitatory synaptogenesis [90]. However, other groups have shown that perinatal opioid administration can cause long-lasting desensitization to opioid analgesia in adult animals [91] and can induce long-term behavioral changes, cognitive deficits, and learning impairment extending into adulthood [13,92–96]. Conversely, as discussed previously, analgesics have also been found to diminish the deleterious effects of painful stimulation early in life.

Putative mechanisms of drug-induced neurotoxicity

The exact mechanisms of deleterious effects induced during exposure in the developing brain to anesthetics, sedatives, and analgesics remain unresolved. Elucidating these mechanisms will be essential for assessing the relevance of toxicity for pediatric anesthesia and neonatal critical care medicine and for devising mitigating therapies, if necessary. Complicating this important line of research is the fact that the phenotype of the phenomenon labeled "anesthetic neurotoxicity" is not well described. While reductions in trophic factors [60,97], synaptic and dendritic aberrations [72,98], impaired neuronal [32], glial [99], and oligodendrocyte viability [68], as well as cognitive abnormalities all seem to be part of the spectrum of anesthetic effects in the developing brain, it remains unclear whether they are part of a dose- and exposure time-dependent continuum. For example with lower doses and shorter exposures leading to trophic factor, synaptic, and dendritic alterations that culminate in cellular death when a certain toxic threshold is surpassed, or whether they represent separate phenomena.

The currently prevailing hypothesis suggests that exposure to $GABA_A$-receptor agonists and/or NMDA-receptor antagonists causes abnormal neuronal inhibition, triggering structural abnormalities in susceptible neurons, which can then lead to adult learning impairment and decreased neuronal density [36,37,100]. Apoptosis, or programmed cell death, represents an inherent, energy-consuming process, which is highly conserved among species and culminates in self-destruction and the elimination of cells that are functionally redundant or potentially detrimental to the organism, utilizing a cascade of enzymes called caspases [101]. As such, apoptotic cell death is an integral part of normal organ development, as demonstrated by the embryonal cell death of mesenchymal tissue between the digits of the hands and feet, as well as during ablation of tail tissue as part of tadpole metamorphosis in amphibians. During normal brain development, neurons are produced in excess and up to 50–70% are eliminated, be it in rodents, primates, or humans [102,103]. This physiological apoptotic cell death establishes proper central nervous system structure and function, and any disruption of this process will lead to massive brain malformation and intrauterine demise [104]. However, apoptotic cell death can also be triggered by pathological insults, such as hypoxia and ischemia [105]. It currently remains unknown whether anesthesia-induced cell death hastens physiological neuroapoptosis.

$GABA_A$-receptor stimulation results in decreased neuronal activity in the mature brain, however it causes excitation in developing neurons [58] which complicates the hypothesis of neuronal silencing as the underlying trigger of neuronal apoptosis. Moreover, the neurotoxic effects of sevoflurane have been associated with excitatory properties and episodes of epileptic seizures in newborn rats [106]. Isoflurane has also been shown to cause excessive Ca^{2+} release from the endoplasmic reticulum via overactivation of inositol 1,4,5-trisphosphate receptors (InsP3Rs) in neonatal rats *in vivo* and *in vitro* [107]. A similar mechanism may be linked to the production of Alzheimer-associated increases in β-amyloid protein levels [108]. Moreover, while xenon and hypothermia cause neuronal inhibition, they do not appear to exacerbate isoflurane-induced neuronal cell death, as expected by their cumulative effects on neuronal inhibition, but rather significantly reduce it [55,56,109].

An alternative mechanistic model proposes that prolonged NMDA receptor blockade by anesthetics upregulates the glutamate receptor NR1 subunit, in turn facilitating pathological calcium entry into the neuron, leading to excitotoxicity and nuclear translocation of nuclear factor κB (NFκB) [43]. However, attempting to link the NMDA receptor to the neurotoxic effect, two *in vitro* preparations have returned conflicting results. When comparing ketamine and S(+)-ketamine, the apoptosis-inducing effect was only marginally stereospecific in one study [110], suggesting that the toxic effect was unlikely to be mediated via the NMDA receptor, whereas in a separate study, ketamine's effects were blocked by glutamate receptor NR1-subunit antisense, suggesting that the NMDA receptor was underlying ketamine's apoptotic-inducing properties [50]. Similar questions regarding the causative role of inhibition of the GABA receptor in anesthesia-induced neurotoxicity have been raised by finding that co-administration of the $GABA_A$ receptor-antagonist gabazine was unable to attenuate isoflurane-induced neuroapoptosis [57]. Decreases in neuronal activity induced by anesthetics may therefore be less important than the disruption of the neuronal balance of excitation and inhibition, as demonstrated by a study in 15 day-old mice [72,73]. While simultaneous blockade of excitatory and inhibitory activity with tetrodotoxin in these animals did not lead to structural changes, as would be expected for a causative relationship between neuronal inhibition and structural damage, the administration of either $GABA_A$-agonistic or NMDA-antagonistic compounds did alter synaptogenesis [72].

Exciting work into the cellular mechanism of anesthesia-induced neuronal cell death has highlighted reductions in synaptic tissue plasminogen activation (tPA) release and increases in proBDNF/$p75^{NTR}$-mediated apoptosis following isoflurane exposure in newborn mice. Another presumptive mechanism of anesthetic neurotoxicity involves intracellular signaling by protein kinases. Straiko and colleagues reported that ketamine and propofol individually suppressed phosphorylation of extracellular signal-regulated protein kinase

and serine/threonine-specific protein kinase 473 ($pAkt^{473}$) in neonatal mice [76]. Moreover, experimental models of neurodegeneration have implicated re-entry of postmitotic neurons into the cell cycle, leading to cell death. Accordingly, a study by one of the authors demonstrated that ketamine induces aberrant cell cycle re-entry, leading to apoptotic cell death in the developing rat brain [111].

It remains unclear whether the overall cell death observed immediately following exposure is predictive of subsequent cognitive outcomes. Even widespread neuronal degeneration in neonatal animals immediately following exposure to isoflurane, sevoflurane, or midazolam does not always culminate in long-term cognitive impairment (Fig. 46.4) [112–114]. Substantial brain cell death during exposure may not always lead to long-term diminution in neuronal density [112,114]. And attenuating neuronal cell death during neonatal exposure, such as by inhibiting the p75 neurotrophin receptor, does not inevitably salvage cognitive impairment in adulthood [115]. Moreover, hypercarbia – oftentimes observed during prolonged anesthetic exposure in spontaneously breathing small rodents [112,116,117] – has been found to induce neuronal cell death by itself without anesthetic exposure, while not being linked to long-term neurocognitive impairment [117]. Combined, these findings suggest that the amount of overall neuronal cell death may not be crucial for cognitive outcomes, but do not exclude that certain subgroups of neurons or alterations in brain structure as part of the repair mechanisms triggered by the neonatal injury may be linked to long-term neurocognitive impairment. Importantly, despite the limitations of small rodent models, the injury pattern observed in monitored, intubated, and mechanically ventilated non-human primates are qualitatively similar to those in spontaneously breathing small rodents [67,118], suggesting that newborn mice and rats can still serve as economical models of research into the anesthetic effects in the developing brain.

Multiple laboratories have demonstrated prolonged cellular effects of anesthetic exposure beyond neuronal death, albeit with somewhat conflicting results. Alterations in synaptic plasticity in neonatal animals include a decrease in synaptic density following anesthetic exposure [98]. In slightly older, postnatal day 15 mice, however, anesthetic exposure increased the density of dendritic spines [72,73,119]. These contradicting observations may indicate an age-dependent difference in the effects of anesthetics on dendritic morphology.

These findings might be explained by anesthetic vulnerabilities of specific neuronal populations, as suggested by studies originating in the laboratory of one of the authors. Dentate granule cells were shown to be susceptible to isoflurane-induced cell death during the late progenitor and immature neuronal stage, but not as immature progenitors or mature neurons, irrespective of the age of the animal [120]. Accordingly, while many brain regions containing immature neurons were vulnerable to degeneration during exposures in the neonatal period, this vulnerability only extended to brain regions with ongoing neurogenesis in adulthood [71]. These findings suggest that different brain regions may be maximally susceptible at different stages of development and different ages and explains the immense vulnerability of the immature brain by the greater number of immature neurons at this stage. As an extension, however, these findings suggest that human vulnerability may extend beyond the neonatal or toddler stage into older childhood or even young adulthood for brain regions serving as neurogenic niches, such as the dentate gyrus and subventricular zone. However, which of the immediate structural abnormalities are causatively linked to long-term neurological dysfunction remains unresolved and represents an important obstacle in translational research efforts into devising mitigating strategies and safer anesthetic regimens. Clearly, additional laboratory research into the mechanism of the anesthetics' structural effects in the developing brain is urgently needed.

Gender differences

Several animal studies have investigated potential sex differences in the structural effects of anesthetic exposure on the developing brain. A study of isoflurane in neonatal rats observed increased neuronal cell death in several brain regions following a 4 h exposure without differences between sexes [121]. However, subsequent learning and social behavior was only impaired in male rats, but not females, suggesting that male animals were more susceptible to behavioral consequences of the exposure. Similarly, studies of 6 h neonatal sevoflurane or 5 h propofol exposures observed neurobehavioral and endocrine abnormalities only in adult male, but not female, rats [122,123]. A third group similarly found a greater detriment of a brief postnatal isoflurane exposure on cognitive performance in adult male rats, compared with their female littermates [124]. However, motor activity was only increased in adult female mice exposed to ketamine *in utero*, but not their male counterparts [125]. Conversely, female rats were more vulnerable to adult cognitive impairment in spatial learning tasks following a neonatal isoflurane-based anesthetic [126]. Similarly, brain structural degeneration following ketamine exposure was more pronounced in neonatal female rats than in male rats [127]. Accordingly, it is currently unclear whether these differences in sex-related outcomes are due to differences in species, age of exposure, or specific to the drug combination.

KEY POINTS: EXPERIMENTAL EVIDENCE FOR ANESTHETIC NEUROTOXICITY

- All commonly utilized anesthetics can alter developing brain structure following prolonged exposures
- Comparison studies of the respective toxic potencies of different anesthetics are difficult to perform and have yielded no conclusive results
- A variety of compounds have been tested to alleviate the deleterious effects, but it is premature to recommend their use in clinical practice
- The immediate structural surrogate of long-term cognitive impairment has yet to be conclusively identified
- Currently, the most viable option is to reduce doses and exposure times of the implicated drugs

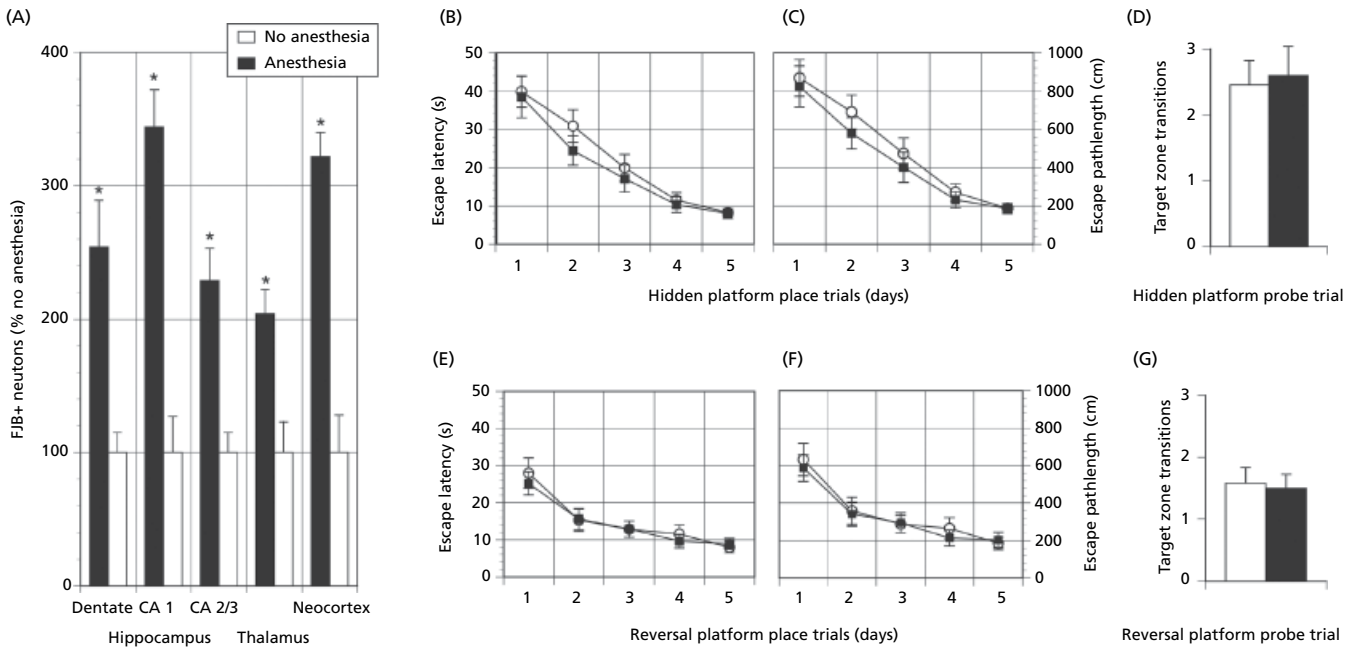

Figure 46.4 (A) Neonatal isoflurane exposure significantly increases the number of dead or dying neurons in the neonatal mouse brain. Columns represent mean number of brain cells staining positive for the cell death marker Fluoro-Jade B (FJB+) for each brain region 2 h following a 6 h exposure to 0.6 MAC of isoflurane (anesthesia, black bars) compared with littermates fasted for 6 h (no anesthesia, white bars). (B–G) However, neuronal cell death in neonatal mice immediately following isoflurane exposure does not inevitably result in impairment in spatial learning and memory in adulthood. Morris water maze place and probe trials in adult mice previously exposed as neonates to 6 h of fasting (no anesthesia, open circles) or to 0.6 MAC isoflurane (anesthesia, black squares) using a hidden platform (B–D) or a more difficult reversal platform paradigm (E–G). Both groups significantly improved over the 5-day trial period and performed equally well in the memory retention tasks. Data are shown as mean ± SEM; n = 8-26 for each group; * $p < 0.05$. *Source*: Reproduced from Loepke et al [112] with permission of Wolters Kluwer.

Safer anesthetic techniques and potential mitigating strategies

While human applicability of the structural effects of prolonged anesthetic exposure seen in animals have not been confirmed, an important translational question directed at animal research is whether any anesthetic can be identified that affords less toxicity than others and might therefore be recommended for clinical research and anesthesia practice. While several studies have addressed this question, no clear consensus has been reached thus far: Comparing inhaled anesthetics with each other, one study in newborn mice identified sevoflurane as causing less neuronal cell death following a 6 h exposure, compared with isoflurane, while no differences in long-term cognitive performance were observed between the two anesthetic regimens [128]. Another mouse study demonstrated sevoflurane and isoflurane to cause comparable degrees of injury following a 6 h exposure, but no long-term dysfunction, while identifying desflurane as more injurious to brain structure immediately following exposure and to cause subsequent cognitive function [129]. In a comparison study using immature rats, Vutskits and co-workers demonstrated differing results of increased dendritic spine density in prefrontal cortex following isoflurane or sevoflurane after only 1 h of exposure, while requiring 2 h of desflurane exposure to demonstrated the same effect [73]. In a different study, a 4 h neonatal isoflurane exposure yielded deficits in both short-term and early long-term memory function in adulthood, whereas sevoflurane exposure only led to early long-term memory abnormalities [130]. While nitrous oxide by itself does not cause neuronal degeneration [36], its administration in newborn animals exacerbates cognitive abnormalities caused by isoflurane or sevoflurane in adulthood [36,131]. Finally, work performed by the Loepke laboratory observed similar degrees of neurodegeneration and caspase-3 expression immediately following a 6 h anesthetic exposure to equipotent doses of 0.6 MAC (minimum alveolar concentration) of all three commonly used inhaled anesthetics, desflurane, isoflurane, and sevoflurane (Figs 46.5 and 46.6) [132].

Combined, these comparative studies suggest that there currently does not exist consistent enough evidence from animal studies to recommend one inhaled anesthetic agent over another for clinical practice. Moreover, while it is much more difficult to compare injectable and inhalational anesthetics with each other in small rodents, separate studies in non-human primates indicate that neuronal cell death is qualitatively comparable between rhesus monkeys exposed to 5 h of propofol or isoflurane [118], albeit quantitative analyses have yet to be performed.

Since all currently utilized general anesthetics as well as many analgesics elicit structure modifying and function -altering

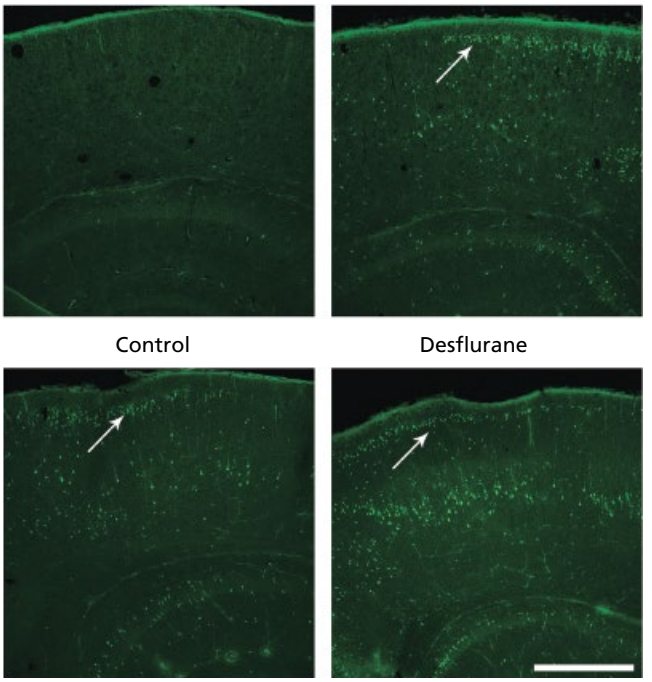

Figure 46.6 Six-hour exposure to desflurane, isoflurane, or sevoflurane similarly increases apoptotic cell death in neonatal mice, compared with fasted, unanesthetized littermates (control). Representative, low-magnification photomicrographs of coronal brain sections, obtained with laser confocal microscopy, demonstrate the pattern of apoptotic neuronal cell death. Brain sections from 7–8-day-old mouse pups were stained for the apoptotic cell death marker activated caspase-3 (bright green) following a 6 h exposure to room air (control), or 0.6 MAC desflurane, isoflurane, or sevoflurane, respectively. Arrows mark clusters of dying neurons in neocortical layers II/III (scale bar = 500 μm). *Source*: Reproduced from Istaphanous et al [132] with permission of Wolters Kluwer.

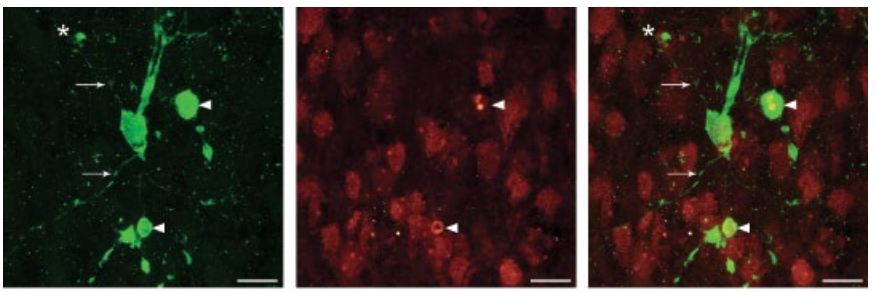

Figure 46.5 Representative, high-power magnification photomicrograph, obtained with laser confocal microscopy, demonstrating co-localization of the apoptotic cell death marker activated caspase-3 (green) and the postmitotic neuronal marker NeuN (red) in the neocortex. The brain section was obtained from a 7-day-old mouse pup following a 6 h exposure to 0.6 MAC of isoflurane, depicting a 9 μm image stack stained for activated caspase-3 (left) and NeuN-stained single optical sections through each cell body, for clarity (middle). Apoptotic neurons, indicated by co-localization of caspase-3 and NeuN in the merged image on the right, demonstrate degenerative changes, such as dendritic atrophy (arrows), dendritic beading (*), and pyknotic neurons (arrowheads), and are surrounded by unaffected neurons (scale bars = 10 μm). *Source*: Reproduced from Istaphanous et al [132] with permission of Wolters Kluwer.

responses in the immature animal brain, alternative anesthetic techniques should be investigated. However, inadequate alleviation of pain and distress may equally trigger neurodegenerative effects. It is therefore imperative to ensure adequate pain relief and to compare equianesthetic states. Decreasing anesthetic doses by combining several deleterious anesthetics may not obviate neurotoxicity according to animal studies, but may rather exacerbate it [36]. Accordingly, several animal studies have now investigated the use of alternative anesthetic techniques and mitigating compounds. Dexmedetomidine represents a promising drug for study as it lacks modulation of NMDA and GABA receptors, which have been implicated in facilitating the toxic effects. Accordingly, when administered as a single drug, dexmedetomidine does not seem to exhibit the same degree of toxicity in small rodents as commonly utilized general anesthetics [78–80,133]. Dexmedetomidine has also been shown to protect from ketamine-induced structural and cognitive abnormalities [134], as well as from the apoptosis-inducing effects of isoflurane [135]. However, none of these studies confirmed comparable levels of sedation.

In a novel approach, two research groups recently conducted a collectively planned study that was performed in parallel in two separate animal laboratories, utilizing the respective methodologies, to address the differential effects of prolonged exposures to sevoflurane, dexmedetomidine, and their combination on level of sedation and brain structure in newborn rodents [78,79]. Both studies confirmed that sevoflurane caused a higher degree of neuronal apoptosis in a variety of brain regions, but also created a deeper plane of anesthesia and reduction in response to painful stimulation, compared with dexmedetomidine alone. Interestingly, however, the findings differed substantially in regard to dexmedetomidine's protective effects, as one study demonstrated diminished neuronal degeneration when a low dose of dexmedetomidine was added to sevoflurane [78], while the other study did not find any neuroprotection [79]. These diverging results, probably due to subtle methodological differences including physiological derangements such as hypoxemia, raise important points regarding the need for confirmation of findings by different research laboratories.

Similar to dexmedetomidine, the noble gas xenon was found to be devoid of toxicity and to protect from isoflurane-induced neuroapoptosis in newborn rats [55,136], whereas some neurotoxic effects were found in two other *in vivo* and *in vitro* studies [56,137]. Lithium co-administration has been utilized as a protective strategy in animal studies as it has been found to alleviate neurodegeneration caused by propofol or ketamine in neonatal mice [76], sevoflurane in neonatal rats [138], as well as isoflurane in non-human primates [139]. Interestingly, even brief preconditioning with isoflurane has been demonstrated to protect from subsequent longer isoflurane exposure [140,141]. Whole-body hypothermia to 24°C has been proposed to reduce isoflurane-induced neuroapoptosis in neonatal mice [109,142]. Moreover, bumetanide has been found to alleviate sevoflurane's neurotoxic effects by inhibiting the Na-K-Cl membrane transport protein NKCC1 [106].

Naturally occurring hormones, such as estradiol [60,143] and melatonin [61], have been successfully tested in *in vivo* and *in vitro* preparations to reduce neuronal injury caused by prolonged exposure to midazolam, isoflurane, and nitrous oxide or to ketamine. Head and co-workers have demonstrated that the administration of tPA or plasmin, or pharmacological inhibition of the neurotrophic receptor $p75^{NTR}$, reduced the neurotoxic effects of isoflurane in neonatal mice [98]. However, more recent data by the same research group showed that inhibition of the p75 receptor, which was successful in reducing immediate neuroapoptosis, was ineffective in preventing cognitive abnormalities in adulthood following neonatal isoflurane exposure [115]. Carbon monoxide and hydrogen gas have been used with varying degrees of success to protect from isoflurane- and sevoflurane-induced structural and cognitive impairment [144–146].

A variety of antioxidants have been tested and found to alleviate several of the structural effects of anesthetic exposure in immature animals, including vitamin C [147,148], L-carnitine [149,150], coenzyme Q10 [64], and resveratrol [151]. Moreover, the mitochondrial stabilizer pramipexole has successfully protected against anesthesia-induced long-term cognitive impairment in female rats [126].

Implementation of these strategies employed in animals into pediatric anesthesia management appears premature, especially since human applicability of this phenomenon remains controversial and the safety of some of the proposed therapies has not been tested in young children. Estradiol, for example, may not be a feasible adjuvant prior to puberty or in boys, lithium has been labeled as harmful for the human fetus [152] and may cause neurocognitive impairment in young children [153,154], and hypothermia of 24°C may only be feasible in procedures involving hypothermic cardiopulmonary bypass, but not during routine pediatric anesthesia or intensive care. While xenon's scarcity renders it a very expensive treatment, dexmedetomidine may be a valid option as a single agent for light sedation or as an adjuvant for reducing doses of "toxic" general anesthetics.

Interspecies comparison

While abundant experimental evidence is available in developing animals implicating anesthetics and sedatives in triggering immediate brain structural alterations and long-term neurocognitive impairment, the relevance of these findings for clinical practice remains unclear. Unlike animal studies, the administration of anesthetics and analgesics in clinical pediatric medicine almost always coincides with significant noxious stimulation, such as during painful procedures and surgical operations. In this setting, some animal models have demonstrated analgesics or sedatives as preventing pain-induced neurotoxicity [6,13], while painful stimulation reduced anesthetic neurotoxicity [155]. Others have found an exacerbation of anesthetic neurotoxicity by concomitant noxious stimulation [156], while yet another group did not find any interaction between pain and anesthesia-induced cell death [157]. Differences exist between the metabolic and respiratory effects of anesthetic exposure in small rodent species and those in humans, such as extensive hypercarbia, metabolic acidosis, and hypoglycemia observed in some animals [112,116,117]. Exposure to clinical doses of anesthetics for only 2–4 h can be lethal in a substantial number of small rodents [112,117]. Moreover, doses needed for injectable anesthetics to cause neuronal degeneration in animals are significantly higher than those used in clinical practice. Animal studies have shown toxic doses for ketamine to be 10 times higher

and doses for propofol to be up to 20–30 times higher than clinically used doses, using a weight-based comparison. Accordingly, plasma concentrations of neurotoxic doses for ketamine, as measured in small rodents and monkeys, were approximately 3–10 times higher than those observed during clinical human practice [43,158]. Some of these discrepancies might be related to differences in body size and whole-body metabolic rates among species, resulting in higher weight-based dose requirements for smaller animals compared with larger animals [159]. However, even with allometric scaling to account for differences in body size [160], toxic doses in animal studies still remain higher than clinically used doses for several of the anesthetics (Table 46.2).

While these aspects limit the immediate applicability of results obtained in small rodents to clinical pediatric anesthesia practice, no obvious biological tenet exists categorically exempting humans from the structural abnormalities observed in animals. Importantly, the pattern of neuronal degeneration immediately following anesthetic exposure is qualitatively similar in small rodents and in intubated and mechanically ventilated non-human primates, suggesting that the more economical and ethically acceptable small animal models still have utility in providing important data to further advance the field.

A critically important finding from animal studies is the observed age window of vulnerability. Prolonged exposure to ketamine or isoflurane inflicts significant damage in developing cortical neurons of rodents aged 5–7 days, or in monkeys during the 3rd trimester or aged 6 days or younger, but not in older animals (Fig. 46.7) [32,34,43,59]. Given these findings of a narrow window of degenerative effects observed in the neoortex, it is imperative to identify the corresponding developmental state of the human brain, in order to predict the age range for possible susceptibility in humans. Previously, simple estimations of brain cell numbers and degree of myelination oversimplified the brain maturational state of the 7-day-old rat to span from the last trimester of pregnancy all the way to the third year of life [100,161,162]. Using a more contemporary neuroinformatics approach, the period of maximum cortical neurotoxic susceptibility in rats and monkeys more closely equates to the human 3rd trimester of pregnancy and 5 months of age, respectively (calculator available at http://www.translatingtime.net (accessed May 2019)) [163]. While it is difficult to translate developmental stages in small animals to humans, these comparisons would suggest that the susceptibility of cortical neurons could potentially be most pertinent in premature neonates, for example during fetal surgery, or in neonatal intensive care, and to a lesser extent during pediatric anesthesia in older children [164]. Importantly, more recent work by one of the authors' group discovered differential windows of vulnerability for different brain regions and anesthesia-induced neuroapoptosis in mice to extend into young adulthood for brain regions with ongoing neurogenesis [71]. These windows of vulnerability paralleled the naturally occurring, developmental cell death, suggesting that anesthetics might interfere with neurogenesis during a specific time of neuronal development during a late progenitor/immature neuron state [120]. Extrapolated to children undergoing prolonged or repeated anesthetic exposures, this may suggest that various neurological domains and cognitive abilities, such as language, motor skills, or executive function, may be particular vulnerable when they are being actively developed and supported by increased neurogenesis. If correct, however, this would substantially extend the window of

Table 46.2 Interspecies comparison of toxic and non-deleterious doses for injectable anesthetics (with references)

	Mouse	Rat	Monkey	Human
Toxic ketamine dose	20–40 or 50 mg/kg [46,48]	14–17 mg/kg/h for 11 h [32,42,158]	20–50 mg/kg/h for 24 h in 5-day-old [43,44]	
Estimated equivalent human dose	1.6–3.3 or 4.1 mg/kg	2.3–2.7 mg/kg/h for 11 h	6.5–16 mg/kg/h for 24 h	
Safe ketamine dose	10 mg/kg [48]	75 mg/kg or 17 mg/kg/h for 6 h [42]	20–50 mg/kg/h for 24 h in 35-day-old [43]	
Estimated equivalent human dose	0.8 mg/kg	12.2 mg/kg or 2.7 mg/kg/h for 6 h	6.5–16 mg/kg/h for 24 h	
				0.5–2 mg/kg or 0.1–1.2 mg/kg/h
Toxic propofol dose	60 mg/kg [49]	25 mg/kg [302]		
Estimated equivalent human dose	4.9 mg/kg	4 mg/kg		
Safe propofol dose	10 mg/kg [49]	n.s.		
Estimated equivalent human dose	0.8 mg/kg			
				2–3 mg/kg
Toxic diazepam dose	n.s.	10–30 mg/kg [34,303]		
Estimated equivalent human dose		1.6–4.9 mg/kg		
Safe diazepam dose	5 mg/kg [46]	5 mg/kg [303]		
Estimated equivalent human dose	0.4 mg/kg	0.8 mg/kg		
				0.1 mg/kg
Toxic midazolam dose	9 mg/kg [48]	n.s.		
Estimated equivalent human dose	0.7 mg/kg			
Safe midazolam dose	n.s.	9 mg/kg [36]		
Estimated equivalent human dose		1.5 mg/kg		
				0.1 mg/kg

n.s., not specified.

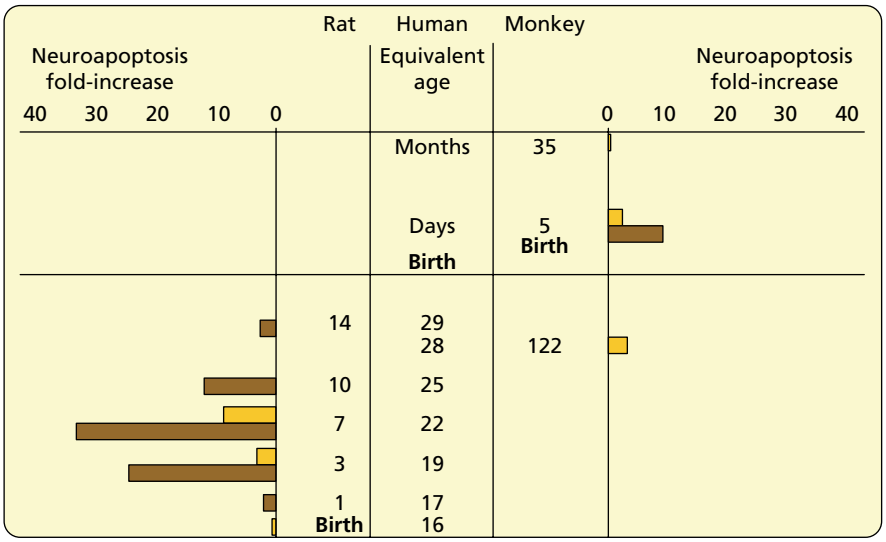

Figure 46.7 Quantification and developmental timing of anesthesia-induced neuroapoptosis. Brown bars signify a relative increase in neuroapotosis compared with physiological apoptosis (fold-increase) following an isoflurane-based anesthetic. Yellow bars signify ketamine exposure. Ages indicate postnatal days for rats (left), embryological and postnatal days for rhesus monkeys (right), and estimated equivalent gestational weeks in humans (center). Data are derived from references [32,43,60,67] and the human developmental equivalency are estimated using reference [163]. *Source*: Reproduced from Istaphanous et al [368].

susceptibility, potentially into adolescence or adulthood, and could explain the difficulties encountered in clinical studies using a wide age range of participants to identify a specifically affected neurological phenotype following anesthetic exposures in children.

KEY POINTS: INTERSPECIES COMPARISON

- Brain regional vulnerability to structural abnormalities is dependent on the age during exposure
- Emerging research suggests this to be linked to the maturational stage of developing brain cells
- This would suggest that the window of vulnerability could potentially extend beyond early childhood into adolescence or young adulthood

Clinical evidence for anesthetic neurotoxicity

While neurotoxic properties of anesthetics are well documented in developing animals, explicit clinical evidence for specific neurological abnormalities in children following anesthetic exposure is much harder to attain. Obvious ethical concerns preclude randomization of young children to undergo painful procedures with or without anesthesia and analgesia. Moreover, prolonged anesthetic exposures cannot be justified without any surgical or diagnostic indication. Hence, possible clinical evidence for the neurological effects of anesthetics and sedatives in young children has mostly been gathered from case reports of inadvertent overdoses, postoperative behavioral studies, epidemiological analyses, or from studies into long-term neurological outcome in children suffering from disorders requiring the administration of anesthetics and sedatives during life-saving surgery and intensive care at a very young age [38,41].

Postoperative behavioral abnormalities

While many studies investigating behavioral changes immediately postoperatively list the specific anesthetic drugs used, and usually involve healthy patient cohorts, their neurological assessment historically only consisted of short-term, parent-reported behavioral questionnaires or observations (Table 46.3). Only more recently have studies emerged utilizing standardized cognitive assessment tools. It has long been known that surgery and anesthesia in young children can lead to prolonged behavioral abnormalities [27,165–174]. Reported behavioral abnormalities, such as attention seeking, crying, temper tantrums, sleep disturbance, and anxiety occur in up to 50% of children early after anesthesia, and diminish significantly during the first postoperative month. These symptoms have repeatedly been associated with younger patient age, severity of postoperative pain, and lack of sedation prior to induction of anesthesia [27,167,169,172,174]. While the phenomenon's exact mechanism remains unknown, psychological factors, rather than structural brain abnormalities, are generally believed to be the underlying etiology [165,166,175]. Importantly, the administration of a benzodiazepine prior to general anesthesia did not exacerbate postoperative behavioral abnormalities, as expected for a cytotoxic etiology, but rather significantly reduced abnormal behavioral symptoms postoperatively [176]. However, since most postoperative behavioral studies rely on parental assessment of the child, no continuing professional observations and long-term neurocognitive assessments were incorporated in any of the behavioral studies. Therefore, the permanence of these neurological abnormalities remains uncertain.

Table 46.3 Behavioral or cognitive assessment following anesthetic exposure in early childhood*

Anesthetic agent	Dose or duration	Study design	Number of subjects	Age during exposure	Neurological sequelae on exam	Duration of symptoms and outcome	Reference
Midazolam (plus fentanyl)	0.07–0.94 mg/kg/h for up to 38 days	Case–control	45	0.03–19.2 years	After discontinuation of sedation, poor social interaction, decreased visual attentiveness, dystonic postures, and choreoathetosis in 11%	No sequelae 4 weeks after discontinuation	Bergman et al [304]
Midazolam (plus pentobarbital)	1–17 days	Retrospective cohort study	40	0.5–14 years	After discontinuation of sedation, agitation, anxiety, muscle twitching, sweating, tremor in 35%. Midazolam dose of >60 mg/kg strongly associated with symptoms	Symptoms abolished by pentobarbital treatment	Fonsmark et al [305]
Midazolam (plus opioid)	1.5–4 mg/h for 10 days	Case series	6	1–6 years	Multifocal myoclonus, dystonia, chorea, facial grimacing, tongue thrusting without seizure activity on EEG. Chemotherapy for CNS malignancies, MRI abnormalities	3–7 days	Khan et al [306]
Midazolam (plus morphine)	0.025–0.72 mg/kg/h for 1–18 days	Cohort study	53	6 days to 11 years	After discontinuation, prolonged sedation for up to 1 week in 8%. Disorientation, hallucinations, and behavioral abnormalities in up to 11%	0.13–7 days	Hughes et al [307]
Midazolam (plus opioid)	0–0.014 mg/kg/min for 4–18 days	Cohort study	15	6 weeks to 2.3 years	After discontinuation, sleeplessness, tremors, agitation, movement disorder in up to 50%. Symptoms occured as late as 6 days after start of taper	3 days	Franck et al [308]
Lorazepam (plus opioid)	0.1–0.4 mg/kg/h for 11–30 days	Prospective, open-label study	29	0.2–3 years	During taper, 24% experienced agitation, irritability, abnormal movements, or hallucinations	Not specified	Dominguez et al [309]
Pentobarbital (plus midazolam)	1–17 days	Retrospective cohort study	40	0.5–14 years	After discontinuation of sedation, agitation, anxiety, muscle twitching, sweating, tremor in 35%. Pentobarbital >25 mg/kg associated with symptoms	Symptoms abolished by pentobarbital treatment	Fonsmark et al [305]
Pentobarbital (plus benzodiazepines and opioids)	1–5 mg/kg/h for 0.6–49 days	Case series	8	0.4–7 years	During sedation, one patient (12.5%) experienced choreiform movements with athetoid features, ataxia, facial twitching. Also received mathadone and phenobarbital	1 week	Yanay et al [310]
Pentobarbital	1–4 mg/kg/h for 4–28 days	Case series	6	0.17–1.4 years	None reported	Not applicable	Tobias et al [311]
Phenobarbital (plus phenytoin)	20–1800 mg/day in mother	Case–control	172	Fetal exposure	Greater need for special education, learning difficulties, lower intelligence (WAIS), decreased attention on D-2, but not CPT test in adults after fetal exposure versus controls. No difference in memory tasks (DS, ALT)	Not applicable	Dessens et al [312]
Phenobarbital	2.5–50 mg for 1–540 days	Cross sectional, case–control	28	Neonate	No difference in Kaufman-ABC intelligence and D-2 tests between 8- and 14-year-old children following neonatal treatment with phenobarbital and "best friend" controls	Not applicable	Gerstner et al [313]
Ketamine	13–56 mg/kg	Case series	18	0.07–7 years	After inadvertent overdose, prolonged sedation and respiratory depression	Sedation for 3–24 h, no neurological sequelae on follow-up, where available	Green et al [314]

Propofol	200 mg/h for 48h *in utero*	Case report	1	Premature neonate 33 weeks GA	Prolonged sedation, no other neurological sequelae reported	12 h	Bacon et al [315]
Propofol	10.9 mg/kg/h for 11 days	Case report	1	23 months	Restlessness, muscle twitching limbs, functional blindness	Motor function impaired for 2 weeks, blindness for 33 days	Lanigan et al [316]
Propofol	Median infusion 2.7 mg/kg/h for >24 h	Case series	20	Median age 3.3 years	No neurological sequelae	Not applicable	Macrae and James [317]
Propofol	6–18 mg/kg/h for 2–4 days	Case report	2	2.5 and 4 years	Muscle weakness, twitching	9–18 days, full recovery	Trotter et al [318]
Propofol	10 mg/kg/h for 54 min	Case report	1	6 years	Seizure, ataxia, hallucinations starting 44 h after discontinuation of propofol	5 days, recovered without overt long-term sequelae	Bendiksen et al [319]
Isoflurane	13–497 MAC-hours	Cohort study	10	0.06–19 years	Agitation, non-purposeful movement in 50% of patients; all received >70 MAC-hours isoflurane, plus benzodiazepines and opioids	Symptoms responded to treatment advocated for opioid withdrawal	Arnold et al [320]
Isoflurane	0.25–1.5% for 1–76 h	Case series, case–control	12	0.5–10 years	Transient ataxia, agitation, hallucinations, and confusion after isoflurane administration >24 h; no symptoms after benzodiazepines or isoflurane <15 h	Normal follow-up exam 4–6 weeks after discharge	Kelsall et al [321]
Isoflurane	81 MAC-hours	Case report	1	2.5 years	Self-limiting, fine tremor in patient with myasthenia	46 h	McBeth et al [322]
Isoflurane	0.4–0.9% for 6–8 days	Case series	3	4–11 years	Temporary involuntary movements, myoclonia, brief seizures, and ataxia	Resolution of symptoms within 4–5 days	Sackey et al [323]
Isoflurane (plus midazolam and morphine)	0.5–1% for 4 days	Case report	1	7 years	Disorientation, hallucinations, agitation, seizure	5 days; reportedly normal behavior	Hughes et al [324]
Sevoflurane	8% during induction	Prospective study	20	1.1–8.4 years	Seizure-like movement and epileptiform EEG in 10%, no neurological exam	Not applicable	Conreux et al [325]
Sevoflurane	8% during induction	Prospective study	31	2–12 years	Epileptiform discharge in 88% with controlled ventilation and 20% with spontaneous breathing. No neurological exam	Not applicable	Vakkuri et al [326]
Sevoflurane	7% during induction	Prospective, randomized trial	45	2–12 years	No seizure activity on induction. Neurological exam not performed	Not applicable	Constant et al [327]
Sevoflurane	2% after IV thiopental	Prospective study	30	3–8 years	No epileptiform EEG activity. Neurological exam not performed	Not applicable	Nieminen et al [328]
Sevoflurane	Dose not specified	Meta-analysis of prospective studies in one center	791	3.3±2.1 to 6.9±2.4 years	increased "maladaptive" behavior in children, who were younger, and whose parents were more anxious on induction	Assessment up to 14 days postoperatively	Kain et al [172]
Sevoflurane or halothane	2–4% for 22±17 min/ 1–2% for 22±15 min	Prospective, randomized trial	120	3.3±2.6 to 4±2.9 years	Negative behavioral changes, such as temper tantrums, loss of appetite, or sleep disturbance in 38% for up to 30 days; no difference between sevoflurane or halothane	Assessment up to 30 days postoperatively	Keaney et al [171]
Sevoflurane or halothane	Doses not specified; outpatient surgery	Double-blinded, randomized, controlled trial	102	3–10 years	PHBQ: no difference between both anesthetics in regard to postoperative anxiety, sleep or appetite disturbance, strength, and energy	Up to 1 week postoperatively	Kain et al [173]

(*Continued*)

Table 46.3 (Continued)

Anesthetic agent	Dose or duration	Study design	Number of subjects	Age during exposure	Neurological sequelae on exam	Duration of symptoms and outcome	Reference
Pentobarbital, scopolamine, ether, nitrous oxide, and/or cyclopropane	Doses not specified; otolaryngological surgery	Survey study	612	2 to >12 years	Parental assessment: Negative behavioral changes, such as night terrors, temper tantrums, fears, and bed wetting most prevalent in under 3-year group (57%) compared with older group (8%)	Questionnaires mailed to parents 2 months postoperatively	Eckenhoff [27]
Pentobarbital, scopolamine, morphine, and ether or nitrous oxide	Doses not specified; otolaryngological, dental, or ophthalmological surgery	Survey, case–control	290	1–15 years	No differences in psychological upset after anesthesia, surgery, and hospitalization compared with siblings or healthy controls	Interview administered to patient's mother 2 weeks postoperatively	Davenport and Werry [329]
Halothane or ketamine	Dose not specified; scheduled and emergency surgery	Prospective randomized study, survey	103	1–12 years	Parental assessment: fear of strangers, sleep disturbance, nightmares, or bed wetting in 38% under 4 years versus 16% in 4-year-olds and over	Parental assessment 1 month postoperatively	Modvig et al [166]
Thiopental, halothane, or methohexital induction, and halothane and nitrous oxide maintenance	Methohexital 15 mg/kg PR, otherwise not specified; routine day-case ENT surgery	Survey study	86	2–10 years	PHBQ: problematic behavioral changes in 51% at 1 day and 34% at 1 month postoperatively. Temper tantrums tended to be more common following stormy induction versus calm induction of anesthesia	Questionnaires given to parents to report behavior 1 day, 1 week, and 1 month postoperatively	Kotiemi et al [168]
Thiopental or propofol, isoflurane, or halothane or enflurane. Midazolam or diazepam premed	Doses not specified; ENT or ophthalmological procedures with mean anesthesia time of 32.8±17.9 min	Multicenter survey	551	0.3–13.4 years	PHBQ: behavioral problems in 47% on day of surgery, 9% after 4 weeks, including attention seeking, crying, temper tantrums, sleep problems, and anxiety	Questionnaires given to parents to report behavior up to 4 weeks postoperatively	Kotiemi et al [169,170]
Halothane/nitrous oxide	Dose not specified; elective minor head and neck surgery	Survey study	122	1–8 years	Parental assessment: behavioral abnormalities in up to 88% of children awake during induction and 58% of children asleep during induction	Questionnaires mailed to parents within 1st postoperative month	Meyers and Muravchick [167]
Predominantly halothane, nitrous oxide, ketamine, and/or thiopental	Doses not specified, stratified by number of exposures for mostly ENT and general surgery	Retrospective, epidemiological study	5357	0–4 years	Review of medical and educational records demonstrate a doubling of the risk of learning disabilities following two or more surgical procedures with anesthesia for more than a combined 2 h, compared with no or one exposure	Review of educational records several years after anesthetic exposure	Wilder et al [211]
Predominantly sodium thiopental, nitrous oxide, and halothane	Doses not specified, general or regional anesthesia for cesarean delivery versus spontaneous vaginal birth	Retrospective review of records	5320	Perinatal	The incidence of learning disabilities was similar among children delivered vaginally without anesthesia and via cesarean section with general anesthesia, but lower following cesarean section with regional anesthesia	Review of school records	Sprung et al [210]

No data	No data	Epidemiological case–control study	5050	0–3 years	Doubling of presence of diagnostic codes for developmental problems in children also carrying a billing code for inguinal hernia repair prior to 3 years of age, compared with those who did not carry this billing code	Presence of diagnostic codes for developmental or behavioral disorder, mental retardation, autism, and language or speech problems	DiMaggio et al [206]
No data	No data	Review of data from monozygotic twin pairs from Young Netherlands Twin Register	1143	0–3 years	Educational scores lower in concordant twin pairs exposed to anesthesia compared with unexposed pairs. However, no difference in educational achievement comparing both twins in discordantly exposed pairs	Educational achievement (Cito test administered at age 12 years) and Connor Teacher Rating Scale	Bartels et al [286]
No data	No data	Sibling case–control study	10,450	0–3 years	Risk for developmental or behavioral disorder increased to 2.9 (95%CI: 2.5, 3.1) following two operations to 4 (95%CI: 3.5, 4.5) following three operations	Diagnosis of developmental or behavioral disorder, as assessed with billing codes	DiMaggio et al [330]
No data	No data	Matched cohort study	1050	0–2 years	Multiple exposures increased risk for learning disabilities by 2.1 (95%CI: 1.3, 3.5) but not need for educational intervention for emotion/behavior	Diagnosis of learning disability, after adjustment for health status	Flick et al [214]
No data	No data	Matched cohort study	4684	Perinatal	Not increased by neuraxial labor analgesia (adjusted OR 1.05, 95%CI: 0.9, 1.3)	Diagnosis of learning disability	Flick et al [331]
Benzodiazepines, chloral hydrate, opioids, ketamine, volatile anesthetics	Cumulative and daily	Prospective follow-up study	95	Neonatal complex heart surgery	No association between sedation/analgesia variables and behavioral or cognitive outcomes at 18–24 months	Bayley II/III, ABAS-GAC, and LDS	Garcia Guerra et al [199]
Benzodiazepines, chloral hydrate, opioids, ketamine, volatile anesthetics	Cumulative and daily	Prospective follow-up study	91	Infant complex heart surgery	Association between days on chloral hydrate and lower performance IQ, cumulative benzodiazepine dose associated with lower VMI scores at 54±5 months	WPPSI II, VMI-V, ABAS-GAC	Garcia Guerra et al [200]
No data	No data	Nationwide case–control study	17,264	Infant inguinal hernia repair	No difference in scores between exposed and unexposed, after adjustment for confounders; rates of non-attainment higher in exposed	Academic achievement in compulsory 9th grade exam and teacher rating	Hansen et al [220]
No data	No data	Nationwide case–control study	17,264	Pyloromyotomy <3 months	No difference in scores between exposed and unexposed, after adjustment for confounders; rates of non-attainment higher in exposed	Academic achievement in compulsory 9th grade exam and teacher rating	Hansen et al [221]
No data	No data	Nationwide case–control study	15,655	Cholesteatoma removal <15 years	No difference in scores between exposed and unexposed, except for lower grades in first foreign language following repeat exposure; rates of non-attainment higher in exposed	Academic achievement in compulsory 9th grade exam and teacher rating	Djurhuus et al [332]

(*Continued*)

Table 46.3 (Continued)

Anesthetic agent	Dose or duration	Study design	Number of subjects	Age during exposure	Neurological sequelae on exam	Duration of symptoms and outcome	Reference
Nitrous oxide, halothane, thiopental, isoflurane, morphine, sevoflurane, and/or fentanyl	Duration ranging from 0.8 to 3.8 h	Retrospective observational study	58	Infant surgery for inguinal hernia repair, orchidopexy, pyloromyotomy, or circumcision	No difference in academic achievement, but higher proportion scored below the 5th percentile; duration of anesthesia correlated negatively with scores	Statewide academic achievement test scores (Iowa Tests of Basic Skills and of Educational Development)	Block et al [333]
No data	No data	Case–control study	208	Surgery in premature infants born at <30 weeks GA	Compared with non-surgical group, smaller brain and deep gray matter volumes, greater white matter injury in infants exposed at term; PDI and MDI similar after adjustment for confounders	Volumetric analysis of MRI at term, Bayley-II at age 2 years	Filan et al [334]
No data	No data	Birth cohort case–control study	2608	Surgery < 3 years of age	Higher risk of language and abstract reasoning deficits at age 10 years, after adjustment for demographics	CELF, CPM	Ing et al [335]
No data	No data	Case–control study	5357	Surgery <2 years of age	Multiple, but not single, exposures associated with increased risk of ADHD, after adjustment for cofounders	Review of records for clinical diagnosis of ADHD and at least one form of supporting evidence	Sprung et al [215]
No data	Mean duration 51 min	Prospective longitudinal study	21	Strabismus surgery between 5 and 10 years of age	No difference in pre- and postoperative performance, except for diminished hand-eye coordination in patients with decreased stereoacuity	Kaufman-ABCadministered prior to and 4 weeks after surgery	Yang et al [336]
Sevoflurane, thiopental, or propofol	30–120 min surgeries	Case–control study	100	Infant surgery	No difference in aggregate score, but 4.5 times higher odds ratio for diagnosis of learning disability following exposure	Singapore primary school leaving examination at 12 years of age	Bong et al [337]
No data	No data	Prospective follow-up study	27	Neonatal laparotomy for bowel obstruction	Abnormal motor function and attention, no other cognitive domains affected	Movement-ABC, abbreviated WISC-III, TEA-Ch, visuomotor integration part of NEPSY-II, and AVLT	Elsinga et al [338]
Sevoflurane, fentanyl	Mean anesthesia time 67±10 min	Prospective longitudinal study	72	Strabismus surgery between 4 and 7 years of age	No adverse effects on cognitive function observed	WPPSI III prior to, 1 month, and 6 months following operation	Fan et al [339]
Opioids, benzodiazepines, volatile anesthetics	4.4±3.1 MAC-hours during 2–4 exposures	Prospective observational study	59	Infant repair of complex congenital heart lesions	Higher volatile anesthetic exposure associated with lower cognitive scores	Bayley-III at 1 year	Andropoulos et al [201]

No data	No data	Case–control study	781	Surgery <3 years of age	Increased risk for measured language deficits and ICD-9-identified disorders, but no change in academic achievement	CELF, mental, behavioral, neurodevelopmental disorders per ICD-9 codes, academic achievement scores	Ing et al [340]
No data	No data	Case–control study	2,868	Surgery between 3 and 10 years of age	Higher risk for motor deficit following exposure between 3 and 5 years of age	CELF, Raven's Colored Matrices, Peabody Picture Vocabulary Test, MAND, CBCL	Ing et al [341]
No data	No data	Case–control study	16,465	Surgery <3 years of age	No difference between diagnosis of ADHD between exposed and unexposed	ICD-9-CM code 314.01 for diagnosis of ADHD >3 years	Ko et al [342]
No data	No data	Case–control study	20,788	Surgery <2 years of age	No difference between diagnosis of autistic disorder between exposed and unexposed	Diagnosis of autism according to ICD-9-CM code 299.00	Ko et al [343]
Propofol, nitrous oxide, sevoflurane, isoflurane, or halothane	Median anesthetic dose 203 MAC-minutes (two outliers of <60 MAC-minutes)	Case–control study	28	Infant, mostly urological surgery	Recognition memory impairment, no difference in IQ	WASI, recognition memory task tested at 6–11 years of age	Stratmann et al [344]
Spinal anesthesia	Mean duration of surgery 40±13 min	Retrospective observational study	265	Infant surgery for circumcision, pyloromyotomy, or inguinal hernia repair with spinal anesthesia <5 years	Decrease in reading and mathematics scores in exposed group; no correlation with duration of surgery	New Standards Reference Examination achievement and New England Common Assessment Program Examination tests	Williams et al [345]
Ketamine 8 mg/kg IM	1–3 exposures	Observational study	49	1–3 laser excisions of facial growth in 3–22-month-olds	Diminished MDI following third exposure	Bayley-II	Yan et al [346]
Etomidate followed by propofol (5–10 μg/kg/min) or sevoflurane (1–3%)	No data	Prospective, longitudinal study	60	Inguinal hernia repair at 7–13 years of age	Transient memory impairment observed in propofol exposed patients 7 days postoperatively, but not following sevoflurane exposure	Wechsler Memory Scale preoperatively, and 7 days or 3 months postoperatively	Yin et al [347]
Halothane, nitrous oxide, sevoflurane	0.2–3.8 MAC-hours	Matched case–control study	53	Surgery <4 years of age, mostly ENT	Impaired listening comprehension and diminished performance IQ, associated with diminished gray matter density in occipital cortex and cerebellum	WISC/WAIS, OWLS, MRI between 5 and 18 years	Backeljauw et al [348]
No data	No data	Nationwide case–control study	536,673	Perinatal for cesarean section	Increased risk for development of autism following cesarean section with general anesthesia compared with regional anesthesia or vaginal birth	ICD-9-CM code 299.0 for diagnosis of autism during mean follow-up of 4.3 years	Chien et al [349]

(*Continued*)

Table 46.3 (Continued)

Anesthetic agent	Dose or duration	Study design	Number of subjects	Age during exposure	Neurological sequelae on exam	Duration of symptoms and outcome	Reference
Halothane ± nitrous oxide ± thiopental	Duration 65–317 min cumulative duration	Matched case–control study	30	Surgery <2 years	Activation differences with unexposed subjects in cerebellum, cingulate gyrus, and paracentral lobule during tests of response inhibition	Blood oxygen-dependent fMRI at 10–17 years of age	Taghon et al [350]
							Clausen et al [351]
Sevoflurane versus neuraxial anesthesia	Duration 41–70 min (median 54 min)	Randomized controlled trial	532	Infant inguinal hernia repair	No difference in cognitive performance between general and regional anesthesia	Bayley-III at 2 years	Davidson et al [226]
Desflurane, halothane, isoflurane, and/or sevoflurane	0–35.3 MAC-hours cumulative	Retrospective observational study	96	Infant surgeries for HLHS or variants	Inverse correlation between MAC-hours and full-scale and verbal IQ scores	WPPSI III between 4 and 5 years of age	Diaz et al [352]
No data	Mean neonatal duration of 145 min (95% CI: 115, 175 min) and cumulative period of 268 min	Ambidirectional case–control study	40	Neonatal surgery for gastrointestinal malformations	Diminished mental development index due to impaired verbal abilities	Bayley-II	Doberschuetz et al [353]
No data	No data	Retrospective matched cohort study	18,056	Surgery <4 years	Single exposure between 2 and 4, but not between 0 and 2 years, associated with deficits	EDI assessment at 5 years of age	Graham et al [223]
No data	No data	Population-based cohort study	188,557	Surgery <4 years	Early developmental vulnerability following first exposure after 2nd birthday, but not if exposure occurred before age 2	EDI assessment age 5–6 years	O'Leary et al [222]
No data	Range from 20 to 240 min (median 80 min)	Ambidirectional sibling-matched cohort study	210	Inguinal hernia repair <3 years	No difference in mean IQ scores compared with sibling control	NEPSY-II at 8–15 years	Sun et al [228]
Morphine	Median cumulative dose of 1905 mg/kg	Prospective cohort study	136	Very preterm neonates (24–32 weeks GA)	Decrease in cerebellar volume, diminished cognitive and motor outcomes associated with cumulative morphine dose	Peabody Developmental Motor Scales, Bayley-III, serial MRI scans	Zwicker et al [354]
No data	Cumulative duration of anesthesia ranged from 0.8 to 22.4 h	Retrospective cohort study	87	Cleft lip and/or palate repair before 7 years of age	Diminished verbal IQ and higher frontal lobe volume associated with number of surgeries with anesthesia	WISC-III or WAIS-III, brain MRI	Conrad et al [355]
Propofol, isoflurane or sevoflurane, fentanyl, sufentanil, or alfentanil	No data	Retrospective cohort study	3441	Surgery with anesthesia before age 5 years	Lower IQ scores in exposed group	Snijders Oomen Niet-verbale intelligentie test – Revisie	De Heer et al [356]
No data	No data	Nationwide cohort study	196,773	Surgery before age 4 years	Less than 1% school grades in exposed children, compared with unexposed	School grades at age 16 years, IQ test at military conscription at age 18 years	Glatz et al [224]

No data	No data	Retrospective cohort study	1036	Surgery before age 3 years	Increased frequency of learning disabilities and attention-deficit/hyperactivity disorder, decreased academic achievement following multiple, but not single, exposures. Decreased reading and language achievement following single exposure	Medical and school records review	Hu et al [216]
Nitrous oxide, halothane, isoflurane, or enflurane, as well as thiopental, propofol, or benzodiazepines	No data	Population-based cohort study	1622	Anesthesia with volatile agents before age 3 years	Lower total and expressive language scores following exposures exceeding 35 min, but not following shorter durations	CELF, CPM	Ing et al [357]
No data	No data	Retrospective matched cohort study	230,958	Single anesthetic exposure before age 5 years	Increased risk of diagnoses for mental disorder, developmental delay, and ADHD, without effect of age when exposure occurred	Presence of ICD-9 coded mental disorder diagnosis	Ing et al [209]
No data	Exposure duration 124±137 min	Ambidirectional case–control study	31	Infant surgery for circumcision, pyloromyotomy, inguinal hernia, orchidopexy, or tympanostomy	Decreased whole-brain white matter volume and diminished white matter integrity in several regions	Structural MRI in boys at age 12–15 years	Block et al [358]

* Test and assessment abbreviations: ABAS-GAC, Adaptive Behavior Assessment System – General Adaptive Composite; ALT, Associated Learning Task; AVLT, Rey's Auditory Verbal Learning Test; Bayley, Bayley Scales of Infant and Toddler Development – 2nd or 3rd edition; CBCL, Child Behavior Checklist; CELF, Clinical Evaluation of Language Fundamentals; CPM, Colored Progressive Matrices; CPT, Continuous Performance Task for sustained attention; D-2, selective attention test; DS, Digit Span memory test; EDI, Early Development Instrument; Kaufman-ABC, Kaufman Assessment Battery for Children; LDS, Language Development Survey; MAND, McCarron Assessment of Neuromuscular Development; MDI, Bayley Mental Development Index; Movement-ABC, Movement Assessment Battery for Children; NEPSY, Developmental NEuroPSYchological Assessment – version II; OWLS, Oral and Written Language Scales; PDI, Bayley Psychomotor Development Index; PHBQ, Vernon Post Hospitalization Behavioral Questionnaire; TEA-Ch, Test of Everyday Attention for Children; VMI, Beery-Buktenica Development Test of Visual Motor Integration – 5th edition; WAIS, Wechsler Adult Intelligence Scale; WASI, Echsler Abbreviated Scale of Intelligence; WISC, Wechsler Intelligence Scales for Children; WPPSI, Wechsler Preschool and Primary Scale of Intelligence – 2nd and 3rd edition.

ADHD, attention deficit hyperactivity disorder; CI, confidence interval; CNS, central nervous system; EEG, electroencephalography; ENT, ear nose and throat surgery; fMRI, functional magnetic resonance imaging; GA, gestational age; HLHS, hypoplastic left heart syndrome; ICD-9, International Classification of Diseases – 9th edition; IM, intramuscular; IV, intravenous; MAC, minimum alveolar concentration; MRI, magnetic resonance imaging; OR, odds ratio; PR, per rectum.

Neurological outcomes in critically ill neonates

Previously critically ill neonates represent a patient population historically closely followed with standardized neurodevelopmental tests. Many of these patients underwent surgical procedures involving general anesthesia early in life, such as for ligation of the patent ductus arteriosus, repair of esophageal atresia, inguinal hernia repair, neurosurgical operations, laparotomies, or tracheotomies [177–186]. However, none of these studies were designed to study the long-term effects of anesthetic exposure and, accordingly, they consistently fail to specify the exact anesthetic agents used and oftentimes involve several potent confounders, such as severe prematurity, prolonged ventilator support, considerable pain and distress, significant co-morbidities, and latent episodes of hypoxia or hypoxia-ischemia, and frequently include major surgical procedures with potentially significant postoperative inflammatory response (Table 46.4). In this context, long-term neurodevelopmental impairment, such as a reduction in IQ, increased incidence of cerebral palsy, deafness, or blindness have frequently been observed [180–184,186]. Coexisting disease and congenital abnormalities were associated with worse neurological outcomes [178,183]. In an attempt to at least partly control for severity of illness, several case–control studies compared neurodevelopmental outcome in survivors of surgical operations for necrotizing enterocolitis and patent ductus arteriosus with those receiving medical management alone. When compared with age-matched controls or medically treated patients in the same cohort, several investigators noticed an impairment in neurocognitive function in surgically treated survivors of laparotomy or thoracotomy [180–182,184,186], while others were unable to find these differences [177,179,185]. However, it remains difficult to separate the effects of neonatal stress and surgery from the effects of the anesthetics. Moreover, study designs did not include randomized controlled trials, but were rather designed as cohort studies or case–control studies. It therefore seems conceivable that, due to selection bias, some of the extremely premature neonates that needed surgery had more concomitant illnesses and were therefore sicker than their matched controls. This notion is underscored by the fact that some of the studies identified longer periods of hypotension, more common use of inotropic support, and longer periods of total parenteral nutrition in the postsurgical patients [180,182]. Accordingly, a prospective randomized trial of 117 preterm infants with necrotizing enterocolitis who were assigned to either laparotomy or to peritoneal drainage without surgery did not find any difference in patient survival and early outcomes [187].

Another patient population that has been followed for evaluation of long-term neurocognitive development following surgical procedures early in life are neonates and infants undergoing congenital heart surgery, such as for hypoplastic left heart syndrome, transposition of the great arteries, or tetralogy of Fallot [188–198]. This patient population frequently requires repeated or prolonged anesthetic exposures, and neurocognitive impairment has been documented in many of these patients when compared with population norms [188–196,198] or with 'best friend' control subjects [197]. However, in these studies the anesthetic regimen was frequently not specified and confounding factors included preoperative neurological lesions, pre-existing or perioperative hypoxia and hypotension, as well as chronic postoperative hypoxemia in many of these patients. Interestingly, in the largest trial, the Boston Circulatory Arrest Trial with patient follow-up for 8 years after arterial switch operation, many outcome measures in a battery of neurodevelopmental tests were within normal population limits, despite major corrective cardiac surgery with anesthesia in the neonatal period [196]. In an important preliminary report in this population, Garcia Guerra et al studied 95 survivors of neonatal open heart surgery with normal chromosomes [199]. They calculated the cumulative dose, dose per day, and number of days each patient received opioids, benzodiazepines, ketamine, and chloral hydrate in the intensive care unit. At 18–24 months, none of the sedation variables was associated with poor performance on the Bayley Scales of Infant Development, or other tests of adaptive behavior and vocabulary [199]. However, a follow-up at 4 years of age uncovered exposure to chloral hydrate to be associated with lower performance IQ, and higher cumulative benzodiazepine doses to be associated with visual motor abnormalities [200]. While the intraoperative exposure to anesthetic gases and other drugs were not recorded in that study, a retrospective review of neonates with complex congenital heart disease undergoing corrective surgery at Texas Children's Hospital identified higher exposure to volatile anesthetics to be associated with lower cognitive Bayley III scores at 12 months of age [201].

Several case–control studies have also attempted to address the neurocognitive implications of prenatal anesthetic exposure *in utero* [202–205]. Abnormal neurological activity observed in neonates early after delivery included increased motor tone and decreased interaction [205], visual test abnormalities [203], and motor weakness [202]. Interestingly, the incidence of early neurological abnormalities following cesarean section did not differ between neonates exposed to general anesthesia, including thiopental and nitrous oxide, or to maternal epidural analgesia using lidocaine 2]. In a small, 4-year follow-up after prenatal exposure to anesthetics for dental procedures [203], children demonstrated decreased intelligence scores compared with unexposed controls, but demonstrated similar performance on tests of their vocabulary [204]. However, anesthetic exposure was not quantified, spanned from the 1st to the 3rd trimester of pregnancy, and consisted of such diverse agents as methohexital, sodium thiopental, lidocaine, and carbocaine.

KEY POINTS: COHORT STUDY EVIDENCE FOR ANESTHETIC NEUROTOXICITY

- Several cohort studies in premature and term neonates undergoing major surgical operations involving general anesthesia demonstrate neurodevelopmental impairment later in life, however none of these studies specified the anesthetic technique utilized
- The effects of concomitant disease and the impact of the surgical procedure cannot be separated from the effects of anesthesia

Table 46.4 Outcomes studies following major surgery in neonates and infants

Study design	Study group	Control group	Number of subjects	Age during exposure	Age during neurological assessment	Neurological assessment tool*	Neurological sequelae in study group	Reference
Case–control study	PDA ligation, inguinal hernia repair, GI surgery, neurosurgery, tracheotomy	No surgical intervention	221	First hospitalization for <27 weeks PCA, ELBW	5 years	Neurological examination, WPPSI-R	Increased incidence of cerebral palsy, blindness, deafness, WPPSI-R >3 SD below mean	Victorian Infant Collaborative Study Group [181]
Case series	Repair esophageal atresia	None, comparison with general population	36	Neonatal	10.2 years	WISC-RN, ADQC, CBCL, TRF	10% reduction in IQ; special education five times as frequent; subgroup without major associated congenital anomalies had normal IQ	Bouman et al [183]
Case series	Repair esophageal atresia	None, comparison with general population	34	Neonatal	12.7 years	WISC, HFT, Rohrschach Test	No statistical difference in IQ compared with age- and gender-matched general population	Lindahl et al [177]
Cohort study, case–control study	PDA ligation	Indomethacin treatment	340	84% neonatal (25–29 weeks PCA), ELBW	18 months	Neurological examination, BSID2	Increase in cerebral palsy, cognitive delay, hearing loss, bilateral blindness	Kabra et al [186]
Cohort study, case–control study	Laparotomy	Peritoneal drain placement	3725	Neonatal, ELBW	18–22 months	Neurological examination, BSID2	Blinded assessor: higher frequency of cerebral palsy and lower BSID2; no difference between medically treated patients with or without NEC	Hintz et al [184]
Case–control study	Laparotomy	Peritoneal drain placement	78	29 weeks PCA, ELBW	18–22 months post-term	Neurological examination, BSID2	Less neurodevelopmental impairment and lower mortality	Blakely et al [185]
Case–control study	NEC	No NEC	802	30 weeks PCA, VLBW	20 months post-term	SBIS, BSID	No blinded assessor: no significant difference in BSID scores; impairment more prevalent in survivors of most severe form of NEC, however not stratified by surgical or medical management	Walsh et al [178]
Case–control study	NEC requiring laparotomy	No NEC or NEC managed medically	115	26–27 weeks PCA, VLBW	12 months, 3 years, and 5 years PCA	GMDS, SBIS	No blinded assessor: higher incidence of neurodevelopmental impairment; use of inotropes and TPN dependence more prevalent after laparotomy	Tobiansky et al [180]
Case–control study	NEC requiring laparotomy	Gestational age and birthweight matched controls	30	26 weeks PCA, ELBW	5 and 7 years	GMDS, SBIS, CBCL, Peabody tests	No blinded assessor: NDI in 70% of survivors of NEC versus 25% in age-matched controls. NDI after laparotomy for NEC 66.6% versus 9.1% after NEC managed medically. Hypotension requiring inotropes more prevalent after laparotomy	Chacko et al [182]
Case–control study	NEC requiring laparotomy	NEC managed medically	18	Neonatal, VLBW	8 and 15 months post-term, 24 months	BSID, INFANIB, DDST	Assessor not blinded: higher prevalence of motor delays early after surgery; no differences detected at 2 years of age	Simon et al [179]

(*Continued*)

Table 46.4 (Continued)

Study design	Study group	Control group	Number of subjects	Age during exposure	Age during neurological assessment	Neurological assessment tool*	Neurological sequelae in study group	Reference
Prospective, randomized trial	ASO with DHCA	ASO with LF-CPB or general population	155	Neonatal	1, 2.5, 4, and 8 years	WISC-III, WIAT, TRF, CBCL, WCST, TOVA, Mayo Test for Apraxia of Speech, Goldman–Fristoe Test of Articulation	Lower full-scale IQ, Perceptual Organization, and Freedom from Distractability scores, WIAT reading and mathematics composites, Memory Screening Index, WCST, and TOVA scores. Most differences were <1 SD	Bellinger et al [190,192,196]
Cohort study	Open heart surgery	None	59	Neonatal	≥2 years	SBIS or BSID	Cerebral palsy in 22%, mean IQ 90, but highly dependent on type of congenital heart disease	Miller et al [188,189]
Case series	ASO	None, comparison with general population	60	Neonatal	3–14 years	Kiphard and Schilling Body Coordination Test, Kaufman Assessment Battery for Children, Oral and Speech Motor Control Test, Nayo Test of Speech and Oral Apraxia	Assessor not blinded: increased prevalence of neurological impairment (27%), speech impairment (40%), motor dysfunction, and language impairment; no difference in intelligence	Hövels-Gürich et al [198,359]
Case–control study	ASO with limited DHCA	"Best friend" control group or general population	148	0–118 (median 9) days	9.1±2.9 years	WPPSI-R or WISC-III, CBCL, Movement-ABC	Lower IQ than control, but still above general population mean; higher prevalence of behavioral, language expression, and comprehension problems	Karl et al [197]
Case series	Open heart surgery	None, comparison with general population	98	Infancy	1–3 years	PDMS, GMDS	Blinded assessor: abnormal neurological exam in 41%, motor delay in 42%, and global developmental delay in 23%	Limperopoulos et al [360]
Case series	HLHS	None, comparison with general population	28	Several procedures as neonates and early childhood	8.6±2.1 years	WISC-III, WJPB, VMI, CELF-R, CBCL	Assessor not blinded: prevalence of mental retardation 18% and borderline IQ in 36%. Learning disability in over 14% of survivors. Performance IQ scores lower than verbal IQ scores	Mahle et al [194]
Cohort study, case–control study	Intrauterine exposure to nitrous oxide	No intrauterine exposure	159	Prenatal: 3rd trimester	5 days postnatally	Prechtl's Neurological and Brazelton's Behavioral Assessments	Weaker habituation to sound, stronger muscular tension and resistance to cuddle, fewer smiles	Eishima [205]
Case–control study	General or local anesthetics	No anesthetic exposure	39	Prenatal: 1st to 3rd trimester	0.8–6 days postnatally	Measurement of visual pattern preference	Prolongation of visual pattern preference	Blair et al [203]
Case–control study	General or local anesthetics	No anesthetic exposure	14	Prenatal: 1st to 3rd trimester	4±0.08 years	PPVT, vocabulary parts of WPPSI and SBIS	Lower PPVT IQ scores, no differences in WPPSI or SBIS	Hollenbeck et al [204]

Prospective, case–control study	Thiopental, nitrous oxide for general anesthesia	Lidocaine 1.5% for epidural analgesia	30	Perinatal for cesarean section	1–7 days	Neurological assessment as per Prechtl and Beintema	Blinded assessor: abnormal neurological activity for up to 7 days in 47%, regardless of group assignment	Hollmen et al [202]
Cohort study	Elective procedures that required anesthesia		340	2–13 years	Up to 2 weeks after exposure	PHBQ, CBCL	Behavioral abnormalities in 34%, especially if age <5 years, postoperative pain or nausea, anxiety during induction, post-tonsillectomy, previous hospitalizations	Karling et al [361,362]
Survey study	General anesthesia for general surgery, ENT, gastroenterology, plastics surgery, orthopedics	None, some sibling controls	1027	3–12 years	3 and 30 days postanesthesia	PHBQ	Behavioral changes in 24% on day 3 after surgery, 16% on day 30, including anxiety and regression, apathy or withdrawal, and separation anxiety	Stargatt et al [174]
Prospective poulation-based study	Prolonged sedation and/or analgesia for intensive care	No exposure to sedation or analgesia	1345	Neonatal: premature infants born 22–32 weeks PCA	Up to 5 years	MPC of Kaufman Assessment Battery for Children	No difference in disability after adjustment for severity of illness (not powered to identify cognitive group differences <10%)	Rozé et al [217]
Retrospective cohort study	General anesthesia for urological procedures	None, comparison with general population	243	0–6 years	Several years after surgery	CBCL/4-18	Incidence of behavioral disturbances higher in children operated on <2 years of age, compared with >2 years	Kalkman et al [218]
Prospective, longitudinal study	General anesthesia, intensive care for correction of congenital anomalies	None, comparison with general population	101	Neonatal period	Up to 2 years	BSID, MDI	Normal mental development, but impaired growth and delayed psychomotor development	Gischler et al [363]
Prospective, longitudinal case–control study	General anesthesia, intensive care, ventilator support following major emergency abdominal surgeries	Healthy controls and neonates requiring intensive medical care	19	Neonatal period	Up to 11 years	GMDS, Reynell Developmental Language Scales, British Picture Vocabulary Scales, Wallin B pegboard, compulsory national curriculum examinations	Continued impaired performance in previously critically ill patients requiring prolonged care, with significant improvements in medical group, but not surgical patients, especially following multiple procedures	Ludman et al [364–367]

* Test and assessment abbreviations: ADQC, Abbreviated Depression Questionnaire for Children Self-Assessment; BSID, Bayley Scales of Infant Development; CBCL, Achenbach Child Behavior Checklist Parental Assessment; CELF-R, Clinical Evaluation of Language Fundamentals – Revised; DDST, Denver Developmental Screening Test; GMDS, Griffiths Mental Development Scales; HFT, human figure drawing; INFANIB, Infant Neurological International Battery; MDI, Bayley Mental Development Index; Movement-ABC, Movement Assessment Battery for Children; MPC, Mental Composite Score of the Kaufman Assessment Battery for Children; PDMS, Peabody Developmental Motor Scales; PHBQ, Vernon Post Hospitalization Behavior Questionnaire; PPVT, Peabody Picture Vocabulary Test; SBIS, Stanford–Binet Intelligence Scales; TOVA, Test of Variables of Attention; TRF, teacher's report form; VMI, Developmental Test of Visual Motor Integration; WCST, Wisconsin Card Sorting Test of Problem Solving; WIAT, Wechsler Individual Achievement Test; WISC, Wechsler Intelligence Scales for ChildrenWJPB, Woodcock–Johnson Psychoeducational Battery; WPPSI, Wechsler Preschool and Primary Scales for Intelligence.

ASO, arterial switch operation; DHCA, deep hypothermic circulatory arrest; ELBW, extremely low birthweight (<1000 g); ENT, ear, nose, and throat; GI, gastrointestinal; HLHS, hypoplastic left heart syndrome; LF-CPB, low-flow cardiopulmonary bypass; NDI, neurodevelopmental impairment; NEC, necrotizing enterocolitis; PCA, postconceptual age; PDA, patent ductus arteriosus; SD, standard deviation; TPN, total parenteral nutrition; VLBW, very low birthweight (≤1500 g).

Focused epidemiological studies

Several research groups have utilized retrospective reviews of large-scale epidemiological datasets to investigate neurodevelopmental outcome following surgery and anesthesia early in life (see Table 46.3). One of these studies used billing codes to identify a birth cohort of children in the New York State Medicaid database who underwent inguinal hernia repair during the first 3 years of life and compared these patients with a sample of more than 5000 age-matched children without the same billing code [206]. After controlling for gender and birth-related complications, such as low birthweight, children who carried an ICD-9 (*International Classification of Disease*, 9th edition) procedure code for inguinal hernia repair were more than twice as likely than their age-matched peers without this procedural code to also possess diagnostic codes for developmental or behavioral disorders. Interestingly, highlighting the importance of co-morbidities in retrospective datasets, surgical patients were more likely to carry secondary diagnoses, including congenital anomalies of the central nervous system (10% of patients), birthweight less than 2500 g (32%), or perinatal hypoxia (17%) and were also more likely to be male and African-American. Accordingly, as the authors correctly pointed out, health and medical care utilization as well as the frequency of mental illness differ in this vulnerable Medicaid study group from the general population [207,208], significantly complicating the generalization of these findings to all patients undergoing surgery with anesthesia. A follow-up analysis of both the New York and Texas Medicaid database by the same group reaffirmed an increased rate of mental disorder, developmental delays, and attention deficit disorder in children undoing surgery before 5 years of age. However, the incidence of these disorders was equivalent if the surgery occurred before or after 2 years of age, thereby negating the practice of delaying surgery to reduce the potential of adverse neurocognitive deficits [209].

Epidemiological studies in more heterogeneous patient populations investigated the effects of anesthetic exposure either during cesarean delivery or for pediatric surgery prior to age 4 years on subsequent learning abilities [210,211]. After adjusting for gestational age, sex, birthweight, and American Society of Anesthesiologist (ASA) physical status, children who underwent multiple surgical procedures with general anesthesia prior to age 4 were found to be at increased risk for learning disabilities (35% of children), while children who only underwent one operation with anesthesia did not differ from unexposed children (21% learning disabilities) [211]. While listing the anesthetic regimen as predominantly halothane, nitrous oxide, and ketamine, the study was not powered to specifically analyze learning disabilities according to anesthetic drug. The important confounding influence of co-morbidities in this patient cohort was highlighted by the fact that almost half the previously anesthetized patients diagnosed with developmental disability had suffered from serous otitis media prior to age 4 years, a controversial predictor of neurocognitive disabilities, whereas only one-third of children without learning disabilities had experienced chronic ear infections [212,213]. However, a more definitive analysis including the unanesthetized children will be needed to assess this potential association.

In a second retrospective review, the same research group collected school and health data from almost 5000 children born via vaginal delivery and compared them to almost 200 neonates delivered via cesarean section with either general anesthesia, consisting predominantly of sodium thiopental, halothane, and nitrous oxide, or with about 300 children undergoing cesarean delivery with regional anesthesia [210]. The overall rate of potential learning disability was found to be 26% in this study population and did not differ between those children delivered with or without anesthesia. This finding could not have been easily predicted, because neonates in the general anesthesia group experienced lower birthweights, lower gestational age, and lower Apgar scores. In addition, their delivery was more commonly complicated by hemorrhage and eclampsia/pre-eclampsia, and was more frequently performed due to an emergency indication. Importantly, other risk factors independent from anesthetic exposure, such as male gender and mother's educational status, were strongly correlated with subsequent learning impairment. Children born to mothers with only some high school education were three times more likely to acquire learning disabilities than children from mothers with college education, suggesting powerful genetic and/or socioeconomic confounders. Interestingly, babies born with regional anesthesia were less likely to be diagnosed with a later learning disability than those born vaginally without anesthesia, most likely because their parents also tended to be better educated. Subsequent reports from this research group demonstrated that a pattern of repeated episodes of surgery and anesthesia were risk factors for an increased hazards ratio for learning disabilities [214] and attention deficit hyperactivity disorder (ADHD) [215]. It should be noted that these reports were based on patient cohorts from 1976 to 1982, thereby reflecting anesthesia practices from that period. A recent reanalysis of similar cohorts from 1996 to 2000 confirmed a similar hazards ratio for learning disabilities and ADHD with current anesthesia management techniques [216].

In a pilot study, Kalkman et al tried to control for the fact that a causal relationship between the requirement for surgery and subsequent behavioral and learning impairment independent of anesthetic exposure may impact neurodevelopment [217]. They examined behavioral outcome following similar urological procedures, performed either before or after 2 years of age. In this small retrospective study involving fewer than 300 patients, parental evaluations of their children's competencies and behavioral/emotional issues were based on a combination of the child's activities, social relationships, and performance in school. There was a non-significant trend towards a relationship between timing of surgery and the risk for developing behavioral problems, even after adjusting for confounders such as parental education, number of total anesthetic exposures, gestational age, and birthweight. However, the authors correctly point out in their discussion that the indication for the surgery or the timing of the procedure may not be entirely independent of factors that could have also influenced neurobehavioral development, such as co-morbidities. In other words, the decision to operate on a child prior to age 2 years could depend on the severity of symptoms resulting from the anatomical anomaly, which in turn may influence neurobehavioral development independent of anesthetic exposure.

Arguably the most vulnerable group of patients potentially susceptible to the effects of prolonged exposure to anesthetics and sedatives during an immature state of brain developmental is not otherwise healthy pediatric patients undergoing brief, elective surgical procedures, but rather premature infants requiring neonatal intensive care [164]. In this particularly vulnerable patient population, Rozé and co-workers employed a prospective, population-based study approach to evaluate the effects of prolonged sedation and analgesia on long-term neurological outcome, as measured by a validated neurocognitive assessment tool [218]. A birth cohort of preterm infants born prior to 33 weeks' gestational age, who were subjected to mechanical ventilation and/or surgery, were examined at 5 years of age using the Kaufman Assessment Battery for Children. While 74% of those treated with sedatives and/or analgesics for less than 7 days or not at all showed no disabilities, only 58% of those treated for more than 7 days were deemed without disability. However, after adjustment for significant confounders, such as birthweight, malformations, complications of pregnancy, characteristics of the delivering hospital, neonatal complications, need for surgery, and postnatal administration of corticosteroids, this association no longer remained statistically significant. While the study did not have the power to detect differences in disability of less than 10%, the long exposure times suggest that effect sizes during comparably briefer surgical anesthesia would be expected to be even smaller.

Big data analyses

Countries that have uniform educational assessment tools applied to a homogenous population afford a unique opportunity to compare the impact of a surgical intervention with concurrent anesthesia in naïve and surgical pediatric patients (see Table 46.3). Utilizing the Danish birth registry, Hansen and co-workers interrogated a database of all 45,000 children who underwent surgical operations in Denmark from 1977 to 1990 before 1 year of age, comparing the academic achievement of exposed children with that of the general Danish population. This was accomplished by linking a nationwide demographic database with a national hospital discharge registry and compulsory school completion test scores. While this approach is limited by the retrospective nature of an epidemiological methodology and the relatively outdated anesthetic methods, the large size of the cohort will help to control for many of the confounders discussed in this review [219]. In three separate reports, this approach resulted in a comparison of children who underwent either an inguinal herniorrhaphy, pyloromyotomy, or cleft palate repairs as infants with age-matched controls. No statistically significant differences were found between the exposed and non-exposed children after adjusting for known confounders [220,221].

Subsequent cohort studies in substantially larger surgical populations from Canada and Sweden revealed that exposure to surgery and anesthesia at age greater 2–4 years increased the odds ratio of cognitive deficits [222–224]. Scrutiny of the these large datasets reveal a lower percentage in academic achievement scores for toddlers undergoing ear, nose, and throat surgery [224]. This finding suggests that early derangements in hearing and speech may have an impact on subsequent cognitive domains assessed by school performance [225].

Prospective clinical investigations

Two high-profile multicenter clinical trials, the GAS and PANDA trials, have recently published their findings (see Table 46.3). The GAS trial is a randomized controlled trial that provided strong evidence that 1 h of anesthesia exposure in infancy does not result in neurological deficit as measurable at 2 years of age [226]. The subsequent 5-year assessment was consistent with the 2-year assessement [227]. However, assessments at both 2 and 5 years of age are insensitive in predicting long-term cognitive outcomes, so the trial does not rule out an effect on higher exectutive function, cognition, and memory. Moreover, the relatively brief exposure time of approximately 1 h does not allow for the assessment of dose–response relationships.

The PANDA study prospectively examined the impact of inguinal hernia surgery prior to 3 years of age on an extensive battery of neurocognitive tests [228]. When compared with a sibling cohort naïve to surgery and general anesthesia, no significant differences in these neurocognitive domains were detected. Due to the relatively brief surgical time, these findings are limited to less than 2 h of anesthetic exposure, which nonetheless represent the length of the typical pediatric surgical procedure. Furthermore, the measured outcome does not distinguish the respective impacts of surgery and anesthesia. Accordingly, both of these negative studies examined the impact of a relatively short exposure to general anesthesia and surgery, which does not exclude effects of prolonged exposures, and, importantly, are consistent with the lack of toxicity and neurobehavioral deficits observed in laboratory animals after short exposures to anesthetics.

The Mayo Anesthesia Safety in Kids (MASK) study performed a battery of neuropsychological tests on two age groups of subjects: 8–12 years and 15–19 years, who had general anesthesia before age 3 years from 1994 to 2007. There were 250 subjects in each age group: 150 with a single anesthetic exposure and 100 with two or more exposures. The control group of 250 unexposed subjects in each age group was propensity matched (attempting to reduce confounding by matching co-variates for characteristics such as age, prematurity, parental education, gender, etc.) [229]. A primary analysis failed to demonstrate deficits in general intelligence [229]. However, a secondary analysis of a subset of multiply exposed patients revealed a pattern of deficits in several neuropsychological tests [230]. The OTB has been shown to detect deficits in non-human primates exposed to ketamine [231]. The patient cohorts in the MASK study were also tested with the OTB and a primary analysis did not detect a difference in scores between the control and exposed groups [232].

KEY POINTS: EPIDEMIOLOGICAL, BIG DATA, AND PROSPECTIVE CLINICAL STUDIES

- Epidemiological studies into the long-term effects of anesthesia for surgery in early childhood are equivocal
- Early outcomes of the only prospective study using a 1 h exposure did not find any effects in addition to those of surgery performed with regional anesthesia
- Prolonged or repeated exposures, as well as long-term cognitive outcomes, require further research

Confounders and anesthetic protection

The presence of powerful, confounding perioperative factors in infants and children undergoing surgery and anesthesia and the lack thereof in animal studies represents a serious limitation of directly applying findings of preclinical studies to humans. Given the overwhelming evidence for pharmacological interference with the normal development of the central nervous system and the lack of anesthetics devoid of cytotoxic effects, one could be tempted to limit the use of suspect medications during medical interventions early in life. However, preclinical and human studies, as outlined earlier, have clearly demonstrated the increased morbidity and developmental abnormalities in animals and children exposed to unmitigated pain and stress. In this deleterious context, anesthetics have demonstrated protective abilities. Similarly, anesthetics may help alleviate the harmful effects from other perioperative stressors, such as inflammation and hypoxia-ischemia.

Inflammatory response

Following physical trauma or surgery, in addition to painful stimulation, neurological impairment of infants may also be related to long-term effects of the inflammatory response to the trauma or due to subsequent bacterial infections. Inflammation plays a major role in the evolution of cerebral injury after cerebral ischemia and traumatic brain injury. Within hours, transcription factors are activated locally in brain tissue and upregulate proinflammatory genes, including the cytokines, tumor necrosis factor α (TNF-α), interleukin 1b (IL-1b), and chemokines such as IL-8, interferon-inducible protein 10, monocyte chemoattractant protein 1, and fractalkine [233]. The production of these inflammatory cytokines promotes the transmigration of the inflammatory cells in the brain parenchyma. Experimental studies in animal models of focal ischemic stroke have suggested that leucocytes play an important role in the development of secondary injury after acute central nervous system injury [234].

In animal studies, local neonatal inflammation has led to excessive hyperalgesia in adulthood [235]. Chronic persistent inflammation experienced early during development is capable of altering behavior and sensitivity to pain later in life, especially in response to recurrent inflammatory events [236]. Systemic infection, as demonstrated in a mouse model of neonatal injection of live bacteria, leads to sustained increases in microglial activation in the brain [237]. In these animals, cytokine levels are exaggerated following an immune challenge in adulthood, which can lead to impairment in memory function [237]. Injection of lipopolysaccharides during a critical postnatal period can affect adult sensation and pain responses [238] and may also cause long-lasting increases in seizure susceptibility [239].

Several injectable and inhaled anesthetics have been found to modulate immune function. Inhaled anesthetics, such as isoflurane and sevoflurane, were shown to interfere with the leukocyte-mediated immune response, which may lead to immunosuppression following surgical procedures [240]. Ketamine and propofol have also been shown to play a role in modulating inflammatory or immune system function [241,242]. However, postoperative immune function may be influenced by dose and timing of the anesthetic drugs, pain, psychological state, perioperative blood loss, or hypothermia [243]. Similarly, opioid analgesics such as morphine have been found to suppress natural killer cell activity, inflammatory cytokine production, and mitogen-induced lymphocyte proliferation [244–246]. However, this response is modulated by the presence or absence of noxious stimulation and the type of opioid used.

Importantly, in an adult mouse endotoxemia model, isoflurane anesthesia immediately following the injection of a lethal dose of *Escherichia coli* lipopolysaccharide dramatically improved survival by 300% compared with unanesthetized animals [247]. In these animals, the administration of isoflurane, pentobarbital, or ketamine/xylazine attenuated serum levels of the inflammatory markers TNF-α, IL-10, and IL-6. These findings suggest that anesthetic administration during endotoxemia may not only improve survival, but also lead to attenuation of the inflammatory process.

In children, abdominal surgery can lead to significant increases in blood levels of the cytokines C-reactive protein and iIL-6 [248,249], which have been linked to increased complication rates in adult patients [250]. Moreover, invasive surgery in children has also shown to depress the patients' immune system [248,251]. Neuromotor abnormalities 6 months following open heart surgery have been correlated with plasma levels of IL-6 that were measured immediately postoperatively [252]. These findings justify further investigations into the long-term effects of anesthetics on cytokine levels and their potential for improved outcome.

Hypoxia and hypoxia-ischemia

Due to the brain's limited ischemia tolerance, even relatively brief episodes of inadequate supply of oxygen or nutrients can lead to long-term neurological impairment in critically ill children, irrespective of anesthetic exposure. Several patient populations at increased risk for neurological sequelae, such as infants with congenital heart disease and premature neonates undergoing surgical procedures, have been studied regarding their long-term neurodevelopmental outcome. Many of these studies demonstrate neurobehavioral abnormalities, motor deficiencies, and decreased intelligence in many of these patients [181,195,253–255]. However, none of these studies describe the anesthetic and sedative regimens utilized or discuss their impact on subsequent neurological outcome. Conversely, neonatal animal models have repeatedly confirmed the protective properties of anesthetics when administered during episodes of brain hypoxia-ischemia [256–262]. These findings in immature animals suggest that critically ill human neonates could potentially also benefit from these protective properties during clinical scenarios of neurological injury.

KEY POINTS: CONFOUNDERS AND ANESTHETIC PROTECTION

- Perioperative stressors and pain have been found to have deleterious effects on the developing brain
- Anesthetics might protect from these deleterious effects, further complicating research into anesthetic neurotoxicity

Co-morbidities and environmental factors

Even patients who do not suffer from life-threatening illnesses may have co-morbidities or be exposed to environmental factors outside of the perioperative period that may act as confounders for neurodevelopmental outcome.

Chronic otitis media

Relatively subtle medical problems, such as chronic otitis media, have been implicated in causing neurological impairment. While this effect is controversial and the exact mechanism unresolved, some studies suggest impairment in language development, literacy, and school performance following chronic otitis media with persistent middle ear effusions before the age of 3 years, while others were unable to find this association [212,213,263–266]. A recent epidemiological review of anesthetic exposure in young children suggested a trend towards an association between serous otitis media prior to the age of 4 and subsequent learning disabilities [211].

Chronic airway obstruction

In contrast to the contentious effects of chronic otitis media, the deleterious consequences of sleep disordered breathing on neurocognition are well documented. Children with obstructive sleep apnea may face behavioral abnormalities, lower intelligence, and diminished academic performance when compared with children with normal breathing patterns [267–269]. In these patients, surgical correction of the obstruction through adenotonsillectomy, which involves exposure to anesthetics, results in improved quality of life, behavior, and cognitive function [270]. Interestingly, even children with a pre-existing neurological condition, such as children with ADHD, demonstrated improved attention and decreased hyperactivity following surgical correction of mild sleep disordered breathing, despite the obligatory exposure to surgery and anesthesia [271].

Environmental factors

Environmental factors and exposures outside of the operating room can significantly interfere with normal brain development in humans. *In utero*, environmental compounds that may negatively influence subsequent neurocognition include such diverse substances as pesticides [272], methyl mercury, manganese, lead, and polychlorinated biphenyls [273]. Fetal exposure to prescription medications have also been found to lead to subsequent neurological sequelae, such as drugs for the treatment of acne [274], antihypertensives [275], and anticoagulants [276]. Prenatal exposure to alcohol and cocaine can impair children's speech, language, hearing, and cognitive development [277]. Intrauterine exposure to antiepileptic drugs, which share many pharmacodynamic properties with anesthetics, have been linked to brain structural abnormalities in young adults [278].

Other "environmental" factors known to affect learning and behavior in children are not as easily measured by subjective standards. Socioeconomic aspects related to family dynamics, neighborhoods, and school environments all contribute to development and learning in children. In this context, factors negatively influencing neurodevelopment include economic deprivation, minority and/or immigrant status, exposure to violence, and chronic poverty [279]. Even when providing a strong community and positive family support, differences in school quality, and negative encounters with teachers and/or peers, can dramatically affect development and learning outcomes [279]. Moreover, negative influences on neurocognition have also been suggested by recreational activities, such as prolonged television viewing or video game play [280–282]. Due to this myriad of confounders, studies into the potential detrimental effects of anesthetic exposures need to take these socioeconomic and environmental influences into account.

Genetic predisposition

Genetic composition can also affect neurodevelopment, even to a greater degree than environmental confounders. Close relationships have been demonstrated between genetic factors and cognitive abilities, including reading and mathematics skills and intelligence [283]. Moreover, genetic predisposition can influence the effects of environmental stressors and vice versa [284]. A compelling example of this is the co-mingling of genetic mutations in infants with congenital heart defects, extracardiac congenital anomalies, and neurodevelopmental disabilities [285]. This provocative finding suggests that patients undergoing corrections of congenital defects and anomalies may be predisposed to subsequent neurodevelopmental disorders regardless of the surgical or anesthetic interventions.

Investigating the effects of anesthetic exposure on learning abilities in young children with an emphasis on genetic predisposition, a twin study found no causal relationship between anesthetic exposure and cognitive impairment [286]. A review of data from more than 1000 monozygotic twin pairs in the Netherlands Twin Registry demonstrated that, while children exposed to an anesthetic prior to age 3 years scored significantly lower on educational achievement tests and experienced more cognitive problems than children not exposed to anesthesia, cognitive performance of the unexposed co-twin did not differ from that of the exposed twin [286]. While not addressing the effects of multiple exposures, no evidence for a causal relationship between anesthesia administration and later learning-related outcomes was found, but rather, the data supported the notion that anesthetic exposure prior to 3 years of age represented a marker for subsequent learning problems, regardless of exposure to anesthetics.

Ongoing and future research

Whereas animal studies seem to unequivocally demonstrate deleterious brain structural changes immediately following anesthetic exposure, long-term neurological abnormalities are not universally demonstrated. Moreover, human epidemiological studies examining developmental outcomes have returned ambiguous results. The immense impact of potential neurotoxicity induced by anesthetics and sedatives on child health necessitates significant future research efforts into this phenomenon. These efforts must include both preclinical studies investigating the exact structural changes, underlying molecular mechanisms, and affected neuronal and glial cell populations, as well as carefully designed clinical studies

delineating human susceptibility, while taking into full account the above-mentioned perioperative confounding variables. Given the public health impact of the potential neurotoxic effect of anesthetic drugs in pediatric patients, the US FDA and the International Anesthesia Research Society created a public–private partnership called SmartTots to support clinical investigators in this area. This collaboration has provided funding for ongoing research studies (e.g. the GAS and PANDA studies). Additional funding sources are required to promote discovery in and improve safety of pediatric anesthesia in young children.

Summary

In conclusion, in animals, neonatal exposure to all commonly used general anesthetics causes widespread neurodegeneration in a dose- and duration-dependent fashion, alters brain architecture, and can lead to long-term neurological impairment into adulthood. The phenomenon's exact underlying mechanism has not yet been determined, but does not seem to be entirely explained by anesthetic-induced neuronal inhibition and most likely affects several signaling pathways. Importantly, while cortical structural alterations are most pronounced during stages of brain development equivalent to the preterm and infant human brain, other brain regions are affected at a later stage and may be vulnerable throughout life in areas of ongoing neurogenesis. While the relevance of these preclinical findings for pediatric anesthesia is still unclear, in an overabundance of caution, the US FDA has released a warning regarding the prolonged and repeated use of anaesthetic and sedative drugs in patients aged 3 years and under. Emerging human epidemiological studies do not exclude anesthetics as a factor for impaired learning and neurodevelopment observed following surgical procedures. However, thus far, neurological sequelae observed in retrospective epidemiological studies seem sporadic and do not affect all exposed individuals to the same degree, suggesting a potential genetic or other influence on this association. Moreover, epidemiological studies cannot establish causality or distinguish between the differential effects of surgery and anesthesia on neurological outcome. Therefore, further well-designed preclinical and clinical studies are needed to determine the phenomenon's mechanisms, assess its clinical relevance, and devise mitigating strategies. The only randomized controlled trial in the field suggests that a 1 h sevoflurane exposure for inguinal hernia repair in infancy has little to no effect on neurocognitive function at 2 and 5 years of age [227,287]. Moreover, given the serious consequences of unopposed pain for the developing brain, there are at present no recommendations to alter current anesthetic practices [288]. However, clinicians are encouraged to keep abreast of scientific developments in the field.

KEY POINTS: SUMMARY

- All currently used general anesthetics have been found to be neurotoxic in neonatal animal studies
- The phenomenon's clinical relevance is unknown
- Lack of causative association between immediate structural abnormalities and long-term cognitive impairment observed in animals limit translation to humans
- Pain and stress in unanesthetized, immature animals and humans similarly cause brain structural and functional abnormalities, further complicating recommendations for clinical practice
- Additional studies in animals and humans are needed before recommending changes to current anesthetic and sedation management

CASE STUDY

A 2.5-year-old boy has a perimembranous ventricular septal defect (VSD) where the right coronary leaflet of the aortic valve prolapses into the defect and has started to cause mild aortic insufficiency (AI). His cardiologist is recommending repair in the next several months to prevent progression of the AI. The boy is otherwise healthy, developmentally normal, and has had one brief general anesthetic at age 18 months for myringotomy and tubes, which he tolerated well. The boy's parents have read the US FDA warning about prolonged (>3 h) or repeated anesthetics in children less than 3 years of age, and possible long-term effects on brain development, including "deficits in cognition, learning, and behavior" [289]. They have contacted you to ask whether they should have the surgery and anesthesia now, or wait until after their child's 3rd birthday. They also have read that dexmedetomidine might be a drug that does not cause brain damage in animals and want to know if he should have it added to the anesthetic.

Your response addresses two major concers: timing of the surgery and the type of anesthetic utilized for the surgery. Firstly, the risks and benefits of proceeding with the cardiac surgery should be weighed against the theoretical "toxic" effect of the prolonged anesthetic exposure. Three factors appear to induce anesthetic-induced neurotoxicity in laboratory models: (1) developmental/age susceptibility; (2) high dose of the anesthetic; and (3) prolonged duration of exposure. However, aberrations in neurobehavior have yet to be linked to equivalent measures in humans, because current clinical investigations have been equivocal. Delaying the surgical repair of this cardiac lesion has significant impact on both the physiological and neurological development of the infant. Furthermore, non-anesthetic drug related events have direct impact on morbidity. The APRICOT study of over 30,000 anesthetics in 261 hospitals in 33 European countries revealed a 5.2% incidence of severe critical perioperative respiratory or cardiac events,

with a 10–15% incidents in infants and neonates [290]. On the other hand, a study of near-infrared cerebral oximetry in 453 infants under the age of 6 months undergoing non-cardiac surgery revealed a very low incidence (2%) of significant cerebral oxygen desaturation, with these periods so brief that they were extremely unlikely to cause any long-term effect [291]. Finally, in the GAS study noted earlier, the relative risk of significant hypotension was 2.8 times greater with sevoflurane general anesthesia than with spinal anesthesia [292]. However, neurodevelopmental outcomes were not different between the groups [226,227]. Although additional data are needed, it seems less likely that physiological derangement is a significant explanation for anesthetic neurotoxicity.

Although preclinical reports demonstrate that specific anesthetic drug classes, GABA receptor agonists and NMDA receptor antagonists, are neurotoxic and lead to neurocognitive deficits, clinical investigations have also been inconclusive. Dexmedetomidine has been shown to mitigate isoflurane-induced neurotoxicity and is less toxic as a sole anesthetic in rodents [57,78,217]. An ongoing multicenter human randomized controlled trial comparing dexmedetomindine to sevoflurane on neurocognitive outcomes is underway [293].

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 47

Patient Simulation and its Use in Pediatric Anesthesia

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Introduction

Simulation has become a well-established part of the medical armamentarium, across most healthcare disciplines and venues. Why has this approach to teaching, evaluation, and research become so popular in medicine? What does it have to offer us in improving the delivery of pediatric anesthesia care to patients? How can we harness it to improve training paradigms, systems of care, and perhaps patient outcomes?

There are many types of simulation, using many types of equipment and facilities, but all can be neatly described as a creation of an artificial environment that replicates a real-world situation to achieve a particular objective (Fig. 47.1). In recreating a critical event after the fact, the objective may be the ability to better understand factors that lead to the undesirable outcome. In developing a crisis scenario for an imaginary patient, it may be the training of a new resident in the management of the medical events portrayed. The set of possible goals is as infinite as the human imagination.

In today's world of shrinking budgets, limited hours for trainees, and dispersal of patients from the inpatient to the outpatient setting, the degree of exposure to a wide variety of patients and critical situations for our trainees in medicine has decreased steadily. The challenge, to ensure that residents and students have the basic tools required to react appropriately to crisis situations or to diagnose rare illnesses, has increased. Private payers, the government, and the public are scrutinizing the medical system, demanding improved patient safety, a decrease in medical errors, and a means of measuring the training and performance of medical practitioners and integrated teams.

Using simulation, we can focus training hours for residents, nurses, staff, and students to elicit the maximum exposure to the specific types of patients and events deemed critical for complete well-rounded training in any particular field. Skills required by the US Accreditation Council for Graduate Medical Education (ACGME) in communication, professionalism, patient care, and medical knowledge can be practiced and tested. Teams can be drilled on critical actions, helping to ensure they will act together in appropriate ways when a real situation presents itself. Potentially harmful issues in the care environments can be identified which can result in changing processes, protocols, and equipment, prior to exposing our patients to imperfect systems. We can even research the effects of different protocols, equipment, environments, and staffing patterns to understand how they affect performance.

It is clear that simulation in medicine is here to stay. Putting it to good use will ultimately benefit not only patients, but improve professional mastery as well. This chapter will explore the many guises of simulation, several of the ways in which it is applied, and many of the applications and current state of simulation use in pediatric anesthesia. It will present a theoretical case of implementation of a simulation program, highlighting the challenges and possible solutions, hopefully assisting the reader in spreading the use of simulation to their own institution.

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

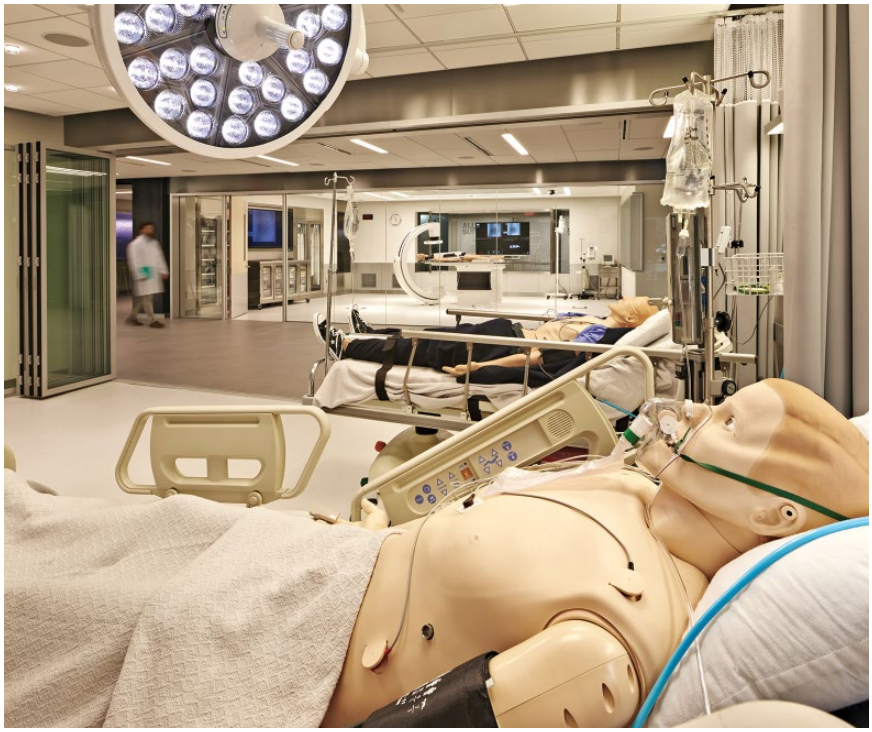

Figure 47.1 Simulation center with multi-bay set up – the Medicine Company Simulation Center designed by Paul Lukez Architecture. *Source:* Photo by Robert Benson, reproduced with permission of Paul Lukez Architecture.

Figure 47.2 Aviation simulation center showing a mock cockpit with computer-generated external environment for landing and take-off simulations. *Source:* Courtesy of Aerospace Industries.

History of simulation

Development in aviation

Aviation is often used as a metaphor for the practice of anesthesia. Both require a high degree of vigilance, attention to detail, and periods of relative inactivity interspersed with critical moments when the need to react quickly and effectively is mandatory to avoid poor outcomes. In both fields, lives are at risk if mistakes happen or if practitioners are unable to respond appropriately. Thus, it is helpful to understand the evolution of simulation in the aviation field and to understand how those methods have been adapted to the anesthesia environment (Fig. 47.2).

Figure 47.3 The Link Trainer built by Edwin Link for flight simulation. *Source:* https://commons.wikimedia.org/wiki/File:LinkTrainerSeymourIndiana.jpg (public domain).

In aviation, simulation in the form of mocked up aircraft controls was used as early as the manufacturing of the first aircraft, between 1920 and 1927. A more sophisticated, pneumatically driven flight simulator was invented by Edwin Link in 1929 (Fig. 47.3) [1]. Improvements have been made over time, with the modern computer-assisted simulators including high-fidelity computer graphics to create the illusion of the real world outside the cockpit [2]. These simulators are routinely used for both the training of new pilots and the review of crisis situations for experienced pilots. However, not all aviation simulators are for flight training, some focus on the physical aspects of surviving in worst case scenarios. In the military, dunker training, a simulated crash of an aircraft into water, is routinely used as a method both to train recruits in the appropriate reactions to survive such a crash and to weed out individuals who do not have the necessary skills and mental focus to respond appropriately in such a situation (Fig. 47.4). Army flight surgeon training includes a day of simulated water exercises, with long bouts in a pool in full flight gear, jumps from high boards into water, and escape from a simulated "downed helicopter" which flips underwater (personal experience, 1988, Army Aviation Medicine Course, Ft. Rucker, AL, USA). Other centers have developed similar training for private and commercial use.

Team training in aviation began in earnest after a series of crashes in the 1970s that were clearly not related to technical or equipment failures. One of the most famous was the Tenerife Airport disaster that occurred in 1977, involving two jet airliners that crashed on the runway at take-off, killing 583 people in all. Review of the crashes clearly demonstrated multiple failures including problems with communication and teamwork [3]. Crew resource management training, teaching crews to work together through a crisis in a simulated environment, was developed as a method to reduce the system and communication errors inherent in these complex environments [4].

Beginnings in medicine and anesthesia

Just as in aviation, simulation in medicine started with simple task trainers and moved to complex high-fidelity simulation environments. Patient simulation was first explored in medicine by Asmund S. Laerdal, with Peter Safar and James Elam, who created a mannequin, Resusci® Anne, for the training of mouth-to-mouth resuscitation (Fig. 47.5) [5]. She was introduced as the first patient simulator in 1960, her face based on the death mask of a young girl pulled from the River Seine at the turn of the century [6]. These first simulation systems were simple and generally task oriented, looking to teach individuals medical skills. High-fidelity patient simulation with the replication of a real-world environment using interactive mannequins, was introduced to anesthesia in 1967 with the Sim One Anesthesiological Simulator by Denson and Abrahamson [7]. Dave Gaba created the Virtual Anesthesiology Training Simulation System in 1986 as the first center-based, high-fidelity anesthesia simulator environment, allowing a full range of individual and team training, and research into the uses of simulation and the assessment of human performance [8].

In aviation, it took a series of disasters to stimulate the use of simulation and the birth of crew resource management training. In medicine, the widespread use of simulation was stimulated after a pivotal report from the Institutes of Medicine was released in 2000 that shocked the medical world. It publically exposed the high degree of medical error that routinely occured in the USA, stating that between 44,000 and 98,000 patients die in US hospitals due to avoidable medical errors each year. The report went on to recommend team training based on both aviation's crew resource management programs and simulation-based education and training in medicine, as a means to create a safer healthcare environment [9]. The widespread acceptance of these techniques and perceived utility in developing and maintaining critical skills is

Figure 47.4 Dunker training for aviation skills – Apache Modular Egress Training Simulator (Apache METS®) by Survival Systems, Inc.

Figure 47.5 Asmund Laerdal with Resusci Anne. *Source:* Courtesy of Laerdal Medical. All rights reserved.

exemplified by the approach taken by Harvard's malpractice insurance carrier, which offers a discounted insurance rate for staff who receive simulation training. This has resulted in all anesthesia faculty at Boston Children's Hospital participating in regular simulation training [10]. This approach has since been taken by other malpractice carriers.

Creating a simulation educational approach

The following situation will serve as an example of how a simulation program might develop in your own institution, with stem questions throughout the remainder of the chapter guiding you through the key areas that would be needed to plan and establish a program to support your own pediatric anesthesia clinical and educational goals.

You are an active member of your Pediatric Anesthesiology Quality Improvement Committee. At the last meeting, it was reported that your department has averaged one cardiac arrest per month for the last 6 months. You also recall that several people involved in these cases have found that the events appeared very chaotic and disorganized. In addition, it seemed that many of the people were unfamiliar with the use of the defibrillator. Most people you ask about previous resuscitations report that most of the issues seem to be related to problems in teamwork and communication (but usually not knowledge). You would like to find a proactive way to improve the response in future cardiac arrests.

You have been asked by the chief of pediatric anesthesiology to develop educational training sessions to target these issues. The hospital recently purchased several medical simulation manikins, and while you have no experience in medical simulation, you believe that it may be a useful modality for your project. You then meet with the simulation medical director, from the hospital-based simulation center, to explore this option. You have several questions to help you develop a better understanding of medical simulation and decide whether this is the right tool for your educational project.

Uses of simulation

Stem question:

- How and where can medical simulation be used, and does it have benefits over other educational tools, such as a case-based discussion?

As the need for simulation in medicine has grown, its use has moved from specialized simulation centers into actual patient care areas, such as hospitals and clinics. It has also progressed from a focus on single medical specialties, to involving all levels of healthcare professionals and disciplines, often working together. In the following section, the application of simulation to education, research, team training, professional evaluation, continuing medical education (CME), and systems evaluation will be reviewed.

Education

Medical schools are now using simulation as a regular part of their curricula, responding in part to the ethical dilemma of allowing novice students to learn techniques for the first time on real patients. From part-task trainers, which allow students to place IV lines or stitches, to standardized patient actors who teach students how to approach a patient, communicate, and perform a physical exam, simulation has become an integral part of medical student education. Five factors have been cited by Issenberg and Gaba as contributing to the increased use of simulation in medical school curricula: "a. problems with clinical teaching, b. new technologies for diagnosis and management, c. assessing professional competence, d. medical errors, patient safety and team training, and e. the role of deliberate practice" [11].

This trend toward simulation-based training has not been restricted to medical students. The continued shrinking of residency training hours is a worldwide trend [12]. In the USA, it is limited by the ACGME to 80 h per week, with strict rules about rest time between shifts [13]. While this may appear to be enough time to expose residents to the myriads of cases required, the restrictions have been felt across all medical disciplines and reflected in residency programs looking for ways in which to accelerate learning apart from the usual "apprenticeship" model currently practiced [14–19]. More and more, simulation is being used to fill the gap.

In anesthesia training, these tools have been used for many years. The operating room (OR) represents a unique environment in medicine. It is full of complicated technology requiring rapid responses, often coordinated among multiple team members when changes in patient status occur. Most medical students have very minimal exposure to this environment prior to residency training. This creates a strong impetus for simulation's use in anesthesia education for development of trainees' skills, both in basic understanding of the equipment and in responding to critical events as part of a team [3,14]. At Stanford, as for many other programs, training for anesthesia residents includes regular simulation training with an increase in the difficulty level of scenarios presented at each level of training. Trainees may spend a day in the simulation center, running through a series of simulation scenarios and debriefing sessions, examining their own performance and that of their peers in a formative review format [15]. *In situ* training, with shortened, focused simulation events, is also becoming more common (Fig. 47.6).

Trying to understand human performance factors, which are critical in achieving positive outcomes in crisis situations, has been a widely appreciated practice since it became a focus in evaluating a series of severe accidents in the aviation industry in the 1970s. These critical human performance factors have been heavily studied and described [16]. Recognizing their importance to a wide variety of situations in medicine, many of the factors are also listed as required competencies for all medical residents by the ACGME [17]. Gaba has also described a set of skills that correlate with successful performance during a simulated anesthesia crisis (anesthesia crisis resource management or ACRM) [18]. Many of these human performance skills, described as non-technical skills by Flin and colleagues in *Safety at the Sharp End: a Guide to Non-Technical Skills* are also noted as essential for effective team work during a crisis within multiple industries [3]. The concurrency in the description of these skills is evident in the listing of some of the factors from these three systems: ACGME, ACRM, and non-technical team skills (Table 47.1). They all have aspects of human behavior and communication as key components, in order for the team to work together well during complex situations. Because of simulation's unique ability to bring team members together to actively work through a scenario, these communication and teamwork skills can be practiced and reviewed in a way not possible using other learning methods, such as table-top case-based discussions. Medical simulation courses, such as the ACRM course based on aviation's crew resource management principles, are geared to help teach these critical human performance factors (see section "Team training and ACRM principles") [11,19]. Simulation, with debriefing sessions focused on these non-technical skills, can help improve overall competency while raising the awareness of these critical teamwork skills [20].

Figure 47.6 *In situ* simulation training with anesthesia resident.

Table 47.1 Comparison of non-technical and team skill characteristics from three systems: non-technical team skills as described by Flin et al, ACRM performance goals, and ACGME trainees' performance criteria

Non-technical skills	Behaviors	ACRM key points	Behaviors	ACGME competency areas*	Interpretation: demonstrated behaviors for anesthesia residents at Stanford University
Situation awareness	• Gathering information • Interpreting information • Anticipating future states	Maintain situational awareness	• Anticipate and plan • Maintain vigilance • Know the environment • Assign team member to monitor patient if involved in task	Systems-based practice Patient care	• Acts to deliver anesthesia services efficiently • Able to call on system resources/providers to improve care • Gathers adequate preoperative information and recommends appropriate diagnostic steps/consults if preparation is inadequate
Communication	• Sending information clearly and concisely • Including context and intent during information exchange • Receiving information, especially by listening • Identifying and addressing barriers to communication	Communicate effectively	• Clearly state requests and commands • Avoid statements into "thin air" • Close communication loop • Foster open exchange between team members • Deal with conflict: what is right for patient not who is right	Interpersonal and communication skills	• Listens effectively, allows patients/families to ask questions. • Leader in the healthcare team • Explains procedures and anesthesia plans appropriately for consent • Creates sound relationship with patient
Teamwork Leadership	• Supporting others • Solving conflicts • Exchanging information • Coordinating activities • Using authority • Maintaining standards • Planning and prioritizing • Managing workload and resources	Take an appropriate leadership role	• Ensure the team knows who is in charge • Prioritize and assign tasks • Make decisions • Elicit participation • Be assertive while respectful	Professionalism	• Takes responsibility and is appropriately self-confident • Respectful, courteous and compassionate • Adheres to professional ethics and respects patient privacy
Decision making	• Defining problem • Considering Options • Selecting and implementing option • Outcome review	Utilize all available resources	• All team members • Equipment • Cognitive aids • External Resources: call for help	Patient care	• Carries out safe and rational anesthetic after proper selection of drugs/techniques and responds appropriately to changes in anesthetic course
Managing stress Coping with fatigue	• Identifying symptoms of stress • Recognizing effects of stress • Implementing coping strategies • Identifying symptoms of fatigue • Recognizing effects of fatigue • Implementing coping strategies	Distribute the workload	• Assign tasks appropriately to skill of individual • Delegate manual tasks unless particular skills required; • Scan for overload or fatigue of team members	Patient care	• Possesses appropriate technical skills in airway management (mask, ETT, LMA, FOB) and vascular access (IV, CVP/PA, arterial line)

* Only includes the subset of ACRM and ACGME areas for which there was some correlation with the other system behaviors noted.
ACGME, Accreditation Council for Graduate Medical Education; ACRM, anesthesia crisis resource management; CVP, central venous pressure; ETT, endotracheal tube; FOB, fiberoptic bronchoscope; IV, intravenous; LMA, laryngeal mask airway; PA, pulmonary artery.
Source: Reproduced from Flin et al [3] with permission of Taylor and Francis.

Most anesthesia residents may spend very little time in pediatric anesthesia training: often just 2–4 months during their 3 years of residency. The approach to patients and families, the method of preoperative sedation and preparation, the induction techniques, and the types of crisis that occur in pediatrics are very different to those in adult anesthesia. This limited clinical time, along with the extensive behavioral knowledge set required, creates an ideal situation for the application of simulation training to enhance the rapid acquisition of this specialized skill set.

The reasons that simulation functions as an effective tool within medical education has been studied, but with some inconsistent results. Issenberg et al searched the literature to identify the key factors of simulation noted to be associated with effective learning [11]. Listed in Table 47.2, the most common element seen in 47% of the journal articles they reviewed was "providing feedback." During high-fidelity patient simulation this is usually done during a debriefing session that immediately follows the simulated scenario. Effective debriefing engages the learners to make an introspective review of the scenario events, soliciting input from all participants. Other common factors include "repetitive practice," cited in 39% of journal articles, and "curriculum integration" in 25%. These two factors require a standardized design to scenario development, which allows for repetition and inclusion in standard curriculum, for consistent objectives and goals [21].

Table 47.2 Factors associated with effective learning

Factor	Relative frequency of citations in reviewed articles	Description
Providing feedback	15.6	Educational feedback
Repetitive practice	13	Repeated practice of behavior
Curriculum integration	8.3	Integration of simulation-based exercises into the standard medical school or postgraduate educational curriculum
Range of difficulty	4.6	Range of task difficulty level
Multiple learning strategies	3.3	Adaptability of high-fidelity simulations to multiple learning strategies
Capture clinical variation	3.3	Capture a wide variety of clinical conditions
Controlled environment	3	Controlled environment where learners can make, detect, and correct errors without adverse consequences
Individual learning	3	Reproducible, standardized, educational experiences where learners are active participants, not passive bystanders
Defined Outcomes	2	Clearly stated goals with tangible outcome measures, appropriate to level of training
Simulator validity	1	Degree of realism

Source: Reproduced from Issenberg et al [11] with permission of Taylor and Francis.

Templates have been designed to facilitate standardization of scenario development and consistency in repeated use of single scenarios [22] (see later in this chapter).

Performance of these types of dynamic, interactive, and interpersonal human performance skills is difficult to observe and evaluate in the normal testing situation. Simulation provides a venue to demonstrate or practice these skills, allowing feedback on effectiveness of leadership, communication, and decision-making abilities [23,24]. The use of simulation for the evaluation of performance of trainees has long been an area of considerable interest [25]. While it has been difficult to convincingly link performance measurements in simulated environments to real clinical situations, tools are beginning to be developed that demonstrate improved reliability and validity [26,27]. Finally, another factor driving the increased use of simulation in medical education is the perceived effectiveness of the learning method itself. By using high-fidelity patient simulation, the learner becomes immersed in the educational domain, participating actively in the learning environment rather than passively absorbing information as in a traditional lecture. This type of performance learning has been shown to be more effective for adult learners, and information is retained at a higher rate than information imparted from passive learning sessions [28,29]. The evocation of emotional responses also improves the learning process, increasing retention as well [30]. Simulation provides just such a learning environment.

Research

Simulation's applicability to research is beginning to be fully realized. From answering basic questions in human performance to teasing out ways to improve protocols, techniques, systems, and equipment, simulation can be used not only for training but to answer multiple questions regarding several types of issues within the healthcare system.

Research in human factors and performance is facilitated with the use of simulation. This has been a particularly fruitful area of investigation, because of the ability to recreate relatively uniform circumstances for testing with more than one practitioner group [31]. Theoretically, questions regarding practice performance can be answered, which otherwise might demand an approach using retroactive reviews of multiple charts, thereby including many uncontrolled assumptions. Investigations have been conducted into human interactions with the environment, fatigue, and response to the stressors inherent in caring for patients during a crisis [32,33]. Looking at the effectiveness of flight crew coordination and the ability to perform to task would be difficult or impossible without the use of a high-fidelity simulated environment in which to create a crisis scenario and elicit a team response [34].

Finally, not only has high-fidelity patient simulation facilitated obtaining answers to many primary research questions, it has also been used by researchers to improve the effectiveness of their clinical trials. Problems in protocol design, procedures, and data collection tools can be exposed prior to the beginning of the trial, saving time and decreasing costs. Simulation can also be utilized to train evaluators and coordinators, helping decrease errors at the start of the trial and ensuring better compliance with trial rules [35,36].

Team training and ACRM principles

Stem question:

- What is crisis resource management?

Anesthesia crisis resource management refers to a system of appropriate team and individual responses to a crisis in a patient under anesthesia. This system is based on principles and techniques derived in aviation: crew resource management. Training in these techniques teaches crews to work together through an aviation crisis in a simulated environment, and was developed as a method to reduce the system and communication errors inherent in the complex aviation environment [37–40]. The primary goal of crisis management is to detect problems early in its evolution, then mobilize an appropriate response in order to prevent an adverse outcome.

Many of the keys to ACRM revolve around maintenance of situation awareness and effective dynamic decision making. Leadership ability and communication among team members is essential, as is the effective use of all available resources. Figure 47.7, an example of a cognitive aid, includes the behaviors that are associated with an improved team response to crisis as taught in ACRM [23].

One of the mechanisms that helps create an effective team is the concept of the "shared mental model," that is the mutually agreed upon set of knowledge and processes used to explain or predict events to achieve certain goals safely and effectively [41,42]. While team training began in the military in the 1950s and 1960s, team training based on the shared mental model concept was first instituted in the 1990s [26]. Crew resource management, used in aviation for many years, works with shared mental models, including a variety of training methods, including simulation, to teach appropriate team skills. These teamwork functions are fleshed out from work that focused on the macrocognitive skill sets required to achieve effective team management of complex tasks [43]. Included are leadership and communication skills such as those outlined in Table 47.1, and others such as adaptability, back-up behavior, mutual trust, and team orientation. Simulation is an effective tool to create a situation in which these skills can be teased out and practiced [44].

Professional evaluation

The ability to grade performance in medicine has long been fraught with difficulty. Testing paradigms that focus on the ability to regurgitate medical knowledge in board examinations ignores the multiple skill sets known to impact performance in real patient care situations, including communication and professional skills, and ability to work in an acute crisis situation within a team structure. Across healthcare disciplines, simulation has been adopted for training and assessment because of its ability to provide the opportunity for learners to demonstrate these critical skill sets [44]. Both standardized patients and mannequin-based simulation activities have been used for summative assessment, and in some cases, are necessary certification and licensure requirements [45,46].

Various simulation modalities, ranging from partial task trainers and mannequins to computer-based case

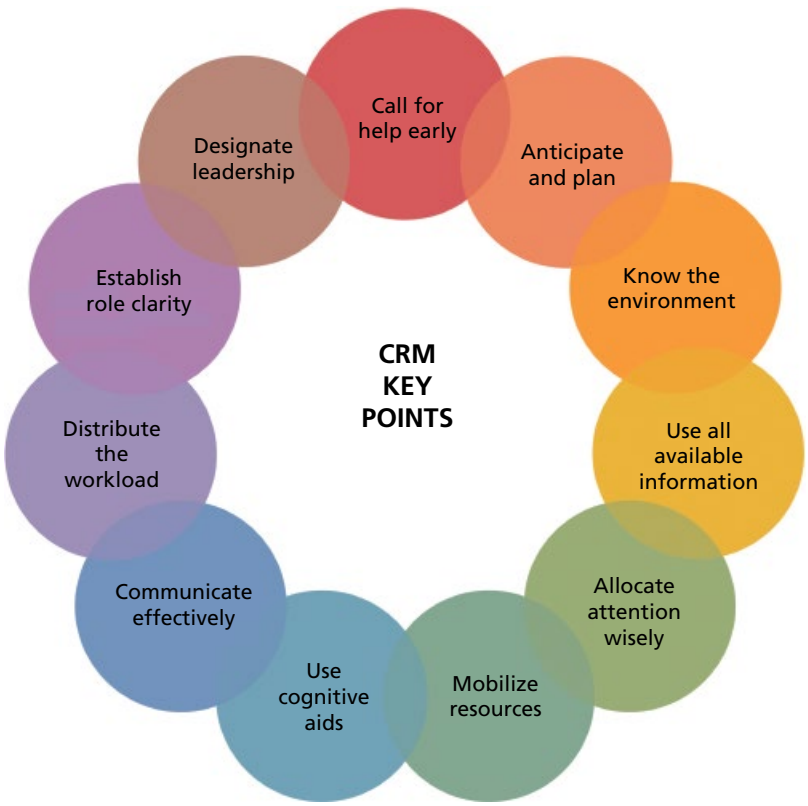

Figure 47.7 Cognitive aid used in the Center for Immersive and Simulation-Based Learning (CISL) at Stanford, crisis resource management (CRM) course. *Source:* © 2008 Diagram by S. Goldhaber-Fiebert, K. McCowan, K. Harrison, R. Fanning, S. Howard, D. Gaba. Creative commons 3.0. http://emergencymanual.stanford.edu/images/7.png.

management scenarios have been adopted for professional assessment in anesthesiology [47]. Using simulation, particular situations can be recreated for the testing of competence. For limited situations, experts come together to develop checklists, which can be tested for reliability and validity, permitting "credentialing" for that particular situation [37,48, 49]. Broadening evaluation in order to comment on a practitioner's ability to practice is fraught with difficulty due to the lack of a widely accepted assessment tool [50]. Despite these challenges, this model is already in place in some countries, and is being used to allow professional accreditation, such as passing of board certification exams [51]. Testing systems are being investigated and developed for residency training in several fields, including anesthesia [52].

While not being used for evaluation, the American Board of Anesthesiology (ABA) has medical simulation exposure as part of the optional requirements within the Maintenance of Certification in Anesthesiology 2.0® Part 4: improvement in medical practice section for board recertification [53]. According to the ABA, simulation activities performed at an endorsed center provides "Simulation that realistically replicates clinical scenarios that participants can work through in a manner similar to what they may experience in clinical practice." In addition, in 2018 the ABA added Objective Structured Clinical Examinations (OSCEs) to the Applied Examinations. The ABA OSCE-type examinations will focus on demonstrating technical and communication skills during several perioperative situations. The robust active learning component within medical simulation makes this an excellent tool to prepare learners for these types of examinations [53].

Systems evaluation

Simulation methods have been used to evaluate the effectiveness of hospital systems, allowing targeting of systematic threats. Team responses to disasters in which multiple patients arriving in the emergency department can be evaluated, as can the ability to respond in a timely and appropriate way to hospital emergency codes [46,54]. The ability to respond to crisis in the use of extracorporeal membrane oxygenation for neonates can also now be evaluated (Fig. 47.8) [55]. Simulation has been used to review new spaces prior to being used for patient care, ensuring adequate equipment, space, workflow, and familiarization of staff with the environment [56]. Prior to opening the new operating rooms at Lucile Packard Children's Hospital in Palo Alto at Stanford University, simulations of the complex information technology systems were created to assist with scheduling of surgical cases and recording of surgical care in nursing and anesthesia documentation. The simulations, which also tested the ability to perform the anticipated surgical cases, were completed prior to using the new OR suites. All surgical services were scheduled for a simulation session in which a test case was scheduled, all required team members were present, and all equipment and supplies were reviewed to ensure no significant faults remained prior to scheduling the first patient. Issues revealed included critical equipment that was discovered to be missing, process and policy problems that interfered with effective communications, and poor patient flow. These problems were then addressed proactively, eliminating their possible impact on actual patients (Fig. 47.9).

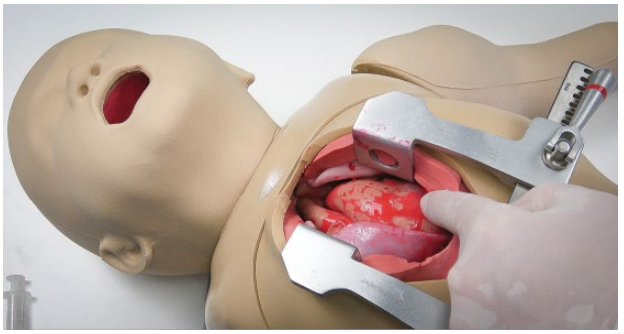

Figure 47.8 The Surgical Sam team trainer is an open-heart simulator that can also be used for ECMO training, co-developed by the Chamberlain Group and Boston Children's Hospital (SIMPeds Program). *Source:* © 2017, The Chamberlain Group, LLC.

Figure 47.9 *In situ* simulation in Lucile Packard Children's Hospital Stanford operating room – team training for improved response time to critical events.

KEY POINTS: USES OF SIMULATION

- With limited hours for standard teaching curriculum and exposure to patients, simulation can fill a large teaching gap at both the medical school and resident level, with ability to target specific learner groups, patient types, procedures, and disease states
- Team training is particularly well suited to a simulated model, enabling practice of crisis resource management skills, assessment of team skill abilities, and enhancement of integrated teamwork
- Simulation can be used for evaluation of everything from the systems affecting the patient care, to the abilities of the team members in responding effectively together, to individual abilities to integrate knowledge and performance in the delivery of care
- Research into human factors and environments of care affecting performance is extremely effective using simulation

Types of simulation

Stem question:

- What type of educational activities should I plan?

Part-task trainers

The performance of procedures requires technical skills that rely on mechanical dexterity. An understanding of the basic mechanical steps can be acquired with the use of part-task trainers; this trainer is typically a portion of the whole patient that represents some part of a patient or physical reality. For instance, a mock arm, with tubing representing vessels, can be used to practice the steps required for starting an IV. A mannequin head, with tongue, pharynx, glottis, larynx, and trachea, can be used to practice mask ventilation and intubation. These trainers can be as simple as a block of gelatin encompassing a target for practice doing ultrasound-guided regional blocks to sophisticated computer-driven sensor-laden systems for the practice of laparoscopic surgical manipulations [57,58]. Complex haptic devices are being developed that meld computer-based virtual simulation and hands-on control of devices [59,60].

Just as adult simulation high-tech mannequins have "evolved" to smaller pediatric models, part-task trainers are now being created to simulate pediatric patients. Limbs for vascular access, "intubateable" neonatal heads, and ultrasound-guided central vascular access trainers are just some of the items that are currently available. Figures 47.10–47.14 represent some of the current pediatric task trainers and simulated infant parts being marketed. As interest in these products has grown, the variety and scale of available models has increased significantly.

Computer-based simulation systems

Sophisticated computer programs have been written to enable practice of various anesthesia tasks and medical crisis scenarios in a virtual format. These types of systems have the advantage of being available at any time to allow learners the chance to practice whenever they have the time (Fig. 47.15) [61,62]. Using the input of large amounts of data, from systems such as magnetic resonance imagining (MRI) and models of human anatomy, based on various patients' idiosyncrasies, this technology can finally be realized and used to provide learners with the type of variety that will be presented to them in practice [63,64]. Some internet-based systems, based on avatars, facilitate multiple users coming together in a virtual world to act as team members in various clinical scenarios. This keeps facility and material costs down, but relies on scheduling participants appropriately, having multiple access ports available, and a teacher/facilitator to guide the action [65].

Other systems allow for a melding of simulated transparency of functions in real time, enabling a deeper understanding of both mechanical anesthesia systems and simulated patient physiology [66]. Taking virtual systems and task trainers and combining them with a full-scale simulator allows for another viewpoint on increasing the perceived reality of the scenario depicted [67,68]. Currently, the American Society of Anesthesiologists (ASA) has partnered with CAE Healthcare to develop a virtual, anesthesiology-based CME product.

Figure 47.10 Infant caudal trainer. *Source:* Courtesy of Enasco, Inc.

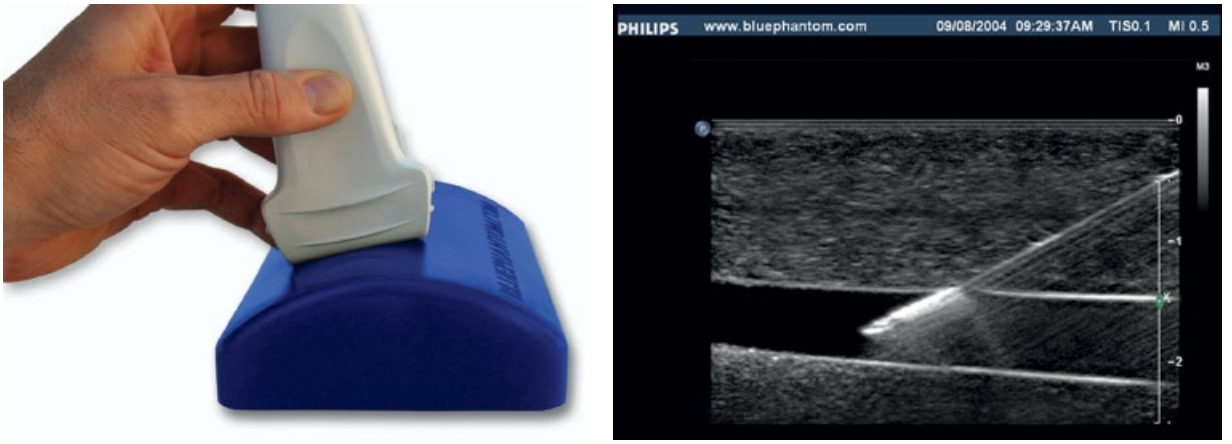

Figure 47.11 Ultrasound-capable simulator. *Source:* Courtesy of Blue Phantom.

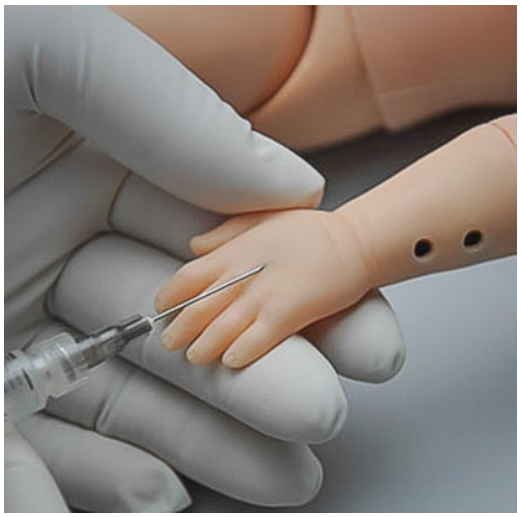

Figure 47.12 Intravenous insertion simulation – Gaumard Premie HAL simulator. *Source:* Courtesy of Gaumard Medical.

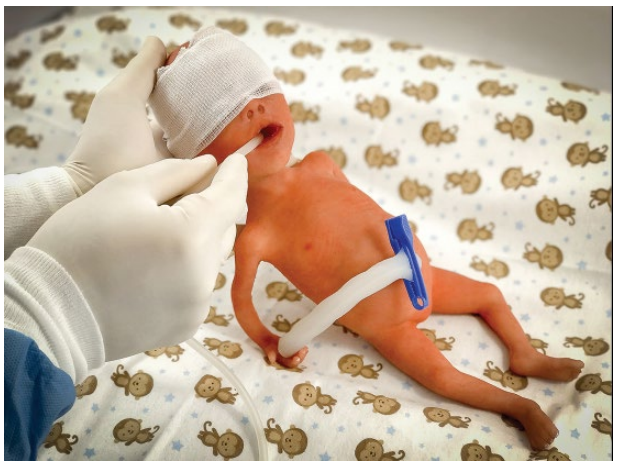

Figure 47.13 Extreme premature simulator showing oral gastric manipulation. *Source:* Courtesy of Medical X.

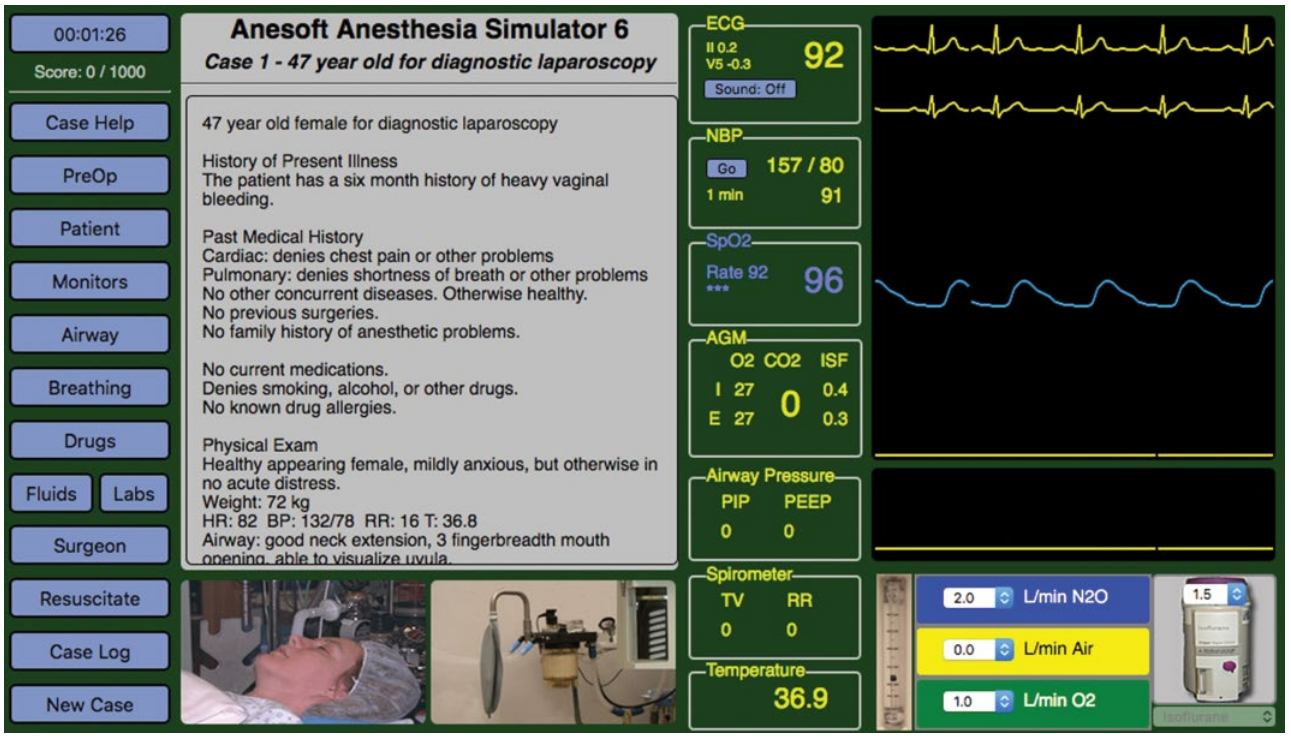

Figure 47.14 Pediatric anesthesia simulation interactive software by Anesoft (Anesthesia Simulator 6). *Source:* Courtesy of Anesoft.

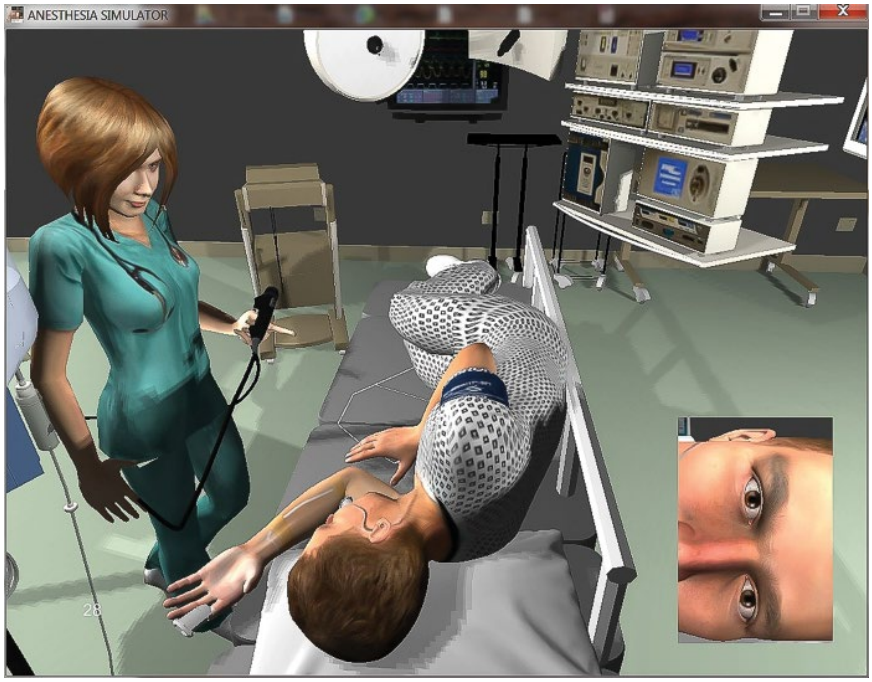

Figure 47.15 Anesthesia simulator program by Chao Mei. *Source:* Courtesy of Chao Mei PhD.

The existing product information currently has no timeline for release and suggests that the product will focus on adult perioperative scenarios [69].

High-fidelity patient simulation

High-fidelity patient simulation refers to simulation scenarios that closely replicate real patients and clinical situations usually using interactive mannequins as the simulated patient, making it easier for participants to believe in the reality of the situation depicted, and thus to apply realistic responses. In any high-fidelity simulation, a learning or evaluative goal is selected, and a scenario is developed to create the opportunity for the goal to be achieved. Using a simulated environment and tools, such as the high-tech mannequins that both simulate a patient's responses to interventions and allow varying degrees of interaction with the participants, the scenario is played out. Expert facilitators in various roles encourage the participants to react to the cues supplied for the scenario and supply real-time feedback supporting the scenario as it unfolds.

High-tech mannequins

High-tech mannequins have been developed by several companies for use in medical simulation. These mannequins are made to represent patients of varying ages, from neonates to adults, and come equipped with mechanical and electrical parts to produce various effects from coughing and wheezing to hypotension and cyanosis (Figs 47.16 and 47.17). Heart tones, chest wall motion, palpable pulses, and closure of the airway can all be mimicked. Interventions are possible including bag–mask ventilation, intubation, IV line placement, defibrillation, and in some cases chest tube insertion or cricothyrotomy. A vital signs monitor shows the patient's current status and can be manipulated by a technician in response to interventions by the simulation participants.)

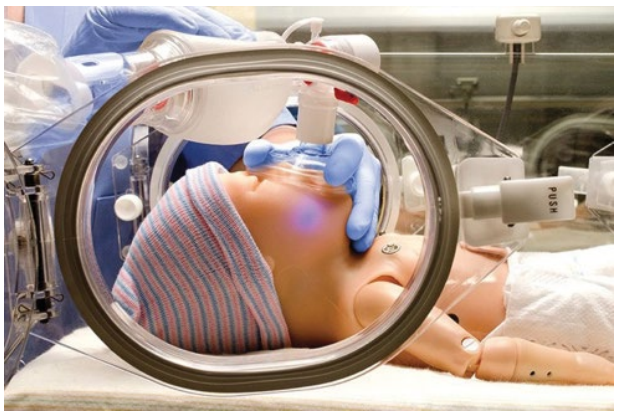

Figure 47.16 Neonatal simulator. *Source:* Courtesy of Gaumard Medical.

Figure 47.17 Premature simulator. *Source:* Courtesy of Laerdal Medical.

Some simulation systems include software that has been created to provide automatic realistic responses to interventions including chest compressions, ventilation, and medication administration. Table 47.3 provides a review of the features

Table 47.3 High-fidelity pediatric simulators are available in premature, neonatal, infant, toddler, and small child sizes from various manufacturers with a variety of features*

Basic features	Advanced features
Airway/respiratory	
Ability to perform positive pressure mask ventilation	Exhaled carbon dioxide measured synchronized with breath sounds
Ability to perform tracheal intubation	Internal air compressor
Right/left mainstem bronchi for differential ventilation/intubation	Ability to perform tracheostomy
Spontaneous breathing	Chest needle decompression detection
Nasal intubation	Chest tube insertion with fluid output
Laryngospasm	Measurable pulse oximeter with actual patient monitors
Blockage of airway, right or left	Ability to ventilate with dynamic airway pressure monitor
Retrograde intubation	
Tongue edema	
Pharyngeal edema	
Lung sounds	
Cardiovascular	
Ability to perform chest compressions	Improved defibrillation and pacing
Heart sounds	Measure BP with actual patient cuff and hear Korotkoff sounds
Carotid and radial pulses	Measurement of compressions and ventilations
Palpable brachial and femoral pulses	Femoral access sites
Interosseous access	Subcutaneous injections
Peripheral venous access sites with drains and flashback	
Ability for catheter placement in umbilical vessels	
IM injections	
Neurological	
Seizure-like movement	Adjustable fontanelle
Vocal sounds	Eyes that blink with variable pupil size
Muscle tone in limbs	
Gastrointestinal/urological	
Ability to place OG/NG tubes	Bladder fillable and able to place Foley catheter
Auscultate bowel sounds	Enema administration
Gastric distension with esophageal intubation	
Other	
Color change with conditions (cyanosis)	Tearing and secretions for ears, eyes, and mouth
Replaceable parts	Ability to track some administered medications
	Washable/reusable parts

* Not all features are available in every model and different manufacturers choose different features to highlight. Premature models have constraints in types and number of features due to size. Most manufacturers charge more for advanced features.
BP, blood pressure; IM, intramuscular; NG, nasogastric; OG, orogastic.

currently available in common pediatric mannequins. Many of the mannequins have common features that allow for basic interactions to control the airway and respirations. Some mannequins provide the ability to perform a variety of invasive interventions. The "consumable" parts, skin and bone, etc., often need to be replaced after a certain number of uses. Setting some rules of engagement for learners with the mannequins before beginning the simulation can allow for near-realistic performance while protecting the unnecessary replacement of mannequin parts. Warranties are often available for purchase, enabling protection of this considerable investment.

Standardized patient actors

When interpersonal and communication skills were made one of the core competencies by the ACGME, the central importance of clear and effective communication in medicine was emphasized. Team communication is very important and can be practiced during simulated scenarios involving mannequins, but effective communication with a patient or family member cannot be simulated well with these tools. Thus, standardized patient actors are frequently being used in many simulated situations in both medical schools and other educational venues (Fig. 47.18) [70]. Using patient actors allows learners to interact with a "patient" or "family member" capable of evoking convincing emotions by improvising and adjusting their response based on the learner's responses. This type of high-fidelity simulation can also create complex and subtle interactions, with the ability to practice the most basic features of medicine: effective history taking or developing a caring and empathetic approach. Videotaping of the interactions for review during debriefing also helps the learner see how they come across to others and the non-verbal communication cues they may be using unknowingly.

This type of simulation has now been incorporated into the United States Medical Licensing Examination® for medical students, in step 2 of the exams. Students must effectively interact with trained patient actors to obtain a history and physical examination, thereby demonstrating not only technical medical knowledge but also the effective communication and interactive skills critical to becoming a physician [44,71]. In addition, the ABA added an additional OSCE-type examination, which is required as part of getting the initial board certification in anesthesiology.

Figure 47.18 Confederate actor playing the role of mother of a simulated infant in a medical student training exercise.

Figure 47.19 A hybrid simulation combines an infant simulator with a standardized patient as the mother to assist in obstetrics simulation at Stanford Children's Hospital.

Hybrid simulation

Hybrid simulations refer to the combination of any two types of simulation, whether it involves the use of a part-task trainer combined with a mannequin, or a patient actor and a simulated body part that can be manipulated by the participant to treat the simulated situation (Fig. 47.19). For instance, a part-task trainer arm can be attached to a patient actor's arm, and used to start an IV line, or a delivery task trainer can be combined with a patient actor for simulating an infant delivery. The patient actor can then provide active and realistic responses to the participant as they attempt to provide the indicated procedural care. This combination of task training and communication with the "patient," such as suturing of a wound or injection of a local anesthetic, creates a much more instructive and meaningful situation for the learner and allows a substantially greater understanding by an evaluator of the participant's skill set and patient management style. The tasks that are performed on patients never happen in a vacuum. Learning to deal with the patient's reactions to the procedures performed is critical for effective patient care. This hybrid model allows the integration of these components for a much more realistic and effective training scenario [72].

KEY POINTS: TYPES OF SIMULATION

- There are many types of simulation, all of which serve specific learning goals, including part-task trainers, standardized patient actors, computer-based simulation, virtual reality simulation, and high-fidelity simulation
- High-fidelity simulation attempts to create as real an experience as possible using interactive patient mannequins that exhibit multiple "physical" signs, can be manipulated in realistic ways, such as intubation, and can respond to learner manipulations
- Hybrid simulation uses combinations of simulation methods, such as part-task trainers with standardized patient actors, to enhance the learner's ability to interact in a realistic manner throughout the scenario in all performance domains

Organizing and running high-fidelity simulation sessions

Stem questions:

- What are the common challenges when using medical simulation?
- What type(s) of learners should attend the session?
- How can an effective educational activity using medical simulation be designed?
- What type of orientation should a learner have prior to using medical simulation?

Elements of high-fidelity patient simulation

Preparation

Prior to starting a simulation scenario, the participants should be familiarized with the simulation environment, the tools to be used, and the roles they will play – elements critical in enabling a positive learning experience. Just as important is ensuring that all learners understand the goals of the exercise and how their performance will be assessed. Some essential points to cover include: goals of the session, who will be participating, who will be facilitating, and how to engage and behave in the environment.

When the simulation scenario is focused on formative, rather than summative, assessment, removing any sense of threat from the session will help ensure a positive learning frame of mind. Many simulation centers ask the participants to sign a consent that emphasizes the importance of keeping the elements of the session, both the scenario and the performance of individuals, confidential. This can help decrease the concern that an "inadequate" performance will be talked about after the event. In these types of learning sessions, participants are told that there is no penalty for "failing" in a crisis simulation, allowing them to take risks in their interactions and actions during the scenario, that will enable their learning.

The scenario

A scenario is created, somewhat like a storyboard for a movie, which sets the framework for the simulation session. It is based on both the goals and the anticipated participants. Content experts are critical in designing a realistic and relevant simulation scenario. No matter what framework is set for the situation, the particular participants during the session will bring their own experience and knowledge base to the interpretation of the scenario, and will often react in unexpected ways. Thus, content experts are key during the running of the scenario as well, allowing credible manipulation of patient vital signs and reactions to any actions made by the participants.

Debriefing

Stem questions:

- What is the purpose of the debriefing portion?
- What are the key elements of an effective debriefing session?
- Are there any risks inherent in running simulations and debriefing?

Arguably, the greatest learning from a simulation session occurs during the final section, called the debriefing. Debriefing has its roots in the military and aviation, where a group leader brings the unit together after an event or mission to review outcomes, both positive and negative, and to develop some lessons learned to apply to the next mission. Similarly, in medical simulations, this part of the session allows the team to discuss what occurred during the scenario and to develop an understanding of how the crisis or situation unfolded (Fig. 47.20). The goals of a debriefing session may vary, but in ACRM, the technique is used to allow members of the team a chance to review their own performance, to evaluate the team's performance, to understand the drivers in the crisis, and to learn some general principles in crisis management that they may then use more effectively during future critical events [35,73].

Facilitated debriefing is the key to reaching your learning goals from a simulation scenario. During a critical event, attention is intensely focused on managing the crisis and completing necessary tasks. It is only in the later analysis, that an understanding of all the factors impacting on the outcome can be evaluated. This then leads to learning from the event, its management, and any failures that occurred. A facilitator is important in guiding the debriefing and framing the learning points. Ideally, the facilitator encourages reflective analysis, leading the participants in the crisis through the event, eliciting their own reactions to occurrences, thus assisting them in developing their own analyses. Material covered in a group discussion is much more likely to be retained than that passively obtained in a lecture-type presentation. In addition, when participants provide their own insights and observations, they feel that their input has been heard and they have more of a stake in the discussion, and a sense that their ideas become part of the conclusion. These conclusions then become more acceptable and believable to the participants. Facilitating a debriefing well takes time and practice. Table 47.4 includes actions that help create a positive learning session and several that can hinder the ability of the group to develop their own conclusions.

Debriefing sessions are most effective when the team members guide their own discussion based on their own observations, using the facilitator to initiate the discussion by setting the objectives and assist in leading the discussion minimally.

Figure 47.20 *In situ* team debrief after simulation in Stanford Children's Hospital recovery room.

Table 47.4 Debriefing "dos" and "don'ts" – factors that can facilitate or detract from the effectiveness of the debriefing portion of a simulation session

Thing to do	Things to avoid
Set expectations for crew participation	Don't lecture
Engage the team to facilitate achieving those expectations	Don't provide your own analysis before it is "discovered" by the team's analysis
Cover all critical topics	Don't give impression that your observations are the most important
Balance the discussion: draw in quiet participants	Limit interruptions of team discussion
Cover teaching points to be made – integrate into discussion at appropriate times	Don't create the sense of an interrogation
Discuss positive actions and how they impacted outcome	Avoid a rigid agenda
Consider using visual cues to track major discussion points	Don't cut sessions short when outcomes are positive

Teams that have not previously participated in this type of analysis or group discussion will require much more guidance on the part of the facilitator.

Starting the debriefing session with an introduction that outlines the expectations for the session, and the ways in which the team members will participate, allows creation of the proper framework for the learning session. Setting a format will then help the team develop an agenda for the session. The facilitator should be sure that all critical items are included in the agenda. Using the basic principles of ACRM to frame the analysis and evaluation can help deflect difficult feelings related to any perceptions of individual inadequate performance among participants. Finally, the lessons learned from the session should be explicitly reviewed and generalized if possible.

Some of the techniques that encourage active team member participation and in-depth analysis of events are the following: (1) ask questions – what, why, and how; (2) engage all team members in the discussion; (3) re-word questions instead of answering – allow the team to answer the questions; and (4) allow pauses and silence to encourage thoughtful analysis and time for answers.

In summary, debriefing creates the opportunity for members of a team involved in a crisis situation to reflect on their performance, review the elements that were active during the crisis, analyze how these factors impacted the outcome, and develop some lessons to be carried away and used in future situations. In addition, basic concepts useful in approaching any crisis can be emphasized during the debriefing, allowing a review of important skills that can then enhance participants' performance over a wider set of circumstances.

Creating scenarios

Stem questions:

- How does one go about creating a scenario?
- What factors should be included to be sure of capture learning for all team members effectively?
- How can the utility of crew resource management learning for the perioperative teams be demonstrated?

The first step in creating a scenario is defining the participants who will be taking part and the learning goals to be set. The resources available to run the simulation must also be considered: from location of the simulation to equipment, to staffing and facilitators. The particular clinical situation can then be set. A simple story line for the scenario, identifying roles to be played by both participants and facilitators/confederates, an outline of the basic clinical situation, the crisis to be dealt with, and the key patient characteristics that will orient the participants to the situation at hand, are all key elements to include. It is helpful to try and anticipate the types of reactions from the participants and map out the likely patient responses, vital signs, etc., to those actions. A map is therefore

Critical Steps in Scenario

Patient State	Physiologic Parameter: no atropine	Physiologic Parameter: atropine	Time	Step Required	Time Occurred: Hour/min
Awake	HR 120 BP 90/50 RR 25 SpO2 99%	HR 120 BP 90/50 RR 25 SpO2 99%	t = –x	Step 1 WHO Pediatric Checklist	
Induction	HR 140 BP 80/40 RR 35 SpO2 100%	HR 140 BP 80/40 RR 35 SpO2 100%	t = 0	Monitors Placed	
Laryngospasm	HR 160 BP 100/60 RR 0 SpO2 95	HR 160 BP 100/60 RR 0 SpO2 95	t = 1	CPAP, alert nurse have issue	
Apnea	HR 160 BP 70/40 RR 0 SpO2 90	HR 160 BP 70/40 RR 0 SpO2 90	t = 2	Ask for IV/IM drugs	
Unable to Mask	HR 120 BP 70/40 RR 0 SpO2 80	HR 160 BP 70/40 RR 0 SpO2 80	t = 3	call for Help, initiate emergency protocol	
Unable to Mask	HR 100 BP 65/35 RR 0 SpO2 70	HR 130 BP 65/35 RR 0 SpO2 70	t = 4	Attempt intubation X 2	
Unable to mask/intubate	HR 80 BP 65/35 RR 0 SpO2 50	HR 100 BP 65/35 RR 0 SpO2 50	t = 5	Attempt LMA	
Unable to mask/intubate	HR 60 BP 50/20 RR 0 SpO2 40	HR 70 BP 50/20 RR 0 SpO2 40	t = 6	Call for surgical airway Start CPR	
Outcome 1: obtain surgical airway	HR 80 BP 70/40 RR 0 SpO2 85	HR 80 BP 70/40 RR 0 SpO2 85	t = 8	Trach placed	
Outcome 2: no airway obtained	HR 0 BP 0 RR 0 SpO2 0	HR 0 BP 0 RR 0 SpO2 0	t = 8	CPR continues, call code at t = 15	

Figure 47.21 Example of template used for planning and running vital signs responses during high-fidelity patient simulation.

created that helps the technician running the mannequin and attached monitor to set the proper circumstances as the scenario plays out (Fig. 47.21).

Development of the scenario relies on content experts for the clinical situation being portrayed to ensure realistic patient responses in a relevant context. In addition, running of the scenario must include confederate facilitators who are experts, allowing the team to modify scenario responses spontaneously based on the actions of the participants. Thus one of the challenges in creating scenarios that are generally applicable to a wide range of practitioners, particularly for evaluative purposes, is the ability to translate the expertise of one group to the expectations of another. Consensus must be developed around scenarios and performance goals.

Creating the environment: where simulations are run

Medical simulation training has traditionally occurred in simulation centers. These centers were designed to recreate specific patient environments such as operating rooms. They were often built with viewing rooms and debriefing conference rooms, allowing postevent reviews of audiovideo sources from the scenario and discussing the trainees' performance [74]. Many large academic centers now include a separate simulation center for education, incorporating multidisciplinary approaches and allowing for training of medical personnel at all levels of training and practice. From Stanford University, where simulation use in anesthesia training was first developed, to Duke University in North Carolina, to the

Figure 47.22 Three-dimensional model of a simulation center – the Medicine Company Simulation Center, designed by Paul Lukez Architecture. *Source:* Courtesy of Paul Lukez Architecture.

University of Florida in Jacksonville and many more, these centers are now an integral part of the fabric of medical education [75,76]. The use of some of these centers is not limited to physician education, but includes nursing education as well, partially in response to increased limits of access to patients during their training. Private free-standing centers are also beginning to be seen, a response to the growing demand by hospitals and physicians for reproducible, reliable training and testing. Many hospital systems are also developing their own simulation centers to target specific populations not necessarily addressed in other systems. Several free-standing pediatric hospitals have developed their own simulation centers (Fig. 47.22).

Taking simulations to the various areas in which actual patient care is provided is called *in situ* simulation and allows a unique ability to test not only the areas for process and equipment deficiencies, but also to see how the teams work in their usual environment. This helps create a highly realistic milieu for training and eliminates many confounders that otherwise inhibit the normal responses of participants. However, the ability to recreate the positive features available in full-blown simulation centers, including audiovideo capture and playback of scenarios, could be a technical challenge. By using a mobile audiovisual cart, simulation can be used in any work environment without giving up the video-facilitated debriefing used in analyzing center-based simulation scenarios. After experimenting with several prototypes, a system was developed and first demonstrated at the 2006 Society for Pediatric Anesthesia Annual Winter Meeting by the Stanford Pediatric Anesthesia group (Fig. 47.23) [77]. Commercial mobile audiovideo systems are now also available and have been used with positive results at other centers [77]. However, *in situ* simulation for pediatric anesthesia also has a set of challenges that must be considered including competition with actual patient care, confidentiality issues, and perhaps parents/families present in the training vicinity.

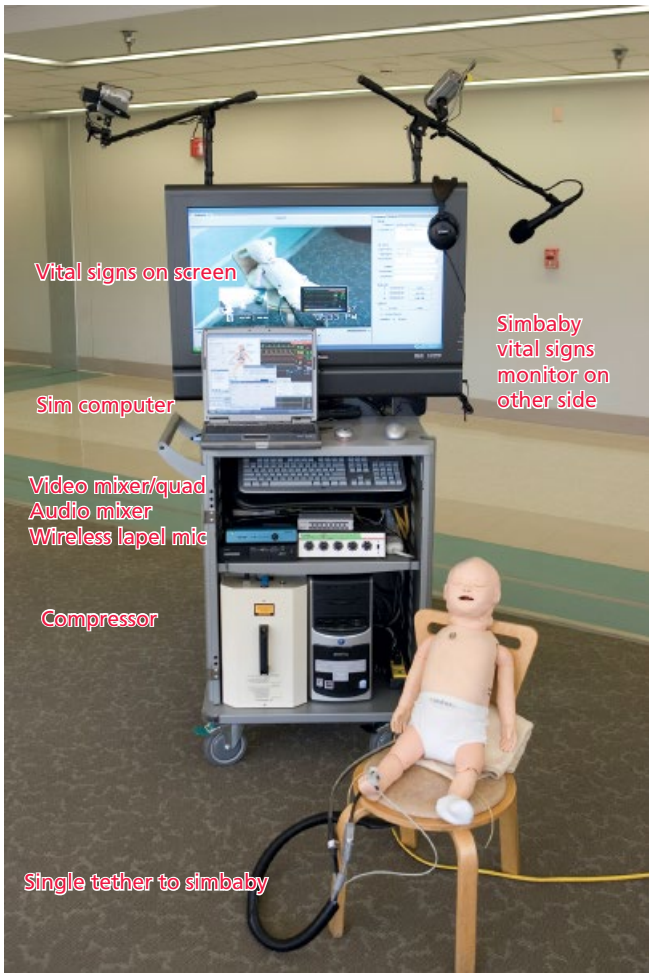

Figure 47.23 *In situ* simulation cart developed at Lucile Packard Children's Hospital. It includes mechanical elements for a high-fidelity simulator with audiovisual system to record and display multiple video and audio channels.

Facilitation: running a scenario

Prior to starting the scenario, the participants must be briefed on the basic setting, helping them to set the proper mental framework in which to play out the scenario. Specific roles are assigned to each participant, allowing them to take part in the scenario as part of the care team. For instance, when the goal is improving medical management of a rare medical crisis in the OR, the learners may be assigned the role of the anesthesiologist, a member of a code team, or a second anesthesiologist responder. However, if the goal is to develop an understanding of team dynamics in the OR, participants may be asked to assume other roles within the team, such as the scrub-tech, which would allow them a different perspective on events as they unfold during the crisis. Alternatively, a group of learners may be summoned "emergently" to a simulated situation with one of the objectives to see how the group assigns leadership and other team roles.

Teaching facilitators will take other roles in the clinical team, such as the surgeon or circulating nurse, playing the parts as the scenario unfolds to help present the appropriate cues for the learner; these roles played by the faculty instructors are termed "confederates." The confederates feed information to the learners at appropriate times, guiding the understanding of the situation for participants or constraining their actions if needed.

A technician is typically required to run the computer that controls the mannequin throughout the scenario, allowing realistic "patient" responses to the actions from the participants. Communication between the confederates within the scenario and the technician controlling the mannequin is important to ensure the mannequin responses are made in an appropriate and timely manner.

An expert facilitator manages the flow of the scenario throughout, perhaps answering queries from the participants when environmental cues are unclear, and providing additional information about the situation, which align with the objectives initially developed for the scenario.

KEY POINTS: ORGANIZING AND RUNNING HIGH-FIDELITY SIMULATION SESSIONS

- Running high-fidelity simulations well takes preparation of the space, the equipment, the facilitators, and the learners
- The simulation environment is key in realizing the learning goals, and can have a great impact on the ability to complete the simulations as planned: simulation centers tend to have regular, well-scheduled sessions while *in situ* simulations may need to happen "on-the-fly" when clinical space becomes available
- Debriefing is the key step in facilitating the full acquisition of lessons learned for participants; ideally it will elicit responses of self-reflection from learners guided by a facilitator ensuring the learning goals are discussed
- Both the creation of the scenario and the running of the simulation activity require content experts to ensure patient parameters are realistically set, reactions to participant actions are within clinically normal bounds, and the background scenario story makes medical sense to the learner group

Pediatric anesthesia simulation

Applications of pediatric anesthesia simulations

Simulation scenarios focused on pediatric anesthesia care can be created to serve many purposes: basic training of medical students or anesthesia residents, advanced training for pediatric anesthesia fellows, and refresher training for non-pediatric anesthesiologists, pediatric anesthesiologists, or perhaps non-anesthesia providers who might be called to sedate or resuscitate a pediatric patient. With the continuing trend to centralize the surgical care of pediatric patients to large pediatric centers, anesthesiologists in community hospitals are exposed to fewer and fewer pediatric patients [78]. This could increase the demand for simulations related to pediatric care in order to maintain a sense of confidence in caring for these patients. Common crisis scenarios, that depict relatively common and potentially critical events, could help in this setting.

Current uses and activities: pediatric anesthesia simulation centers and activities

Centers offering simulation experiences in pediatric anesthesia have multiplied over the last decade. Academic centers across the country have developed pediatric-focused groups, allowing training of fellows and residents, OR teams, and support personnel. Fellowship training in pediatric anesthesiology includes simulation to varying degrees. With the gradual decline in numbers of cases of neonatal emergency surgery in the past decade, some centers are beginning to develop scenarios targeted at exposing fellows in pediatric anesthesiology to these rare cases critical to becoming competent consultants in pediatric anesthesia. Medical simulation can be effectively utilized in many capacities to fulfill learning gaps, conduct research, and promote a culture of safety [79].

Factors in creating pediatric-specific anesthesia simulations

There are six major factors that affect the types of anesthesia simulations that are created for pediatrics versus adults: anatomy, psychology, physiology, procedural locations, types of surgery required, and parental involvement. The first relates simply to the size of the patients: children come in a large variety of sizes as a normal function of growth and development. This requires a whole different range of equipment, including mannequins specialized for the appearance of infants and small children. The second factor is that children present psychological challenges in IV access, cooperation, and the desire to avoid trauma. Therefore, they are frequently anesthetized using an inhalational mask induction, without IV access in place. The third factor relates to the propensity for children to exhibit rapid reactions and decompensation based on their physiology, such as rapid hypoxemia following laryngospasm because of low functional residual capacity and high metabolic rate. These reactions present challenges in management, unique to pediatric anesthesia. The fourth factor is the relatively wide variety of locations in which anesthetics are administered to children routinely,

Box 47.1: List of pediatric anesthesia simulation scenarios used at Cincinnati Children's Medical Center

- Supraventricular tachycardia
- Ventricular tachycardia arrest
- VFIB arrest
- Hemorrhage shock
- Cardiogenic shock
- Pulseless electrical activity (no CPR initially)
- Hypovolemia – basic (ECMO)
- Septic shock
- Meningococcal disease
- Anaphylaxis
- Child diabetic ketoacidosis
- Status asthmaticus
- Spontaneous pneumothorax
- Airway trach crisis
- FBOA arrest
- Laryngospasm-induced pulmonary edema
- Pneumothorax (ECMO)
- Respiratory failure
- Fentanyl reaction
- Ketamine reaction
- Opiate ingestion
- Calcium channel blocker overdose
- Malignant hyperthermia (PACU specific)
- TCA overdose
- Hypertensive encephalopathy
- Seizures
- Child burn victim
- Smoke inhalation
- Near drowning
- Head injury requiring RSI
- Child gunshot wound
- Pediatric blunt trauma
- Infant blunt trauma
- Infant multiple trauma
- Head injury requiring RSI – complication
- Infant heat illness

CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; FBOA, foreign body obstructing the airway; PACU, postanesthesia care unit; RSI, rapid sequence intubation; TCA, tricyclic antidepressant; VFIB, ventricular fibrillation.

Source: Courtesy of Paul Samuels MD.

because of their inability to cooperate with procedures or remain still such as for diagnostic imaging. The limited equipment and support systems available in these diverse locations create opportunities for interesting scenarios. The fifth factor pertains to the types of surgery required by infants, which are often rare but require a high skill and focused knowledge set to manage well. Finally, the sixth factor acknowledges the parents' relation to and role in their children's lives: they have the legal authority for their children and extremely strong emotional bonds. This relationship creates some unique situations ideal for simulation learning. See Box 47.1 for examples of scenarios created at the Cincinnati Children's Medical Center (personal communication, Paul Samuels).

The early patient simulation mannequins were developed with the adult model in mind. This not only targeted the vast majority of medical care delivered, but the larger mannequin provided more space for the mechanical and electrical components needed to create the various desired physical effects. With advances in computer technology and the miniaturization of components, smaller high-tech mannequins have become possible. Selection of the most appropriate equipment for the learning objectives of the session will promote engagement of the learners into the scenario [80]. Several companies now offer pediatric, newborn, and even premature newborn size mannequins with a wide range of realistic physical effects and interactive capabilities. Table 46.3 lists some of the various mannequins, the modeled age range, and the simulated qualities available for each as an example of how far this technology has come. For instance, the newborn simulator by Guamard not only delivers heart tones, breath sounds,

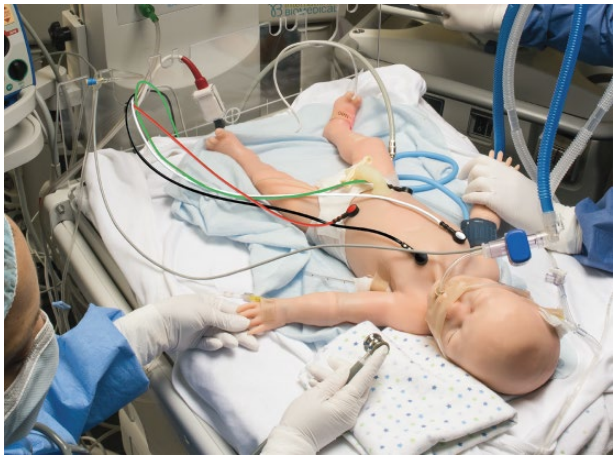

Figure 47.24 Guamard's Super Tory neonatal simulator – wireless with "dynamic lung compliance" to allow for realistic ventilator support. *Source:* Courtesy of Gaumard Medical.

peripheral pulses, and patient phonation, but will exhibit chest wall motion with either spontaneous or positive pressure ventilation, increased peak inspiratory pressures with various pathological conditions being simulated, and random rapid motion of the extremities to simulate a seizure. Advances in wireless signaling allow this mannequin to be picked up and moved without any cables, allowing for an increased degree of realism and flexibility in creating scenarios, during which an infant might normally be moved from one location to another in a caregiver's arms (Fig. 47.24).

Scenarios based on infants can only be realistically created using these appropriately sized mannequins. Everything in the environment is then appropriately sized as well, engaging the participant learner to more easily "suspend disbelief" and react to the crisis. Indeed, sizing of equipment and materials such as authentic laryngoscopes and endotracheal tubes is one of the key elements in effectively working in any pediatric milieu. For applications in either learning or checking for proficiency, this size barrier was essential to overcome before pediatric scenarios were possible.

Anatomy, psychology, and physiology affect another fundamental aspect of pediatric anesthesia, which is the induction technique. Pediatric patients have small veins, often masked by copious subcutaneous tissue, making IV access difficult. They do not have the ability to understand the circumstances bringing them to medical care, nor to cooperate and follow directions. These characteristics create a situation in which the child can become agitated and combative when attempting an IV start while awake. In addition, their physiology, including a high metabolic rate, heart rate, and respiratory rate, combine to ensure rapid uptake of inhaled anesthetic agents, allowing for rapid induction using a mask technique. For these reasons, inhalation induction is commonly the method of choice when anesthetizing small children. Because there is no IV access for drug delivery yet available, this also creates some unique circumstances in which life-threatening reactions that are difficult to treat can occur during induction. Pediatric scenarios dealing with laryngospasm, bronchospasm, desaturation, bradycardia, and hypotension during induction are both realistic and rich in teasing out both technical and non-technical skills for debriefing and learning.

Figure 47.25 *In situ* simulation in computer tomography scanner with infant simulator.

A practiced pediatric anesthesiologist becomes facile at the critical steps involved in these types of situations, and working through these reactions and steps in simulation scenarios, with anesthesiologists that do not care for children every day or trainees, is extremely useful.

The basic physiology in children is fundamentally different to that of adults in many ways, as noted earlier. In neonates, particularly if born prematurely, the airway reflexes are physiologically immature, creating the propensity for apnea, laryngospasm, and bronchospasm, at times with no clear stimulation. Desaturation occurs very rapidly due to the limited functional residual capacity and rapid metabolic rate. Bradycardia is a common sequela of desaturation and, as opposed to adults, is commonly accompanied by significant hypotension due to the fixed ejection fraction of the still developing heart. These combined circumstances allow for a varied set of crisis to deal with in simulated scenarios, often simply manipulating the patient's vital signs to create very realistic sequences. Also, the crisis can be attributed to minor triggers in healthy patients without major pathology, enabling a quick, rich scenario with full recovery of the patient which creates a sense of positive engagement and reinforcement for the learners.

When designing pediatric anesthetic scenarios, the full range of hospital locations can be utilized. Unlike the adult population, children often require anesthesia for painless imaging studies and minimally invasive procedures (Fig. 47.25). As a result, it is common to anesthetize pediatric patients in various venues, such as MRI suites, radiotherapy rooms, endoscopic suites, and dental offices. Scenarios based on some of these remote locations can take advantage of the variable constellation of equipment available, unfamiliar personnel on hand, and unique environmental concerns. For example, one common scenario involves anesthetizing patients in the MRI suite, which requires special precautions around the magnetic field. Resuscitation cannot occur within the magnet, so the simulated patient must be removed to an adjacent location for treatment. In these remote locations, the availability of back-up support or help in the event of a crisis is likely to be markedly different. A focus on the system requirements in these locations during debriefing of these scenarios can open the participants' minds to the depth of safeguards that have been put in place in their usual work environment and what might in fact be lacking.

Figure 47.26 Simulaid Neonatal Wound kit including gastroschisis and omphalocele wounds. *Source:* Courtesy of Simulaid.

Pediatric patients undergo many types of surgery and procedures that are not performed in adults. Some of these operations are becoming rarer. Thus it can be more difficult to acquire the skills needed to successfully navigate the appropriate anesthetic and the ability to develop an understanding of the physiological aberrations that are commonly seen. Emergent operations in neonates such as tracheoesophageal fistula repair, congenital diaphragmatic hernia repair, and omphalocele and gastroschisis repair are becoming less and less frequent (Fig. 47.26). This, coupled with the increasing

use of thoracoscopic and laparoscopic surgical approaches, which adds additional challenges to the anesthetic management, creates an ideal circumstance for the use of simulation training. Simulation scenarios created to mimic these rare operations can be used equally for fellow trainees and for maintenance of skill in senior faculty. Using high-fidelity simulation can be extremely useful to improve interdisciplinary communication and coordination, key to successful management of these types of cases. Debriefing topics could include communication related to sharing the airway with the otolaryngologist during direct laryngoscopy and bronchoscopy, or the decision to intermittently ventilate both lungs in single-lung ventilation cases, forcing a pause in the surgery for stabilization of the patient.

Finally, since children are minors, and unable to consent for their medical care without an adult or legal guardian, working with the patient's caregivers is a normal part of every pediatric anesthetic plan. Parents must be interviewed for a preoperative evaluation, counseled for consent to be obtained, and at times be present during induction. Their own anxieties in facing the procedure or surgery for their child are often extreme and can impact the behavior of the child. Scenarios that incorporate a parental presence component not only add a great deal of realism to pediatric simulations but can be used to create the crisis or circumstance that is the scenario's learning objective. Whether this is effective communication before, during, or after an event, or successfully disengaging a parent as a crisis begins to unfold, there is much to work with. Scenarios are often derived from the real-world experiences of faculty members. One example involves a parent-present induction in which the parent became panicked as the child went into laryngospasm on induction and fled with the baby from the OR. This prompted a scenario with the parent present in the OR with their infant at induction. The patient developed laryngospasm and hypotension, and the parent moved to "protect" their child. This forced our participant learner to effectively communicate with the parent, engage the team members for assistance in managing the crisis, and direct a team member to assist the parent out of the room, all while beginning effective management of the patient.

Pediatric-specific anesthesia simulation equipment

An essential element of high-fidelity patient simulation is the creation of a realistic environment with appropriate equipment and props. Pediatric anesthesia simulations had to await the production of mannequins sized to approximate pediatric age ranges. In 1999, METI (Medical Education Technologies Inc., Sarasota, FL, USA; acquired by CAE Healthcare in 2011) was the first to develop and introduce a pediatric mannequin known as the PediaSIM®. This mannequin was approximately the size of a 5–7-year-old child. Challenges in developing components small enough to fit in the smaller size of an infant mannequin delayed introduction of an infant mannequin for many years. In 2005, both Laerdal Medical (Stavanger, Norway) and METI brought infant mannequins to the market [78]. There are many features, and the availability of connected vital sign monitors, allowing for the creation of complex and realistic scenarios. Now other companies, such as Gaumard Scientific (Miami FL, USA), have created infant and neonatal models (Fig. 47.27). See Table 47.3 for a listing of many of the features available in current mannequin systems.

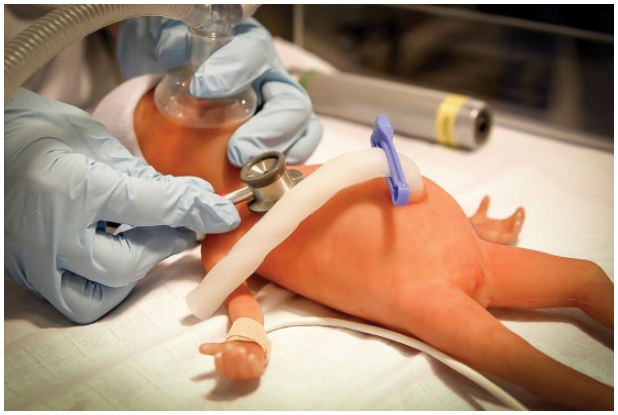

Figure 47.27 Extreme premature simulator mannequin being examined with attempts at resuscitation. *Source:* Courtesy of Medical X.

Creating pediatric anesthesia scenarios

While some scenarios may be available from a variety of sources, such as the *Journal of the Society for Simulation in Health Care*, the Society for Pediatric Anesthesia Simulation Interest Group, or the Managing Emergencies Paediatric Anesthesia site, most people will most likely want to create simulation scenarios that suit their own particular needs. After choosing the participant group, the first step in creating a scenario is to decide upon the learning or evaluative goals. Goals can be based on general team dynamics, focusing on some of the ACGME core areas or ACRM team skills, or on medical knowledge areas required for the learner group, such as the proper medications for induction of a critically ill infant, or on technical skills, such as effective bag–mask ventilation or compressions in cardiopulmonary resuscitation, or any combination of the above. The target learner group should have a needs assessment that drives the choice of goals.

Once the goals have been decided, the setting for the scenario must be chosen to support them. Available resources, including personnel, time, equipment, or supplies, will play a large role in where and when the scenario can be run. And these in turn will affect the specific scenario elements choosen. For example, the number of facilitators might influence the ability to run a team crisis scenario versus an individual medical knowledge and skills learning opportunity. And the mannequin at hand would dictate the ability to run scenarios based on the appropriate matching age ranges.

Various templates have been used to prompt inclusion and organization of all the diverse elements required to create a scenario for high-fidelity patient simulation. All templates include the basic premise for the scenario to be acted out with a description of the patient's condition, the procedure or circumstance in which the patient is found, and the sequence of events that is planned to occur. This plan is created to specifically test the skills and teamwork of the participants in the scenario, targeting the particular learning goals. The roles for facilitators and participants must also be carefully delineated. The supporting equipment required, either to create a realistic

environment or for use in responding appropriately to the scenario, must be listed. Expected reactions to the script and the typical physiological responses are planned as well, so that any actions taken by the participants will have realistic responses. Figure 47.28 depicts a typical short template for a scenario, listing all critical elements required. A longer format adds detail to each element or includes references to support reactions depicted in various steps of the scenario. A vital signs "map" for the technician, to help guide them through the expected physiological reactions to different steps in the scenario, can also be included (see Fig. 47.21). Learning objectives are explicitly spelled out to ensure their inclusion during the debriefing section of the simulation.

KEY POINTS: PEDIATRIC ANESTHESIA SIMULATION

- Numerous applications are achievable using medical simulation in pediatric anesthesia including procedural training, complex medical scenario sessions, crisis management/teamwork performance training, and managing professional issues
- Many different learner groups can participate in pediatric anesthesia medical simulation activities including physicians in training, attending physicians (both anesthesiologists and surgeons), nurse anesthetists, nurses, and ancillary staff
- Developing pediatric anesthesia medical simulation scenarios requires a deliberate process with particular attention paid to the identification of the key learning objectives for the session
- Learning objectives can be achieved in a variety of venues with modification of equipment, simulation methods, and teaching approach

Measuring the effectiveness of simulation learning

Stem questions:

- How will you know if the medical simulation sessions were effective?
- How will you use this information to make future improvements to the medical simulation sessions?

Educators want to understand the true impact of providing medical simulation activities. However, demonstrating a true relationship from the simulated venue to an actual medical environment is challenging [81]. This is relevant from a program development perspective since simulation education is relatively resource intensive, and when team training is involved, it requires a great deal of coordination and preplanning to ensure all team members are present and well prepared. Exposing whole clinical units to regular educational sessions is both time and cost prohibitive. In contrast, simulation-related activities are advantageous due to their emphasis on using active learning formats [82]. Measuring general patient outcomes for relatively rare events therefore is unlikely to show a direct correlation to the specific training of the units' teams. However, when smaller groups, such as code teams, are deployed to assist with resuscitation management in entire hospitals, focused training is possible. Knight et al demonstrated an improvement in patient survival to discharge and in code team adherence to standard operating performance variables for patients who suffered cardiopulmonary arrest after a simulation-based resuscitation team training program was implemented [83]. While exciting in concept, it is not possible to completely attribute causality to the training program.

How then should the effectiveness of the simulated training sessions be measured? Three approaches have been used extensively in the past: review of participant survey data, pre-and post-training teamwork scoring, and comparison of pre- and post-training timed/measured actions in well-protocoled procedures and processes, such as pediatric advanced life support (PALS) or advanced cardiac life support (ACLS). Questionnaires for self-assessment and/or knowledge-based tests are often used to gauge the educational effectiveness of the simulation sessions. These are usually administered prior to the educational intervention, immediately postintervention, and perhaps again at some future interval to determine the sustainability or longevity of the educational outcomes as well as improvements in knowledge and/or psychomotor skills.

Evaluation tools utilized in medical simulation to determine the effectiveness of training typically incorporate one, if not several, of the four levels in the Kirkpatrick model [84]. The most common Kirkpatrick levels utilized within medical simulation include level 1 (reaction) and level 2 (learning). Attainment of level 1 could be achieved by surveying the learner group regarding their reactions to training, while level 2 could be achieved by measuring the knowledge of each learner by the administration of a post-test. The ideal goal within the medical simulation community would be to demonstrate evidence at Kirkpatrick level 4 (results). Kirkpatrick level 4 would include exhibiting targeted effects (e.g. patient outcomes) as a direct result from receiving medical simulation training. Establishing this degree of direct outcomes becomes significantly challenging and very complex to substantiate.

Medical simulation participants often report an improved sense of confidence and comfort in working through communication-based scenarios and crisis resource management scenarios after receiving focused training. Indeed, when high-fidelity simulation is used for teams in high-acuity settings, such as intensive care units, operating rooms, and emergency departments, participants often report being confronted with a similar actual situation post-training which provides a feeling that the simulation training has primed their abilities to respond more effectively [85,86]. In addition, common qualities from simulated crisis resource management training may be extrapolated for use in the future by the learners (e.g. leadership skills and duties related to specific role assignments).

Most frequently, the teamwork scoring is achieved as part of a series of simulation educational events, in which a researcher watches live or taped simulation scenarios and uses a standard scoring system to grade various teamwork skills, such as closed-loop communication, clear designation of a code leader, and effective delegation of tasks. Using the Clinical Teamwork Scale, Gilfoyle et al demonstrated clear gains in teamwork effectiveness, and in effectiveness of

Case Title (**Not to be read to participants**)	**Management of Anaphylaxis in Patient with Congenital Cardiac Disease for Hernia Repair: inaccurate paperwork causes confusion about allergies, and wrong med given** ***NOTE: scenario is preliminary for follow up scenario in which the "hot seat" anesthesiologist must disclose the events to the patient's mother***		
Patient Information	**Name Baby Sim Packard**	**Age 13 m**	**Gender Male**
MRN (will be changed)	**Weight 14 kg**	**Height 90 cm**	**Race Caucasian**

Case Presentation (**To be read to participants**)	**13 month old boy, scheduled for Hernia Repair one week after difficult reduction of incarcerated hernia**	
Past medical/surgical/family history	**Original surgery planned for day of hernia reduction but patient with Down's Syndrome, h/o AV Canal repair with small PFO, mild PHN, therefore surgery delayed for cardiac consult, now one week later, consult states patient is stable with no active cardiac symptoms and OK for surgery, "avoid hypotension and hypoxia"; URI and OM 2 weeks prior, no other medical history, family history negative for problems with anesthetics**	
Diagnostic Tools	**ASA monitors**	
Narrative Case Description (describe how the case unfolds, including major patient trends and consequences of interventions)	**Patient in the OR and already induced when "hot seat" participant comes in to take over care - original anesthesiologist acutely severely ill (chest pain, presyncopal); patient is stable at the time of handoff, immediately after intubation; surgeon is impatient to begin, draping completed and surgeon asks for antibiotics, which are already drawn up (Cefazolin), antibiotics given by hot-seat participant, surgeon states that patient moves with incision and anesthetic deepened, shortly thereafter desaturation and hypotension occur. Congenital Cardiac Disease, causes confusion about immediate diagnosis in OR, "red herring"/complicating factor. Wheezing, increased PIP's, and hives appear within next few minutes. Anaphylaxis treatment ensues, with patient not responding completely, requiring pressors/remain intubated, transfer to ICU for observation and treatment; the primary circulating nurse is not in the room at "time-out" to relay new allergy information to team, she presents this information when clear that allergic reaction is occurring and asks what antibiotic was given, this information does not correlate with information on anesthesia preop assessment form. Surgery cancelled with incision already made, transfer to ICU. Surgeon states will go speak with mother while team takes patient to ICU.**	
Clinical Diagnosis and "Correct" Treatment	**1. Recognize signs and symptoms of anaphylaxis.** **2. Understand likely manifestations of congenital heart condition.** **3. Manage ventilation, hypotension.** **4. Initiate post-op care plan.**	
Educational Objectives (with references to core competencies when applicable)	**1. Understand the importance of timeout procedures** **2. Increase understanding of Congenital Cardiac Condition** **3. Review of Anaphylaxis manifestations and treatments.** **4. Understand critical behaviors for effective team performance in ACRM, leadership and communication in a crisis situation (Communication & system based practice)**	
3-5 Teaching/Debriefing Points (include references)	**Proper Steps for Timeout (WHO Checklist?)** **Paperwork/System problems with mixed information** **Team Roles in Crisis Management - anaphylaxis** **Sorting out differential diagnosis in patient with congenital heart disease**	
Staffing (roles - participants needed to reenact case)	**Simulation Facilitator (run computer)** **Circulating Nurse** **Surgeon** **Hand-off anesthesiologist (becomes computer facilitator)**	
Learners (med students, residents, etc.)	**Participants: SPA attendees,**	**1. Hot Seat** **2. First Responder** **3. Scrub Tech** **4. 2nd circulating nurse**
Props needed	**SimBaby, Anesthesia Machine, IV poles/sets, IV materials/supplies, syringes and needles for sim meds, airway equipment, suction, defibrillator (?), stethoscopes, drapes/surgical instruments**	
Timing	**Scenario: 20 minutes** **Debriefing: 20 minutes**	

Figure 47.28 Example of a template used to capture and organize the critical elements in a scenario, from a short description of the basic clinical situation being depicted, to the staffing and equipment needs and the learning goals and objectives. *Source:* Adapted from the Duke University Simulation Scenario Development Template available at http://simcenter.duke.edu/support.html and the Scenario Preparation and Script by P. Dieckmann and M. Rall, TuPASS Germany, published in the IMSH 2008 Instructor Training Course manual.

Table 47.5 Example of a performance checklist for timed elements in a lost airway crisis scenario for team training, giving the anesthesiologist's performance parameters (part of Stanford Children's Hospital operating room team training)

Anesthesiologist performance parameters	Maximum points	Not done	Done/delayed	Done within time limit
1. Participate in checklist/timeout	10	0	5	10
2. Recognize difficulty in masking with apnea	5	0	2	5
3. Apply CPAP/oral airway	5	0	2	5
4. Communicate to team: having difficulty with patient's airway	5	0	2	5
5. Call for help	20	0	10	20
6. Limit DL attempts to two (will be unable to intubate)	5	0	n/a	5
7. Attempt placement of LMA (will be unable to achieve ventilation)	5	0	2	5
8. Alert surgeon that surgical airway may be required	10	0	5	10
9. Start CPR – direct team	5	0	2	5
10. Stop all anesthetics and attempt to awaken patient	10	0	5	10
11. Ensure IV line started	5	0	2	5
12. Alert surgeon that surgical airway may be required	10	0	5	10
13. Ask for cricothyrotomy kit to be brought to room	5	0	2	5
Total:	100	0	44	100

CPAP, continuous positive airway pressure; CPR, cardiopulmonary resuscitation; DL, direct line; IV, intravenous; LMA, laryngeal mask airway.

resuscitation using the Clinical Performance Tool after a full-day simulation-based training program for multidisciplinary teams [87–89]. Effectiveness of clinical performance scoring requires observation of simulated or real events by a person thoroughly trained in the key components of the standard protocol and the designated learning objectives for the simulation scenario. Typically, an evaluation tool with key elements, many of which are time sensitive, is used to frame the scoring (Table 47.5). For simulated events this is relatively straightforward to execute, but with unanticipated events in real clinical environments, a predetermined process for ensuring trained observers are present is significantly challenging to consistently provide.

Evaluations for medical simulation activities can be achieved in several capacities. Evaluations can be formative or summative. Formative evaluations are utilized to focus on improving future performance and may consist of generalized comments or observations; these findings may then be utilized to promote discussion during debriefing sessions. Summative evaluations are primarily utilized to assign various types of scores to previous performance. These scores can be related to a wide variety of characteristics such as individual performance, team performance, team characteristics, medical knowledge, psychomotor skills, and professional attributes. The scores can be assigned to individual actions (e.g. a list of the 10 steps in the placement of a central venous catheter) and/or as part of a global overall rating [90,91]. Scores can be assigned for a single simulation scenario or as part of a series of scenarios contained within a long-term course [92]. The scores from summative evaluations can also be used for several purposes such as providing certification in PALS as well as for research projects.

Analysis of evaluation data is another critical component of maintaining an effective and sustainable simulation program. The simulation educator should be open and willing to receiving ongoing feedback regarding their simulation activities from several sources. Review and reflection of learner evaluation data should become a required and automatic process to identify areas for improvement. The review of learner evaluation data will allow valuable insight from the learners' perspective. In addition, postcourse debriefings that occur with the simulation instructors and support staff will provide further critical information from another perspective. All viewpoints can be utilized to make meaningful adjustments in the educational activity to make it as effective as possible.

Effectiveness of the medical simulation activity can and should be determined in several ways. Learner evaluations bring one perspective while instructor interpretations add a different layer of insights. In addition, adherence to the original learning objectives is another consideration. Accordance with pre-established standards or guidelines (e.g. PALS) can also provide additional guidance on educational effectiveness. Finally, long-term learner satisfaction, and perhaps performance change, is another overarching goal to seek. Improvements to future simulation sessions may be adapted to reflect changes in several elements including learning objectives, learner levels or backgrounds, advances in technology, and changes in medical knowledge.

KEY POINTS: MEASURING THE EFFECTIVENESS OF SIMULATION LEARNING

- Simulation educators should attempt to determine the true impact of providing medical simulation activities, despite the challenges in extrapolating to patient care and educational outcomes
- The most common evaluation tools utilized in medical simulation to determine the effectiveness of simulation training are learner surveys and performance checklists for both individuals and teams
- Evaluation tools utilized in medical simulation commonly assess several categories of performance including medical knowledge, psychomotor skills, and team performance

Summary

Medical simulation has become a standard in medical education among medical schools and resident training, used for research, systems evaluations, and human performance evaluation. With the development of pediatric-sized equipment, the use of simulation has been expanded within the area of pediatric anesthesia, with multiple and varied applications. It seems clear that these tools will continue to be developed and extend within medicine to improve education and ultimately patient care.

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 48

Databases, Registries, and Outcome Research in Pediatric Anesthesia

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Introduction

The use of data aggregation for the purposes of detecting trends, factor associations, or prediction of future outcomes – sometimes referred to as "Big Data" analysis – is part of everyday life. One need look no further than opening an internet browser to find customized advertisements that have been chosen for you based on your previous browsing history and analysis of purchases by individuals with similar histories. Similarly, sports executives, particularly in baseball, use large datasets of previous performance to predict the likely future outcomes of individual match-ups. It is hardly surprising then that the same kind of database creation and analysis has been applied to medicine, including pediatric anesthesia.

Large data analysis of healthcare outcomes is nothing new. There are numerous national registries in the United States including those from the National Surgical Quality Improvement Program (NSQIP) [1–3], the Society of Thoracic Surgeons (STS) National Database [4,5], and the Closed Claims Registry that has long been utilized by anesthesiologists [6,7]. Similarly large data analysis has long been available in Britain through data developed by the National Health Service [8] and by even larger collaboratives throughout Europe [9]. While the specialty of anesthesia has taken some time to adopt large data as a primary analysis tool, the current environment has accelerated this trend to a fever pitch. The (almost) universal adoption of the electronic medical record and intraoperative record, the collection of almost infinite amounts of perioperative data has become both low cost and relatively simple. The creation of multi-institutional data-sharing collaboratives has expanded the scope of data gathering even further [10,11]. The result is data aggregation that is larger than could ever have been imagined 20 years ago.

The growth of database outcomes research in pediatric anesthesia is further spurred by the ethical, financial, and regulatory pressure to optimize patient care and outcomes. Large data analysis is optimally suited to allow evaluation of various outcomes of interest and associations between care factors and outcomes. While randomized controlled trials (RCTs) remain the standard by which all studies of health outcomes are judged, the current financial/funding environment has made execution of these trials more difficult than ever. RCTs are expensive to perform and often difficult to approve on ethical grounds. In addition, it is simply impossible to study all of the different aspects of pediatric anesthesia practice with RCTs. Finally, there is evidence that well-conducted large data observational trials provide similar findings when compared to controlled trials that investigate the same outcomes [12,13].

This chapter reviews a variety of registries and large data studies relating to anesthesia and pediatric anesthesia. In addition it highlights the advantages, contributions, and pitfalls of large data studies.

Outcome research from data registries

Why large data analysis?

Outcomes analysis is essential to healthcare quality improvement efforts. Pediatric anesthesia faces unique challenges when analyzing outcomes, since it involves a one-time point of care interaction where work flow precludes detailed

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

feedback to caregivers. In addition, pediatric outcome evaluations must take into account the patient's age, development, and underlying illness when attempting to establish benchmarks. The deployment of "Big Data," including preoperative, operative, and postoperative data, offers an opportunity to create datasets large and inclusive enough to offer useful information on the nature and rate of the most pressing outcomes of interest. Consider the fact that at any large pediatric hospital there are at least 10 different ways in which an anesthesiologist may provide care – using varying methods for airway management, maintenance of anesthesia (e.g. total intravenous anesthesia versus volatile anesthetic), and extubation/recovery choices. The care delivered is driven by personal experience and "choice" of the provider based on their understanding of a very confusing body of evidence. In fact, there is little evidence base for many of the options that face anesthesiologists daily. Conversely, other areas of commerce and industry that involve similar levels of risk and complexity do not allow such a free-form process. In order to continuously improve outcomes, anesthesiologists need to evaluate care delivery with respect to patient-centered perioperative outcomes, quality improvement, resource utilization, risk-adjusted outcomes, and clinical prediction modeling. These concepts are completely in line with the concept of "perioperative surgical home" (see Chapter 15) wherein anesthesiologists evaluate patient-centered outcomes in creating safe and efficient systems of care for operative patients.

As mentioned, RCTs are particularly difficult to accomplish in perioperative children. Instead, over the last 10 years there has been an explosion in the use of observational registry research (databases) to evaluate outcomes of surgery and anesthesiology. For perioperative children, many treatments and exposures cannot be randomized due to ethical issues. For instance no one can randomize groups to an exposure to a major surgery versus no surgery. Many institutions are likewise convinced that their specific method of delivering analgesia for children after surgery is the best and do not believe it is appropriate to expose patients to other alternatives. In light of this, databases created from multiple institutions serve as the next best mechanism for evaluating quality outcomes in children undergoing tests or surgeries. Aggregated outcomes from institutions using different methodologies for accomplishing the same care can be compared in an effort to simulate a randomized trial [14]. Furthermore, the availability of large amounts of data from geographically diverse sources has made large registry data the primary source for health services research in anesthesia (which primarily evaluates cost versus outcome).

Considering the data

Well-conducted large data studies result in risk stratification that correlates with RCTs [12,15], although they tend to overestimate treatment effect. In spite of this, it is reasonable to utilize data from large observational trials to help direct clinical care. The adoption of huge data resources now available from electronic medical record (EMRs) for this purpose, has proven to be the primary source for this outcome analysis. However, data collected for the purposes of clinical care is not always reliable for use as "research data." These issues become amplified when tens or hundreds of institutions are involved in data collection. For instance, what is meant when a clinician states that "laryngospasm" occurred during a case [16]? Different clinicians might have very different ideas as to what constitutes this clinical entity, causing data from varying centers to have different meanings. In light of this, when considering data from observational studies, it is critical that clear definitions for outcomes are agreed upon by those gathering data. Large data reports from clinical interactions are most accurate when considering major adverse events (e.g. death or intensive care unit (ICU) admission) which are impossible to ignore (and are less subject to interpretation). In this way, they are much more likely to be captured accurately than minor events that do not result in a change in patient status.

Large data registries and collaboratives are most helpful when they focus on outcomes that are "meaningful." Appropriate outcomes for analysis are often not clear. For instance, many studies of anesthesia or sedation techniques report the frequency of minor oxygen desaturations as an outcome [17]. Unfortunately, events such as these are of uncertain importance, since brief oxygen desaturation has little or no impact on the patient's overall health or outcome. These outcomes would be important only if the frequency of these finding correlated with more concerning adverse events, but this connection is almost never made. On the other hand, severe prolonged oxygen desaturation events (such as those associated with unexpected tracheal reintubation, ICU admissions, etc.) are much more important and deserve careful consideration.

Retrospective and prospective cohort studies

The most common use of large registry data is for retrospective cohort studies or case–control studies. These methodologies are ideal for studying rare problems or patient factors that are not modifiable. Retrospective cohort studies examine the outcomes related to a specific disease or intervention over a prolonged period and (usually) involve a particularly large total population [6]. A report of the outcomes of hypoplastic left heart patients undergoing non-cardiac surgery would be in this category. On the other hand, a case–control study would identify two cohorts, one having the characteristic of interest and the other *not* having that characteristic. These studies then look at the outcomes of these two cohorts with respect to a given intervention or exposure in a retrospective manner. An example of this kind of study would be the assessment of pain after tonsillectomy (the characteristic) with respect to various exposures (age, race, surgical approach, anesthetic management).

Large data registries are also used to perform prospective cohort studies. In these cases cohorts that are similar, except for having a specific exposure, are compared in a prospective manner. Such studies are preferable to retrospective analyses because outcomes of interest can be specifically defined and followed in a predefined manner that is not possible in a retrospective design. Studies from the Pediatric Regional Anesthesia Network (PRAN) or other such collaboratives fit into this study design type.

Large data quality improvement and research efforts can be broadly divided into three groups: (1) those with tens or hundreds of investigators/institutions collecting data on literally

millions of patient interactions where a huge number of patient encounters can be evaluated, but the density and quality of data is relatively low; (2) more circumscribed collection efforts that aggregate data from a single or smaller number of institutions (20 or fewer) using a more detailed and specific data collection strategy; and (3) very comprehensive data collection from single institution that include copious data on a relatively smaller number of patients. The trade-off for these strategies is clear, the larger data collection efforts allow information to be collected on issues that have very low frequency and are usually accurate in their estimate of outcome frequencies. Unfortunately very large national sources such as the US Centers for Medicare and Medicaid Services (CMS) database usually only contain primarily basic demographic information, billing codes, hospitalization duration data, and mortality data. Very large data collection also occurs at the expense of data quality and detail. When the total number of sites involved is very large, there is inevitable variability in recording accuracy.

KEY POINTS: OUTCOME RESEARCH FROM DATA REGISTRIES

- "Big Data" from the now ubiquitous anesthesia electronic medical record offers an opportunity to create datasets to offer useful information on the nature and rate of the most pressing perioperative outcomes of interest
- Randomized controlled trials are difficult to accomplish and expensive; over the last 10 years there has been an explosion in observational registry research (databases) to evaluate outcomes of surgery and anesthesiology
- The most common use of large registry data is for retrospective cohort studies or case–control studies

"Big Data" in anesthesia research

There are innumerable examples of EMR collaboration to produce large data collaborations in the field of anesthesiology. The Anesthesia Quality Institute (AQI) was founded in 2008 with a vision of improving anesthesia quality and safety in the clinical care of patients undergoing anesthesia. In order to meet these goals, the AQI created the National Anesthesia Clinical Outcomes Registry (NACOR) in 2010 – it was then, and continues to be, the largest and perhaps the most ambitious data-gathering organization in anesthesia [10,18,19] (information available at http://aqihq.org). NACOR is designed to automatically capture electronic data specific to anesthesia cases. Data are gathered from billing systems, hospital electronic healthcare records, and anesthesia information management systems. The database is intended to serve several purposes. First and foremost, it functions as a quality improvement tool for all centers that participate. Data are initially entered and go through a portal that performs validation checks and feedback. Once this step is completed, the data can be sent to a central data repository to undergo processing and analysis. This registry aggregates data from hundreds of institutions that house literally tens of millions of patient encounters for review. NACOR then feeds back information in the form of reports to member organizations that allows benchmarking of provider factors and outcomes. From its conception, data collection for this effort goes on "in the background" of day-to-day clinical activity – invisible to the care providers [20]. Data on all types of factors or outcomes can be collected and analyzed, from the frequency of adverse events to the age of patients undergoing surgery at a given institution. The convenience of this type of data collection is undeniable and has garnered excitement from clinical researchers around the globe (Fig. 48.1).

Data are also shared with the CMS as the organization is a qualified clinical data registry as well as a qualified registry within that organization. The NACOR Qualified Registry includes 31 merit-based incentive payment system measures. Data from centers can be automatically shared with the CMS to allow reimbursement for performance that meets specific criteria. NACOR reports on 26 Physician Quality Reporting System metrics and 19 American Society of Anesthesiology (ASA) Quality Clinical Data Registry metrics. These metrics include items such as perioperative mortality and the use of combination therapy for the prevention of perioperative nausea and vomiting.

Data collected through NACOR's efforts have also been used for research purposes. Reports from the AQI have addressed broad and (at times) controversial issues involved in anesthesia practice. Papers have been published on multiple topics, including the variability in choices of anesthesia for patients undergoing total knee arthroplasty [21]. In this report over 100,000 knee replacements were analyzed and the percentage having surgery under regional (11%), neuraxial (31%), and general (58%) anesthesia were reported. A more recent report delineated the frequency of neuraxial anesthesia for caesarian delivery [22]. This study looked at almost 220,000 caesarian deliveries and found that general anesthesia was used in just 5.8% of elective cases and 14.6% of emergency cases. These manuscripts point out the power of a database such as NACOR to investigate operative and anesthetic demographics and trends in anesthesia delivery.

Other reports from the NACOR database have tracked differences in care-based payer mix, as noted by Flood et al who investigated labor analgesia duration at various sites around the United States [23]. These data are also very helpful for defining demographic trends in anesthesia delivery – such as the delivery of neuroanesthesia [24]. To date there have been no research reports on issues of pediatric anesthesia from this group, but helpful population-level data may exist in this database and reports of anesthetic outcomes and performance of providers caring for children will doubtless be forthcoming.

Data collected and analyzed for NACOR to date have largely involved population health and are intended to be analyzed at this level. To address the need for some level of individual patient data, the AQI created the Anesthesia Incident Reporting System (AIRS). This system is intended to collect information on specific adverse events reported from a large number of institutions and for subsequent incident analysis. A subspecialty module for pediatric anesthesia exists in AIRS; however, the overall purpose and methodologies involved have been largely taken on by the Wake Up Safe initiative outlined later in this chapter.

The Multicenter Perioperative Outcomes Group (MPOG) is another large data-gathering organization in the field of

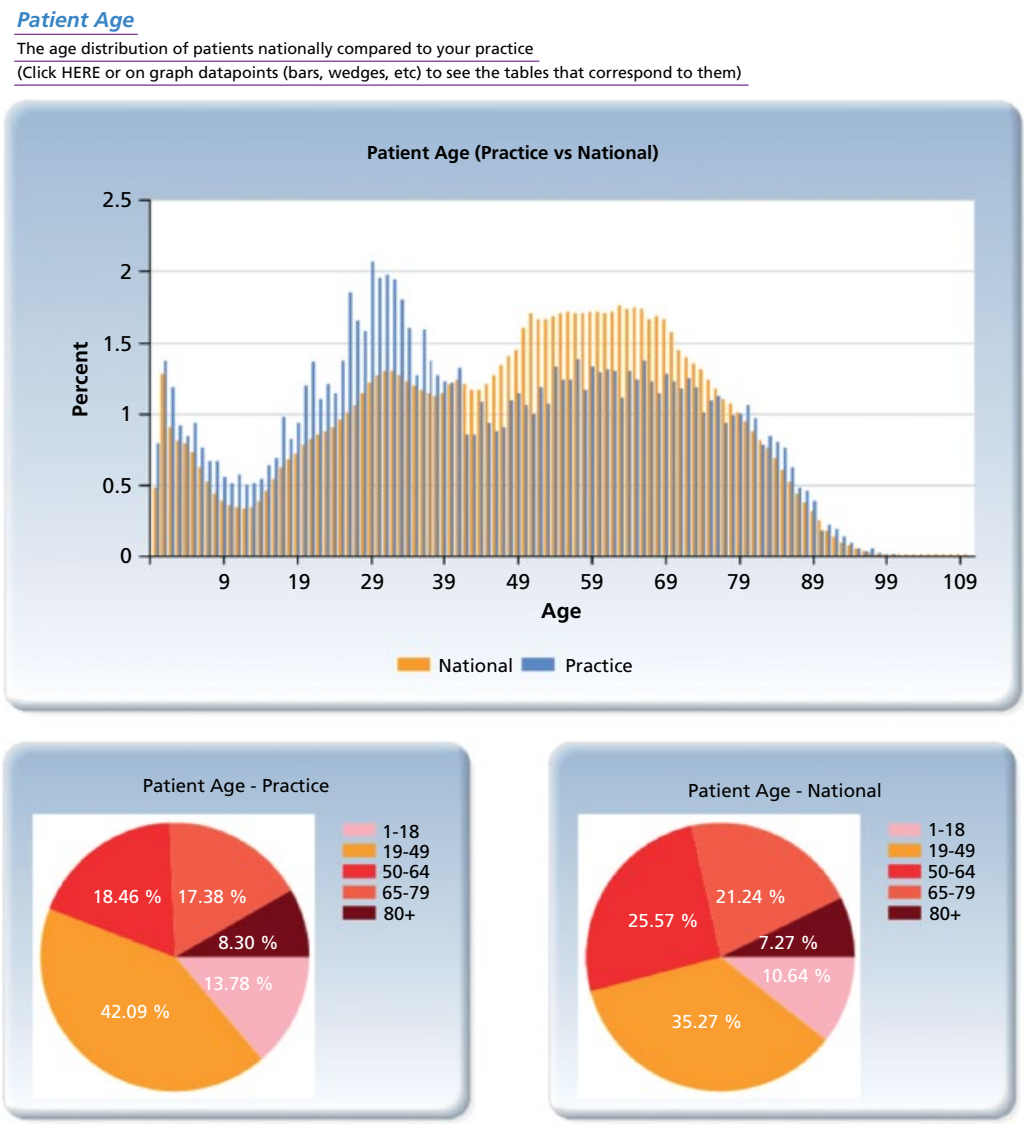

Figure 48.1 Example of data from the National Anesthesia Clinical Outcomes Registry (NACOR) database on the age of patients undergoing surgery. *Source*: Data from Anesthesia Quality Institute, http://aqihq.org.

anesthesiology. This data collective was initiated in 2008 with the mission to develop policies, procedures, and the infrastructure required for collaborative outcomes research in anesthesiology. This group now has 58 participating medical centers in the United States and Europe and has accumulated millions of patient encounters that include patient outcomes and administrative outcomes. Members have published multiple manuscripts in highly regarded peer-reviewed journals and have presented work at numerous national meetings. This group has also created a performance improvement arm (Anesthesiology Performance Improvement and Reporting Exchange) that is partially funded by Blue Cross Blue Shield of Michigan and is based on the data infrastructure of MPOG. This group utilizes the clinical and administrative data to analyze the relationship between patient factors, surgical procedures, anesthesia techniques, and perioperative outcomes.

To aid in establishing improved practices, MPOG members have published on topical issues, such as the rate of hematoma formation after neuraxial anesthesia in parturients, and has related these rates to platelet counts – showing that the rate of hematoma formation is increased with decreasing platelet counts [25,26]. Other low-frequency events have been evaluated and reported – including the success of tracheal intubation rescue techniques after failed direct laryngoscopy in adults [27]. This study documented the high frequency of use and high success rate of videolaryngoscopy techniques. MPOG has also produced publications on the nature of anesthesia practice in general including the relationships between anesthesia pump alarm settings and the infusion rates that are routinely utilized [28], the use of lung protective strategies for intraoperative ventilation [29], and the incidence and predictors of difficult mask ventilation [30].

In its first publication concerning pediatric anesthesia, MPOG analyzed oscillometric blood pressure values from the EMRs in 116,362 ASA physical status (PS) 1 and 2 pediatric cases from 10 institutions [31]. This paper reported normative blood pressure ranges during the postinduction and surgical phases (Fig. 48.2). Reading it, one is struck by how low the normative blood pressure ranges under anesthesia are in patients with no or minimal co-morbities who have good outcomes. For example, from birth through 3 months, the mean arterial pressure corresponding to 2 standard deviations

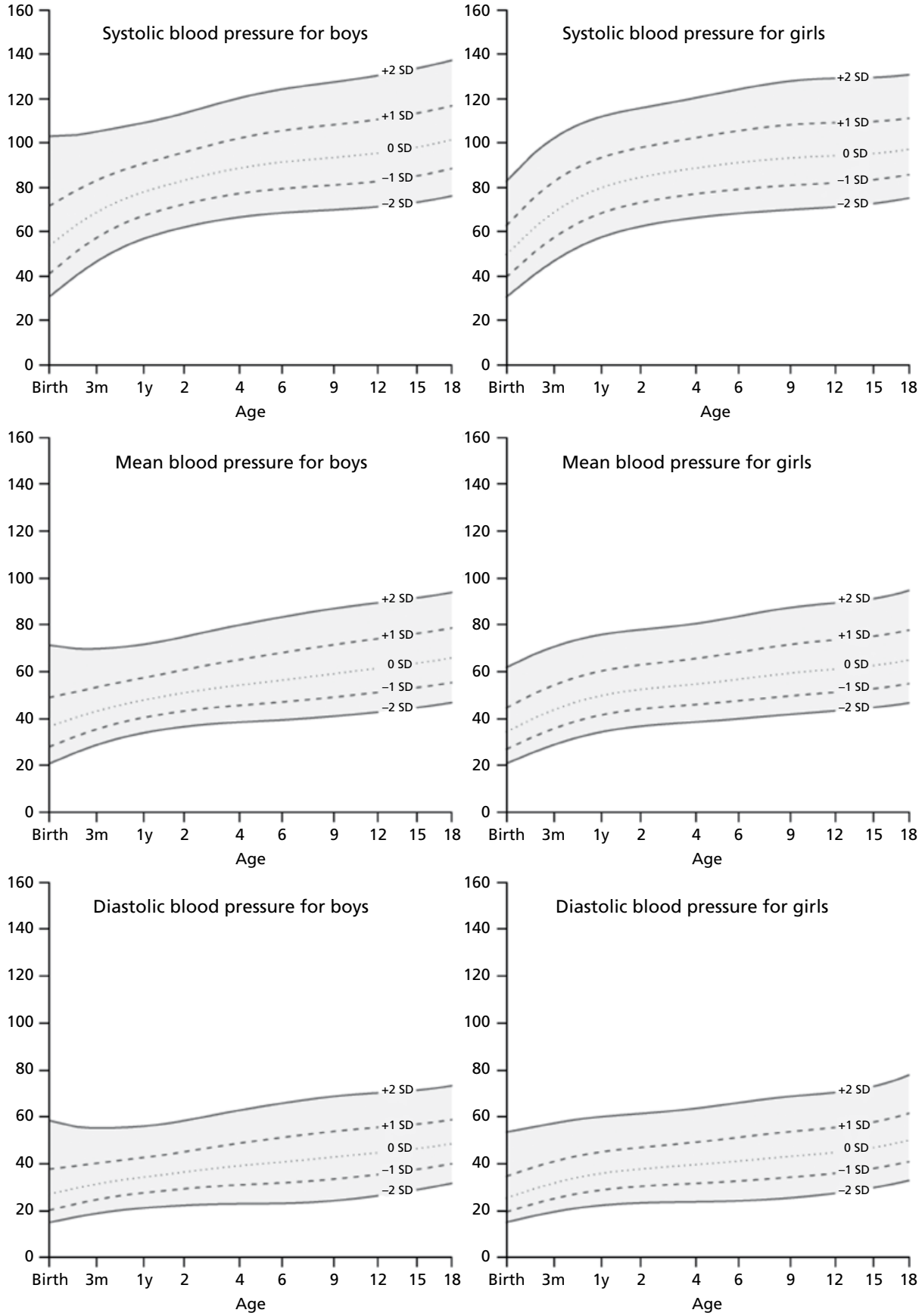

Figure 48.2 Normative oscillometric blood pressure ranges for 116,362 patients from the Multicenter Perioperative Outcomes Group (MPOG) registry during the surgical phase of the anesthetic in relation to age. Source: Reproduced from rde Graaff et al [31] with permission of Wolters Kluwer.

below the 50th percentile is 18–22 mmHg. This is an example of how a large dataset could be used to establish norms for blood pressure in daily clinical care, and develop tools for clinical care and research to rapidly screen blood pressure values for defining hypo- and hypertension.

Both the AQI/NACOR and MPOG data initiatives have helped describe anesthesia practice and correlate outcomes with specific patient characteristics or anesthesia techniques. The power of large data aggregation is clear. The data analyzed by these organizations could not be aggregated by a single institution or small group of institutions. On the other hand, data gathered by large numbers of geographically diverse centers is very difficult to audit and assure consistency or reporting. Analysis is limited to clearly definable outcomes that are not ambiguous or do not lend themselves to interpretation. Still, while observational large data collaboratives are limited in their detail and accuracy, their ability to describe practice patterns and general outcome parameters has the potential to revolutionize the practice of anesthesia in the future. These efforts have just started to define pediatric- specific practice parameters, and active pediatric work groups exist in these organizations and should increasingly bring the power of these large data collaboratives to pediatric anesthesia [32].

KEY POINTS: "BIG DATA" IN ANESTHESIA RESEARCH

- The Anesthesia Quality Institute created the National Anesthesia Clinical Outcomes Registry to automatically capture electronic data specific to anesthesia cases
- Quality assurance and research can be conducted from this databse, and the millions of anesthetic cases constitute a rich source for data mining on a myriad of questions of anesthetic practice and outcomes
- The Multicenter Perioperative Outcomes Group (MPOG) is a consortium of 58 institutions in the USA and Europe collecting data directly from anesthesia EMRs that has allowed detailed analyses of anesthetic practice and outcomes. Their first pediatric publication established blood pressure norms in pediatric patients

Databases and registries specific to pediatric anesthesia

Pediatric Regional Anesthesia Network

The PRAN was organized in 2007 as a consortium of six institutions in the United States where pediatric regional anesthesia was regularly performed. Their goal was to collect prospective data for multicenter collaborative research projects concerning pediatric regional anesthesia. This group now involves 22 centers and has close to 150,000 patient encounters in the database and is growing daily. The original members established guidelines for data collection and auditing of the data and developed online data entry methodology. The first report from this group was published in 2012 and outlined the outcomes of almost 15,000 regional anesthesia encounters in children, including a large number of neuraxial blocks (particularly caudal blocks) as well as peripheral nerve blocks (Table 48.1) [33]. This report described in general terms the techniques used for regional anesthesia in children and the adverse event rates in this cohort – which represented the largest such collection of regional anesthesia cases in children ever studied. The most notable findings included the fact that there were no deaths or long-term complications, and that the vast majority of blocks were placed while the patients were sedated or anesthetized. They also noted the fact that ultrasound guidance was almost universally used in the placement of these blocks. This information has served to

Table 48.1 Pediatric Regional Anesthesia Network (PRAN) summary of single injection blocks and adverse event rates in 14,917 regional blocks

	Total procedures	Total adverse events (%)	No sequelae	No sequelae – change in treatment
Neuraxial				
Caudal	6011	172 (3)	60	112
Lumbar	103	5 (5)	1	4
Thoracic	13	2 (15)	0	2
Subarachnoid	83	5 (6)	4	1
Total neuraxial	6210	183 (3)	64	119
Upper extremity				
Interscalene	80	0	0	0
Supraclavicular	164	6 (4)	2	4
Infraclavicular	40	0	0	0
Axillary	99	2 (2)	1	1
Musculocutaneous	5	0	0	0
Elbow	1	0	0	0
Wrist	7	0	0	0
Other	58	0	0	0
Total	455	8 (2)	3	5
Lower extremity				
Lumbar plexus	78	6 (8)	4	2
Fascia iliaca	221	1 (0.5)	0	i
Femoral	872	6 (0.7)	3	3
Sciatic	413	14 (3)	3	11
Popliteal fossa	319	2 (0.6)	0	2
Saphenous	78	0	0	0
Other	325	5 (2)	2	3
Total	2307	33 (1)	11	22
Head and neck				
Supraorbital/ supratrochlear	58	0	0	0
Infraorbital	139	0	0	0
Greater auricular/ superficial cervical	157	0	0	0
Occipital	101	0	0	0
Greater palatine	11	0	0	0
Other	89	0	0	0
Total	556	0	0	0
Other block type				
Intercostal	39	0	0	0
Ilioinguinal/ iliohypogastric	737	3 (0.4)	1	2
Rectus sheath	294	0	0	0
Paravertebral	14	1 (7)	0	1
Penile	230	0	0	0
Transverse abdominis plane	140	1 (0.7)	0	1
Other	395	0	0	0
Total	1849	5 (0.3)	1	4

Source: from Polaner et al [33] with permission of John Wiley and Sons.

reinforce (with data) the generally accepted practice of placing major conductive nerve blocks while patients are under general anesthesia or deep sedation.

Over the last several years, the PRAN has continued to produce reports on the safety of pediatric regional anesthesia. Papers cataloging the adverse event rates associated with interscalene blocks [34], caudal blocks, continuous peripheral nerve catheters, transversus abdominis plane blocks [35], and neuraxial catheters in neonates [36] have been published. In every case, the collaborative has shown that the incidence of serious complications with these blocks is low, even though in some cases (such as neuraxial catheters in neonates) the risk of minor adverse events could be significant (13%). Perhaps more importantly, the PRAN has helped clinicians understand the nature of pediatric regional anesthesia practice by providing insights into the frequency of nerve block application.

The PRAN has allowed data to be developed concerning peripheral nerve blocks that would have been impossible to obtain in the absence of a data-sharing collaborative. RCTs involving relatively limited number of patients could not lead to the broad understanding of this practice that this collaborative has developed. The ability to both describe a wide range of practice, and understand the nature and frequency of outcomes that are infrequent, is impossible without this type of data accumulation and analysis. The ongoing work of this group has shaped the practice of pediatric regional anesthesia and will continue to do so going forward.

Pediatric Perioperative Cardiac Arrest registry

The Pediatric Perioperative Cardiac Arrest (POCA) registry was perhaps the earliest registry effort specifically organized to address issues related to pediatric anesthesia and perioperative care. It was developed in 1994 to track anesthesia-related cardiac arrests and deaths in children during the administration of or recovery from anesthesia and to determine the clinical factors and outcomes associated with cardiac arrest in anesthetized pediatric patients. In this case, rather than collect ongoing data on practice from medical records, the organizers sought to enlist centers that would voluntarily and anonymously agree to send standardized information on all perioperative cardiac arrests to the database. A representative from each participating organization also provided annual demographic information for the surgical population. In this way, the POCA registry could provide both analysis of severe adverse events and estimated rates at which these events occurred. Given that this collaborative was started before the era of EMRs, much of the data was collected through painstaking chart review.

In the first report from this collaborative, data was gathered from 63 institutions; 150 cardiac arrests were evaluated that were thought to be related to anesthesia care [37]. The overall rate of arrest was calculated to be approximately 1.5 in 10,000 anesthetics. Cardiovascular depression related to halothane alone or in combination with other medications was found to be responsible for two-thirds of the arrests. Two factors were found to be independently related to arrest – ASA status of 3–5 (odds ratio 12.99) and emergency status (odds ratio of 3.99). Infants younger than 1 year of age accounted for 55% of all anesthesia-related arrests. A subsequent report from this registry tracked arrests occurring in children with underlying cardiac disease [38]. In this case data came from 80 institutions and the authors evaluated the underlying anomalies in those who experienced arrest. Patients with single-ventricle anomalies were most commonly involved, but those with aortic stenosis or cardiomyopathy were found to have the highest mortality rate (62% and 50%, respectively) (Table 48.2).

The outcomes from the POCA registry helped codify risk concerning the rare, but all important, issue of perioperative cardiac arrest in children. These data would have been impossible to accumulate and analyze without the significant effort of all involved. While the outcomes analyzed in this effort are unarguably important, the POCA registry was limited by its ability to only analyze the most critical incidents in pediatric anesthesia practice. Current electronic medical record technology, combined with data-sharing networks, can/should allow investigators to evaluate much more nuanced

Table 48.2 Cardiac diagnoses in children with anesthesia-related cardiac arrest in the Pediatric Perioperative Cardiac Arrest (POCA) Registry

Lesion	*n* (% of 127)
Single ventricle	24 (19%)
Hypoplastic left heart syndrome	9
Double outlet right ventricle	5
Unbalanced AV canal	4
Tricuspid atresia	3
Pulmonary atresia	2
Double inlet left ventricle	1
Left-to-right shunt	23 (18%)
Ventricular septal defect	9
Patent ductus arteriosus	5
Atrioventricular canal	4
Combined lesions (ASD, VSD, PDA)	5
Obstructive lesions	20 (16%)
Aortic stenosis*	13
Coarctation of the aorta	6
Aortic obstruction	1
Cardiomyopathy	16 (13%)
Dilated	4
Hypertrophic	2
Restrictive	1
Disease specific	
Duchenne muscular dystrophy	4
Renal disease	2
AIDS	1
Unspecified	2
Tetralogy of Fallot	15 (12%)
Truncus arteriosus	6 (5%)
Miscellaneous	23 (18%)
Pulmonary hypertension	4
Status post heart transplant	3
Heart block	3
Wolff–Parkinson–White	2
Other†	11

* Two with Williams syndrome and four with pulmonary stenosis.
† Other includes anomalous pulmonary veins, coronary artery disease, Ebstein anomaly, interrupted aortic arch, left ventricular hypertrophy, myocarditis, prolonged QT syndrome, sick sinus syndrome, systemic hypertension, transposition of the great vessels, and unspecified (one each).
AIDS, acquired immunodeficiency syndrome; ASD, atrial septal defect; AV, atrioventricular; PDA, patent ductus arteriosus; VSD, ventricular septal defect.
Source: Reproduced from Ramamoorthy et al [38] with permission of Wolters Kluwer.

precursor events, along with future rates of pediatric perioperative cardiac arrests. Automated data collection makes more comprehensive, real-time, data collection possible and affordable.

Congenital Cardiac Anesthesia Society database

In order to more completely understand the nature of outcomes in anesthesia for children with congenital heart disease, the Congenital Cardiac Anesthesia Society (CCAS) created its own database to collect data on treatment of this population. This registry has the distinction of partnering with a surgical society with overlapping patient interest (the STS) to further the analysis of the care of these children.

There are multiple uses for the data gathered by the CCAS and STS. These organizations used data extraction from their combined database over the years 2010 to 2013 to describe the use of dexmedetomidine in patients undergoing congenital heart disease surgery [39]. Outcomes were analyzed for 12,142 operations of which 3600 (29.6%) received dexmedetomidine. Patients who received the drug were generally of a lower risk profile and (not unexpectedly) had better outcomes (Table 48.3). As such, the report is somewhat limited by selection bias, but shows the power of collaborative efforts between anesthesia and surgical interest groups that will doubtless result in an enormous amount of new and helpful outcome data in the near future.

Wake Up Safe registry

The Quality and Safety Committee of the Society for Pediatric Anesthesia initiated the Wake Up Safe (WUS) registry as a quality improvement effort in 2006. The aim of this collaborative has been to create a registry of serious adverse events in a de-identified manner. The ultimate goal of this group has been to implement change in processes of care that will improve patient safety and quality through analysis of collected adverse events. As with the POCA registry, the WUS effort requires participating centers to submit data on the types and numbers of anesthetics performed in addition to the index events themselves. Analysis of each adverse events is reviewed by three anesthesiologists who were not involved in the event. Root cause analysis is used to identify causal factors [40].

Recently Christensen used data from this collaborative to report on the nature of cardiac arrests occurring in the postanesthesia care unit. The study reported 26 such events and found that 67% were likely preventable. Along with analysis of the errors associated with these events, the authors noted that events of cardiac origin were much more likely to result in permanent harm or death than events of respiratory origin. Another report from this group evaluated medication errors [41]. In this case 32 institutions submitted 276 medication error events. The authors outlined the phase of the medication delivery when these events occurred along with the nature of the error (e.g. wrong dose administration (30%) versus syringe swap (18%) (Table 48.4) and types of medications involved in the errors (Box 48.1). Notably, 80% of the errors actually reached the patient; 50% were thought to result in patient harm; almost all events (97%) were thought to be preventable.

As with the POCA registry, the WUS registry offers the opportunity to evaluate events from a number of institutions. This type of data aggregation and analysis allows evaluation of relative small numbers of events collected from large numbers of cases. The resulting reports (that include contributing factors and possible corrective actions) are not possible from single-center data collection.

Report on pain prevalence and trajectories following pediatric spinal fusion surgery

A very different recently published project involves reports on pain prevalence and trajectories following pediatric spinal fusion surgery [42]. This multicenter registry collected survey information on very specific pain issues in patients undergoing correction of idiopathic scoliosis. In this case the investigators wished to specifically determine the pain prevalence of patients at various points before and after scoliosis surgery. The outcome measure was the Scoliosis Research Society Questionnaire-Version 30, which includes pain, activity, mental health, and self-image scales. Patients were evaluated just prior to surgery and then at 1 and 2 years postsurgery. Thirty five percent of patients reported pain in the moderate to

Table 48.3 Unadjusted outcomes of patients receiving versus not receiving dexmedetomidine (DEX) from the Congenital Cardiac Anesthesia Society Registry

Variable	Level	Overall, *n* = 12,142 (%, 95%CI of %)*	No DEX *n* = 8542 (%, 95%CI of %)*	Yes DEX *n* = 3600 (%, 95%CI of %)*	p
In-hospital mortality	Yes	399 (3.3, 3.0–3.6)	351 (4.1, 3.7–4.6)	48 (1.3,1.0–1.7)	<0.0001
Any complication	Yes	4894 (40.3, 39.4–41.2)	3811 (44.6, 43.6–45.7)	1083 (30.1, 28.6–31.6)	<0.0001
Any major complication	Yes	1474 (12.1, 11.6–12.7)	1193 (14.0,13.2–14.7)	281 (7.8, 6.9–8.7)	<0.0001
Arrhythmia	Yes	2236 (18.4, 17.7–19.1)	1779 (20.8, 20.0–21.7)	457 (12.7, 11.6–13.8)	<0.0001
Postoperative neurological deficit	Yes	277 (2.3, 2.0–2.6)	231 (2.7, 2.4–3.0)	46 (1.3, 0.9–1.6)	<0.0001
Duration of mechanical ventilation	Median, 95% CI (h)	16.0, 15.3–16.7	23.5, 22.8–24.1	6.0, 5.8–6.2	<0.0001
Patient LOS	Median, 95% CI (d)	6.0, 6.0–6.0	7.0, 7–7	6.0, 5.0–6.0	<0.0001

* 95%CIs of median for continuous variables were attained using distribution-free confidence limits for percentiles. 95%CIs for binary variables were attained using asymptotic Wald confidence limits for binomial proportion.

CI, confidence interval; LOS, length of stay.

Source: Reproduced from Schwartz et al [39] with permission of Wolters Kluwer.

Table 48.4 Medication errors by phase of delivery in the Wake Up Safe Registry

Phase of delivery	Error type	Number of reported events
Preparation (non-prefilled syringes)	Vial or ampule swap	25
	Labeling error	5
Prescription (lack of provider knowledge)	Wrong dose	42
	Wrong drug	14
	Allergy to drug	11
Administration (accidental error)	Wrong dose	84
	Syringe swap	49
	Duplicate administration	13
	Omission/failure to act	11
	Overdose	7
	Wrong infusion rate	5
	Wrong time	4
	Wrong route	4
	Expired medication	1
	Wrong patient	1

Source: Reproduced from Lobaugh et al [43] with permission of Wolters Kluwer.

Box 48.1: Types of medications involved in errors in the Wake Up Safe Registry

	N
• Opioid	50
• Sedative/hypnotic	38
• Antibiotic	29
• Vasoactive	26
• Non-opioid analgesic	26
• Anticoagulant/heparin/protamine/thromboxane	23
• Paralytic reversal agent	16
• Local anesthetic	16
• Neuromuscular blocker	13
• Crystalloid solution (saline/LR/D5)	12
• Electrolytes/furosemide/mannitol/dextrose/insulin/nutrition	9
• Antiemetic	8
• Volatile anesthetic/nitrous oxide	6
• Steroid (non-antiemetic)	2
• Unknown	2

Source: Reproduced from Lobaugh et al [43] with permission of Wolters Kluwer.

severe range presurgery and 11% reported pain at 1 year; 15% reported pain at 2 years. Of the different pain trajectories reported, there were significant differences on the self-image, mental health, and age metrics. The authors suggest that identifying factors that predict poor long-term outcomes in children with postsurgical pain may prevent the development of chronic pain into adulthood. Unlike the PRAN database mentioned earlier, this report does not detail the anesthetic management of these patients or any adverse events related to their interventions. A future data registry that includes information on the surgical correction and the anesthetic/pain management of these patients would add important information on potential confounders.

Pediatric Craniofacial Surgery Perioperative Registry

The Pediatric Craniofacial Surgery Perioperative Registry was established by the Pediatric Craniofacial Collaborative Group to promote understanding of the practices and outcomes in children undergoing operative procedures for craniosynostosis. These procedures involve complex cranial vault reconstruction which often is associated with significant blood loss and lengthy operative times. This collaborative is interested in promoting quality improvement through shared data on key aspects of patient management. For their first peer-reviewed publication, data collected from 2012 to 2015 were extracted from the registry, including demographics, perioperative management, length of stay, and blood management [43]. Outcomes analyzed included intraoperative and perioperative transfusion volumes and length of stay data. Adverse events and significant outlier data were analyzed. In all, 1223 cases were analyzed with over 70% being below 24 months of age at the time of their procedure (Table 48.5). The results revealed a very high rate of transfusion (95% for those under 2 years old) and a number of significant adverse events, including cardiac arrest, seizures, unplanned ventilation, and second surgeries. As is the case for many pediatric anesthesia registry efforts, this project allows clinicians to understand the nature of the care provided patients undergoing these procedures as well as some idea of the frequency and nature of adverse events. These kinds of data are impossible to assemble from a single institution's experience and allow some element of benchmarking for those who provide anesthesia for these patients.

Pediatric Sedation Research Consortium

The Pediatric Sedation Research Consortium (PSRC) is a consortium of hospitals and medical centers dedicated to sharing information on sedation in an effort to understand better what works and what does not work for sedation of children. This group is made up of a variety of pediatric specialists from 40 institutions in the United States and Canada. Information includes demographic data, procedure, coexisting illness, provider of sedation, drugs used, monitors, outcomes of the sedation, etc. This database is somewhat unique in that it is a collaboration between anesthesiologists and a variety of other specialists in pediatrics. After more than 10 years, there are almost 500,000 sedation encounters in the database. In September 2006 the first paper from the PSRC describing the types of adverse events and unexpected airway management issues encountered during the first 30,000 sedations collected by this consortium was published in the journal *Pediatrics* [44]. Serious adverse events were rare, but this study described the incidence of airway interventions and other unexpected adverse events (Table 48.6).

The authors suggested that these data help define the critical competencies necessary when providing procedural sedation. These competencies include recognition of apnea, clearing of an airway, airway adjunct insertion, and provision of positive pressure ventilation. A subsequent paper was published in *Anesthesia and Analgesia* in 2009 [16]. This paper discussed data from 49,836 sedation encounters utilizing primarily propofol. Data were evaluated for complications and

Table 48.5 Selected perioperative outcomes in patients younger than versus older than 24 months of age from the Pediatric Craniofacial Registry*

Outcome	≤24 months (*n* = 935)	>24 months (*n* = 288)	p-value†
Intraoperative erythrocyte-containing blood products (mL/kg)‡	33.9±27.2	21.9±19.4	<0.0001
>40	30%	16%	<0.0001
>60	11%	3.5%	<0.0001
>80	5%	1.0%	0.003
Total perioperative blood products (mL/kg)§	45.3±41.6	26.7±27.1	<0.0001
Total perioperative blood donor exposures	1 (1–2)	1 (1–2)	0.01
≥1	95%	79%	<0.0001
≥2	46%	43%	0.54
≥3	20%	19%	0.90
Duration of surgery (min)	227±85	268±118	<0.0001
Initial postoperative hemoglobin (g/dL)‖	11.3±2.3	10.9±1.9	0.002
Δ hemoglobin (g/dL)‖	0.5±2.4	1.5±1.9	<0.0001
Last hemoglobin before discharge (g/dL)	10.7±1.8	10.4±1.5	0.01
ICU LOS (days)	2 (1–3)	2 (2–3)	0.03
Hospital LOS (days)	4 (4–5)	5 (4–6)	0.20

* Data presented as mean ± SD for transfusion volumes and duration of surgery. Data are presented as median (25th to 75th interquartile range) for the LOS and total blood perioperative donor exposures.
† Student's *t*-test for comparisons of transfusion volumes, duration of surgery, and last hemoglobin before discharge; Wilcoxon rank sum test for overall blood donor exposure and LOS comparisons; and chi-square test for comparisons of percentages in transfusion volume and percentages of patients having specified blood donor exposures.
‡ Intraoperative erythrocyte-containing products include packed red blood cells, whole blood, and reconstituted blood.
§ Total perioperative blood products include erythrocyte-containing products, fresh frozen plasma, platelets, and cryoprecipitate.
‖ Initial postoperative hemoglobin measurement (day of surgery) available in 855 patients less than or equal to 24 months old and 266 patients more than 24 months old. Preoperative and initial postoperative hemoglobin measurements available in 798 patients less than or equal to 24 months old and 253 patients more than 24 months old.
ICU, intensive care unit; LOS, length of stay.
Source: Reproduced from Stricker et al [43] with permission of Wolters Kluwer.

Table 48.6 Adverse events from the Pediatric Sedation Research Consortium Report on pediatric procedural sedation

	Incidence per 10,000	*n*	95%CI
Adverse events			
Death	0.0	0	0.0–0.0
Cardiac arrest	0.3	1	0.0–1.9
Aspiration	0.3	1	0.0–1.9
Hypothermia	1.3	4	0.4–3.4
Seizure (unanticipated) during sedation	*2.7*	8	1.1–5.2
Stridor	4.3	11	1.8–6.6
Laryngospasm	4.3	13	23–7.4
Wheeze (new onset during sedation)	47	14	25–7.8
Allergic reaction (rash)	5.7	17	33–9.1
Intravenous-related problems/complication	11.0	33	7.6–15.4
Prolonged sedation	13.6	41	9.8–18.5
Prolonged recovery	22.3	67	173–283
Apnea (unexpected)	24.3	73	19.1–305
Secretions (requiring suction)	41.6	125	34.7–49.6
Vomiting during procedure (non-gastrointestinal)	47.2	142	39.8–55.7
Desaturation below 90%	156.5	470	142.7–171.2
Total adverse events	339.6(1 per 29)	1020	308.1–371.5
Unplanned treatments			
Reversal agent required (unanticipated)	1.7	5	0.6–3.9
Emergency anesthesia consult for airway	2.0	6	0.7–43
Admission to hospital (unanticipated; sedation related)	7.0	21	43–10.7
Intubation required (unanticipated)	9.7	29	65–13.9
Airway (oral; unexpected requirement)	27.6	83	22.0–342
Bag–mask ventilation (unanticipated)	63.9	192	55.2–73.6
Total unplanned treatments	111.9(1 per 89)	336	853–130.2
Conditions present during procedure			
Inadequate sedation, could not complete	88.9(1 per 338)	267	78.6–100.2

Source: Reproduced from Cravero et al [44] with permission of Pediatrics.

effectiveness of sedation. The study outcomes showed a very high rate of success (over 99% completed procedures) with a low rate of serious adverse outcomes. Other papers from this group have included analysis of adverse events between different specialists [45], the use of end-tidal CO_2 monitoring during sedation [46], the association between nil per os status [47] and adverse events, the effect of obesity on adverse event rates [48], sedation provided by pediatricians [49], sedation for gastrointestinal procedures [50], and several others [51–53]. Taken together, the prospective cohort studies from the PSRC have helped investigators describe outcomes of pediatric sedation practice with data. The information provided has the potential to help shape sedation recommendations and guidelines going forward.

Pediatric Difficult Intubation Registry

To address the issues relating to the incidence and nature of difficult intubation in children, the Pediatric Difficult Intubation Registry was formed by 13 children's hospitals in the USA. The group has established standard data collection methods and has successfully established a web-based registry for difficult intubation encounters. As with many of the large data analysis groups mentioned, this collaborative has the advantage of both reporting on the outcomes of interest (adverse events associated with difficult airway management) and on airway management practices as they exist across the participating centers. In one published report, investigators reported on multiple aspects of pediatric airway management involving 1018 difficult pediatric tracheal intubation encounters (Table 48.7) [54]. In children who were proven to have a difficult airway, the first attempt at intubation was by direct laryngoscopy in 46%, followed by fiberoptic bronchoscopy in 28%, and indirect videolaryngoscopy in 18%. Success rates were widely different, ranging from 3% with direct laryngoscopy to 55% with indirect laryngoscopy. The authors also separated "severe" (3%) from "non-severe" (30%) outcomes. They were able to describe patient characteristics that were most likely to be associated with complications – weight less than 10 kg, short submental distance, and more than three direct laryngoscopy attempts prior to trying another method of intubation.

The findings from analysis of this registry are not surprising, but the approach is promising for the future of this effort and others like it. The strict definition of the data elements and outcomes selected allows for consistency in reporting that is not possible without very large data collection efforts that look at broad aspects of pediatric anesthesia practice. Ongoing data collection from the Pediatric Difficult Intubation Group will allow tracking of the frequency and nature of adverse airway events, as well as the evolving nature of airway management as centers shift from direct to indirect laryngoscopic methods for all types of airway management.

APRICOT registry study

The APRICOT (**A**naesthesia **PR**actice **I**n **C**hildren **O**bservational **T**rial) registry study of 31,127 anesthetics in 261 hospitals in 33 European countries consisted of detailed prospective data collection for every anesthetic for patients aged 0–15 years over a 2-week period in 2014 or 2015 in each hospital [55]. The primary outcome was the incidence of perioperative severe critical events requiring immediate intervention. A severe critical event was defined as the occurrence of respiratory, cardiac, allergic, or neurological complications requiring immediate intervention and that led (or could have led) to major disability or death. This study revealed a 5.2% incidence of severe critical perioperative respiratory or cardiac events, with a 10–15% incidence in infants and neonates (Fig. 48.3). This rate of severe events is considered to be high, and the study also revealed a large variability in the practice and outcomes of pediatric anesthesia in Europe. This study could be repeated after targeted education and quality improvement strategies are implemented to assess whether they are associated with lower rates of critical events.

KEY POINTS: DATABASES AND REGISTRIES SPECIFIC TO PEDIATRIC ANESTHESIA

- Registries collect data about specific features of anesthesia of interest, such as regional anesthesia, cardiac arrests, medication errors, craniofacial cases, difficult intubation, etc.
- Databases collect more comprehensive information about every anesthetic in a particular field, regardless of complication rate. Examples are databases of anesthetics for pediatric cardiac patients, or pediatric anesethetics and sedations outside of operating rooms

Pediatric anesthesia data-based outcomes analysis from single institutions

Consideration of large datasets can influence pediatric anesthesia practice in many ways. As outlined in this chapter, studies using this methodology have added greatly to the collected knowledge concerning adverse events (and safety in general) in the areas of practice that each of these efforts is based in. Many individual institutions have ongoing efforts that use large amounts of integrated data from their own practice to establish systems that help evaluate the quality of care by continuously evaluating outcomes. As an example, the system at Boston Children's Hospital continuously integrates data from preoperative assessment, intraoperative care, postanesthesia care unit recovery status, and remote postoperative information into one relational database (Fig. 48.4) [56]. Once data have been consolidated into the application, it is available in numerous output formats, depending on the audience. For this project, two separate strategies can be chosen:

1. Researchers tend to want large amounts of very detailed information relating specific factors/interventions and outcomes that can be presented in tabular form (Fig. 48.5). Relationships are analyzed for statistically significant correlations using well-described methods.
2. Clinicians and administrators desire large amounts of information that indicate trends in care or overall performance. They desire a method of viewing information that makes the trends easy to visualize. For this, the data dashboard has been developed (Fig. 48.6). In this case, data

Table 48.7 Association between airway management techniques and complications in 1018 patients in the Pediatric Difficult Intubation (PeDI) Registry

	Anticipated difficult airway (*n* = 821)			Unanticipated difficult airway (*n* = 197)			Total (*n* = 1018)		
	No complications (*n* = 664)	Complications (*n* = 157)	p-value	No complications (*n* = 150)	Complications (*n* = 47)	p-value	No complications (*n* = 814)	Complications (*n* = 204)	p-value
Induction technique			0.36			0.15			0.083
Mask induction	430 (65%)	99 (63%)	..	93 (62%)	24 (51%)		523 (64%)	123 (60%)	
IV induction	180 (27%)	43 (27%)	..	53 (36%)	20 (43%)		233 (29%)	63 (31%)	
IV sedation	36 (6%)	8 (5%)		2 (1%)	0 (0%)		38 (5%)	8 (4%)	
Tracheal induction	9 (1%)	1 (1%)		0 (0%)	0 (0%)		9 (1%)	1 (0%)	
NA	9 (1%)	6 (4%)		2 (1%)	3 (6%)		11 (1%)	9 (4%)	
Anesthesia approach			0.11			0.04			0.005
General	610 (92%)	145 (92%)		145 (97%)	44 (94%)		755 (93%)	189 (93%)	
Sedation	47 (7%)	7 (4%)		3 (2%)	0 (0%)		50 (6%)	7 (3%)	..
Awake	6 (1%)	4 (3%)	..	2 (1%)	0 (0%)		8 (1%)	4 (2%)	
None	1 (0%)	1 (1%)		0 (0%)	3 (6%)		1 (0%)	4 (2%)	
Intubation route*			0.12			0.22			0.088
Oral	488 (74%)	109 (73%)		128 (90%)	40 (87%)		616 (77%)	149 (76%)	
Nasal	166 (25%)	37 (25%)	..	10 (7%)	5 (11%)		176 (22%)	42 (21%)	
Surgical	0 (0%)	1 (0%)	..	0 (0%)	1 (2%)		0 (0%)	2 (1%)	
Other	5 (1%)	3 (2%)		4 (3%)	0 (0%)	..	9 (1%)	3 (2%)	
First attempt device†			0.006			0.30			0.001
Direct laryngoscope	220 (33%)	69 (45%)	..	128 (87%)	44 (94%)		348 (43%)	113 (56%)	
Flexible fiberoptic bronchoscope	226 (34%)	51 (33%)		5 (3%)	2 (4%)		231 (29%)	53 (26%)	
Glidescope	158 (24%)	19 (12%)		5 (3%)	1 (2%)		163 (20%)	20 (10%)	..
Other or combined	57 (9%)	15 (10%)		10 (7%)	0 (0%)		67 (8%)	15 (7%)	..
Successful device†			0.06			0.49			0.037
Direct laryngoscope	41 (6%)	17 (12%)		46 (34%)	17 (37%)	..	87 (11%)	34 (18%)	
Flexible fiberoptic bronchoscope	281 (43%)	69 (47%)		22 (16%)	6 (13%)		303 (39%)	75 (39%)	
Glidescope	241 (37%)	42 (29%)		48 (36%)	13 (28%)		289 (37%)	55 (29%)	
Other or combined	89 (14%)	18 (12%)		18 (13%)	10 (22%)		107 (14%)	28 (15%)	..
Neuromuscular blockade use	268 (40%)	63 (40%)	0.96	72 (48%)	30 (64%)	0.06	340 (42%)	93 (46%)	0.32

Data are *n* (%), unless otherwise stated.
* Data are missing in 19 cases.
† Data are missing in eight cases.
IV, intravenous; NA, not applicable.
Source: Reproduced from Fiadjoe et al [54] with permission of Elsevier.

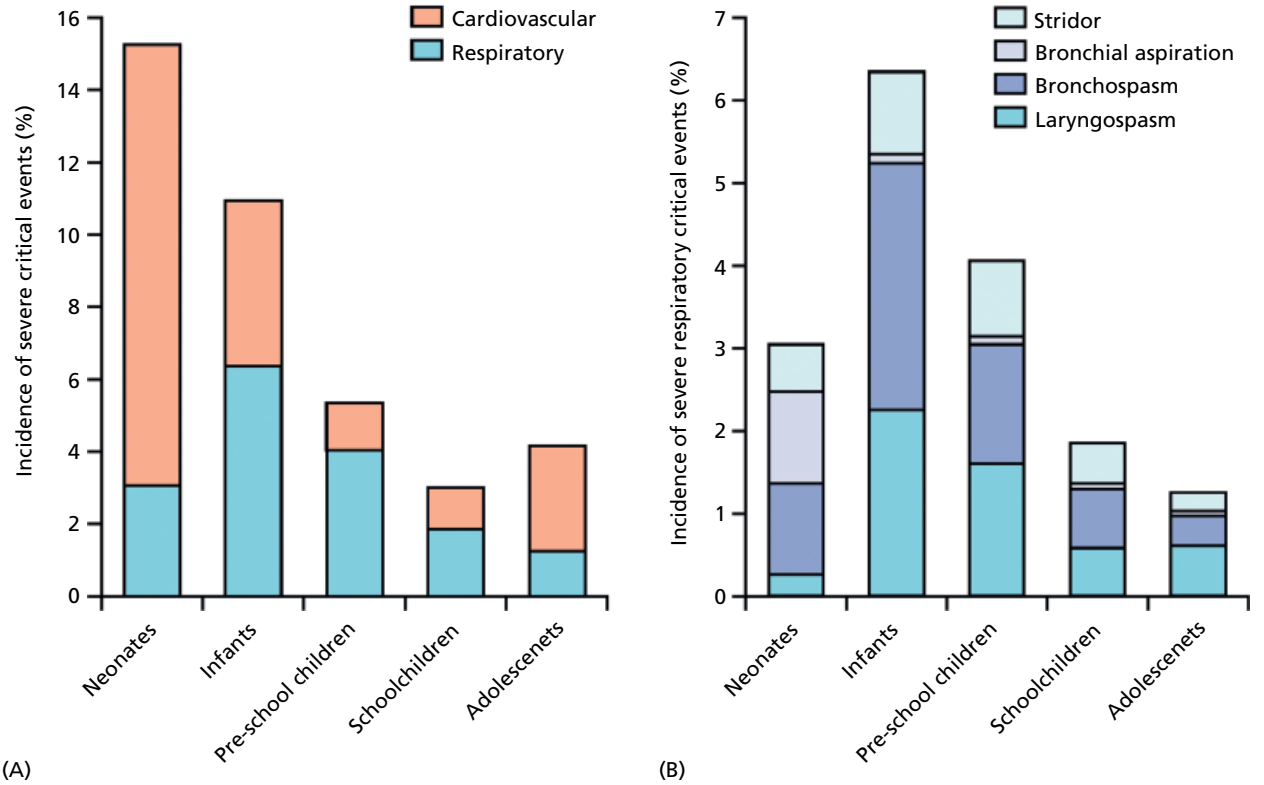

Figure 48.3 Incidence of severe critical perioperative events from the APRICOT Registry study. (A) Cardiovascular events by age group. (B) Respiratory events by classification and age group. *Source*: Reproduced from Habre et al [55] with permission of Elsevier.

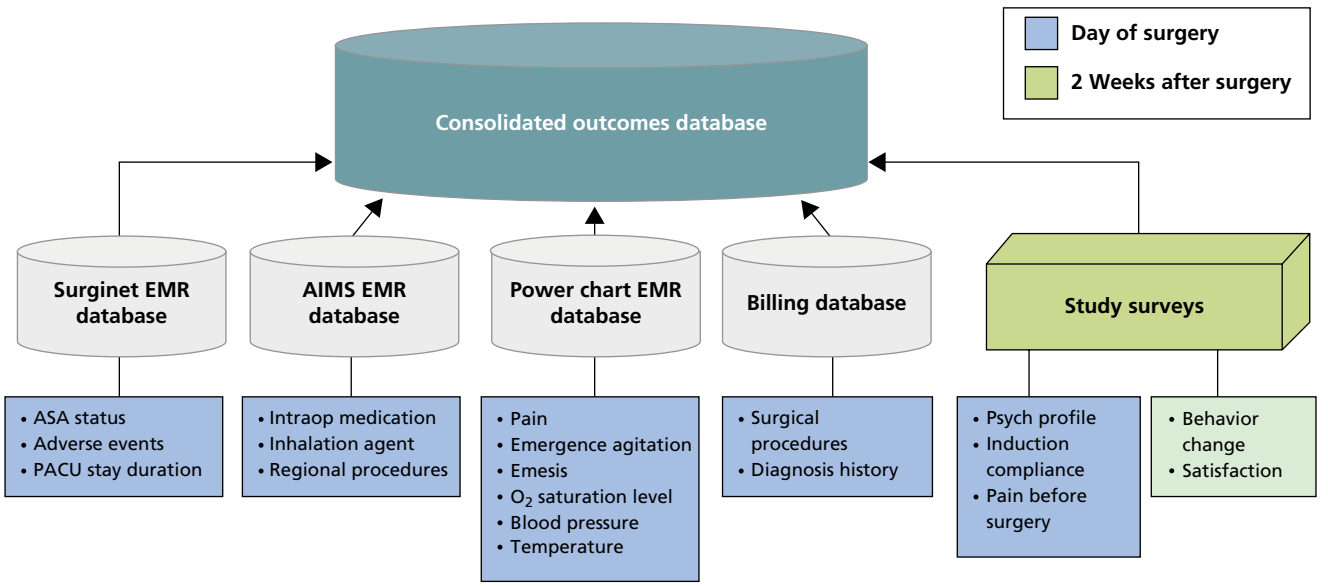

Figure 48.4 Schematic of data acquisition and integration for comprehensive continuous outcomes analysisshowing the ongoing collection and aggregation of data from the preoperative medical record (Surginet EMR), intraoperative record (AIMS EMR), postoperative care unit data (Power Chart EMR), billing data, and any added study surveys into a consolidated outcomes database which is searchable. AIMS, anesthesia information management systems; ASA, American Society of Anesthesiology; EMR, electronic medical record; PACU; postanesthesia care unit. *Source*: Data from Boston Children's Hospital.

visualization software allows individuals to choose the surgery, age group, contributing factors, and outcomes they want to analyze.

These two visualizations are made possible through the data export (detailed view for researchers) and data dashboard (feedback clinicians' view). The data export component contains a large number of standard metrics, but also allows for the researcher to specify specific derivations from housed data (e.g. what is the rate of severe pain in patients undergoing tonsillectomy). Alternatively, the data dashboard

	Total *N*	Patients with high pain scores		Univariate analysis (*P* value)
		Number of patients	% With 95% CI	
Gender				
Male	354	78	18 (±3.1)	0.29
Female	237	61	20 (±3.2)	
Age				
0–2	263	65	20 (±3.2)	0.59
3–6	85	22	21 (±3.3)	
7–9	146	28	16 (±3.0)	
10–15	91	22	19 (±3.1)	
16–21	6	2	25 (±3.5)	
Weight				
<25 kg	252	62	20 (±3.2)	0.57
≥25 kg	339	77	19 (±3.1)	
ASA				
1 or 2	555	130	19 (±3.1)	0.68
3 or 4	34	9	21 (±3.3)	
Dev delay				
No	501	121	19 (±3.1)	0.45
Yes	88	18	17 (±3.0)	
Procedure				
Tonsillectomy	355	108	23 (±3.3)	0.000 (0.200 coefficient)
other	236	31	12 (±2.6)	
Propofol				
No	501	121	19 (±3.1)	0.452
Yes	88	18	17 (±3.0)	
Dexmedetomidine				
No	508	114	18 (±3.1)	0.098
Yes	81	25	24 (±3.4)	
Induction compliance				
No	132	34	20 (±3.2)	0.947
Yes	213	50	19 (±3.1)	
Agitation				
No	258	44	15 (±2.8)	0.000 (0.328 coefficient)
Yes	165	66	29 (±3.6)	
Two-day behavior changes				
Negative changes	173	47	21(±3.3)	0.224
No changes	56	13	19 (±3.1)	
Two-week behavior changes				
Negative changes	140	41	23 (±3.4)	0.039 (0.126 coefficient)
No changes	129	22	15 (±2.8)	
Length of stay in PACU				
0–30 min	9	1	10 (±2.4)	0.000 (0.190 coefficient)
30–60 min	83	8	9 (±2.3)	
60–120 min	302	63	17 (±3.0)	
120–180 min	103	34	25 (±3.5)	
180+min	94	33	26 (±3.5)	

Figure 48.5 Detailed tabular display of outcome data from tonsillectomy surgery. *Source*: Data from Boston Children's Hospital.

displays a subset of aggregated data from the integrated database through the use of standard pie charts. These aggregated data are transferred into a cache, which increases performance when the data are retrieved in the dashboard. The controls on the dashboard allow for clinicians to easily explore different relationships within the data that are of interest to them. Ultimately, all of the data are stored in a database environment that is managed by the hospital database administrators.

The result of this system is an ongoing data collection and reporting strategy that is expected to meet both the research and ongoing quality improvement goals of the department.

KEY POINTS: PEDIATRIC ANESTHESIA DATA-BASED OUTCOMES ANALYSIS FROM SINGLE INSTITUTIONS

- Many individual institutions are now using data from the anesthesia and hospital EMRs to produce reports about outcomes of interest for administrators or clinicians for quality improvement purposes
- Researchers can also harvest very detailed data fields from the EMR and other hospital information systems to address research questions

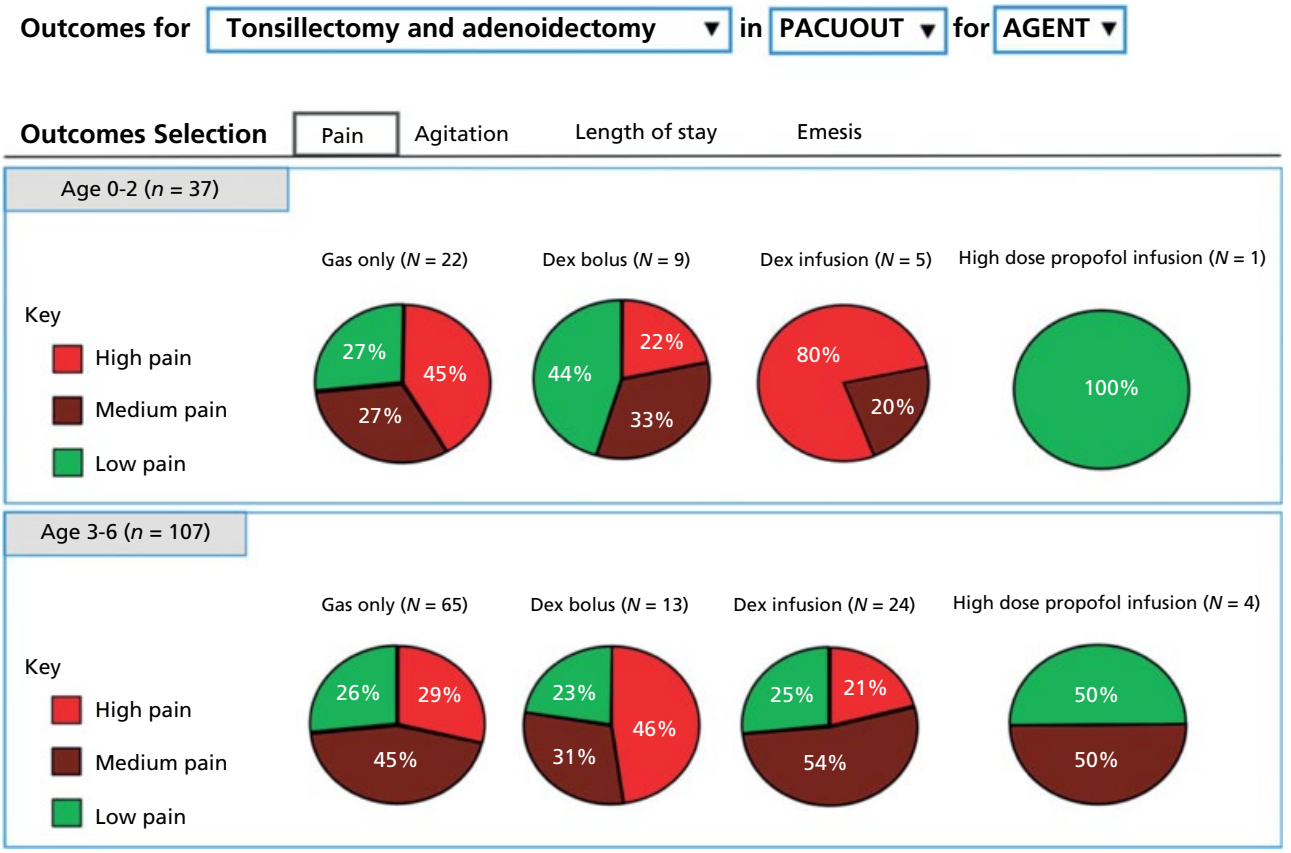

Figure 48.6 Data presentation from the integrated database. The continuously aggregated data include pain outcomes for patients undergoing tonsillectomy and adenoidectomy in the 0–2- and 3–6-year-old age groups. Data are presented based on the type of anesthesia delivered – inhaled agents (only) or inhaled agents with dexmedetomidine. Anesthesia providers choose the surgery, location, age group, and type of outcome they want to view on a daily basis. *Source*: Data from Boston Children's Hospital.

Artificial intelligence and machine learning

The database efforts outlined so far in this chapter are focused on aggregation and analysis of clinical data. The availability of large amounts of data from ubiquitous EMRs has fundamentally changed the manner in which we can evaluate our practice. The next phase of this revolution will take place in the manner in which we process the data that is gathered – through the use of artificial intelligence (AI) and machine learning. AI is revolutionizing the use of large and super-large datasets. This is notable in the way internet search engines and social media companies are utilizing this technology to enhance data processing. For instance, AI is critical to natural language translation and the way in which photos are searched or stored using facial recognition. In its simplest terms, AI allows computer programs to respond to data in a manner that is similar to human intelligence, by learning through experience. All AI is built on machine learning platforms that match input with output data – in large quantities [57]. The application of AI and machine learning to anesthesiology has lagged behind more commercial fields of enterprise, but it is increasing and will continue to revolutionize our field.

Examples of the application of AI and machine learning in anesthesiology can be found in many areas. One of the best examples was described by Lee et al [58] to harness the power of AI in the analysis of total intravenous anesthesia dose–response relationships and the creation of improved closed loop anesthesia algorithms. Because of machine learning techniques, the model used needed no programming of pharmacokinetics or pharmacodynamics, it simply used millions of data points relating dose of drug to bispectral index readings to predict future relationships between infusion rates and bispectral index values. While the performance these investigators were able to describe was better than model-driven pumps, it was still not perfect. Future efforts that would include orders of magnitude more data, could enhance performance and result in performance that is better than ever imagined.

AI will also be helpful in improving the utility of clinical decision support (CDS) software. While CDS tools have been shown to be helpful in reminding anesthesia providers about common tasks (antibiotic administration or blood pressure management), they have been criticized for being generic and ignoring the subtle differences between patients that are inherent in real world applications [59]. Future CDS tools will use machine learning to yield improved predictive analytics. The resultant clinical pathways will be truly "evidence based" since they could be derived from an analysis of huge amounts of data that will be continuously updated and customized for the individual characteristics of the patient who is being treated at any moment [60].

The only logical conclusion from a review of current literature on AI and machine learning is the likelihood of exponential growth in anesthesia and the ultimate evolution

of semi-autonomous anesthesia delivery systems. While this future may seem disconcerting to some, it will (doubtless) lead to increased productivity that could also free up anesthesiologists for more personal patient interactions (such as direct care coordination) that will leverage significant improvements in quality of overall perioperative care and patient satisfaction. Moreover, these developments will only take place through the collaboration of information technologists and clinical scientists who will have to conceive of, and validate, the models that utilize AI in anesthesiology.

Data registry concerns

The current explosion of large data research grows out of the switch from paper to electronic records (also known as EMRs). Electronically collected data are now available on patients concerning both their overall medical history and care and on their operating room data. Data can be included from many geographically or temporally distinct sources into common outcome-oriented databases. This aggregation of data allows investigators to evaluate a total number of patient encounters (or "*n*") that would otherwise be impossible to approach. This chapter has noted some of the most notable data-related research in pediatric anesthesia. There are many advantages to database-centered research. However, there are also many issues that can lead to misinterpretation of the data and undermine appropriate use and conclusions from data registry research [61].

Data mining

In traditional clinical studies, investigators begin with a hypothesis and test its validity by comparing interventions in different cohorts of patients. Studies utilizing data registries, on the other hand, are mostly observational in nature and evaluate outcomes by analyzing the data. There is a temptation to search for interesting associations and then further evaluate data elements that are found to be correlated. This is frequently done without strictly defining a hypothesis for data relationships. When embarking on such a study, it is critical for investigators and clinician readers to remember that the phrase "statistical significance" means a given result is unlikely to have occurred by chance. However, there is a possibility that the relationship is by chance. If one simply searches a large database for cause and effect between enough factors, without a reasoned hypothesis, "significant" relationships will be found, even in data that are unrelated. For instance, if we take $p < 0.05$ as the threshold for significant association, one out of 20 random data associations will appear to be related statistically even though the finding simply occurs by chance.

Many methods attempt to account for this possible error. The simplest and most commonly employed is the Bonferroni correction [62–65]. With the Bonferroni methodology, each additional test requires significance to be reached at $1/n$ times what it would be if one was testing only one hypothesis. For example, if one is trying to relate the rate of lung injury to major surgery in neonates and consider five possible factors in addition to a primary factor (such as postconceptual age), the threshold for significance should be held at $p < 0.05/5$ or 0.01 rather than 0.05 – as it would be for the original comparison.

Data mining is a major problem in database research. When considering outcomes derived from registry research, the analysis should be hypothesis driven and planned before analyzing data.

Quality of data

Data collected in the course of clinical care are not always consistent from one person (or institution) to another. Strict definitions for specific outcomes and metrics must be explained and agreed upon by all participants. If this is not done, data collected can be inconsistent and conclusions inaccurate. Furthermore, data registries should establish a framework of procedures for data quality assurance [66]. The procedures in such a framework exist at the coordinating center level as well as at the centers where the data are collected. Auditing of data is required to prevent insufficient data quality, to detect imperfect data, and to define actions to be taken to correct insufficient data. Data systems that collect information for registries should be designed with automatic data "checks" that prevent the inclusion of spurious data. For instance, it should be impossible to enter data that are an order of magnitude higher or lower than that which is expected. Furthermore values that are at the extreme of the expected values should generate messages to assure this is the intended entry.

In terms of anesthesia for pediatric patients, consider the terms "respiratory distress," "bronchospasm," or "laryngospasm." The exact definition applied to each of these terms can vary greatly from one clinician to another. Do these terms imply change in physiological state or simply the appearance or sound of difficulty with air exchange? For instance, the clinical entity that represents "laryngospasm" might be met by a patient with extreme stridor in one institution yet may require complete obstruction of the airway and oxygen desaturation in another. Unless registries have clearly defined outcome terminology, a great deal of uncertainty will be generated when these outcomes are encountered. Registries that restrict analysis to relatively unambiguous outcomes may largely avoid these issues.

Statistical methodology

The use of multivariable regression with stepwise variable selection can lead to results that are difficult to replicate from one large dataset analysis to another. Regression techniques consider patient characteristics as statistical variables in themselves across a large population. Risk calculations are amended with respect to their cumulative known effect on a given outcome of interest. Newer and more sophisticated methods, including propensity score techniques and mixed effects modeling, are better suited for evaluating treatment effects in large registries with multiple possible confounding factors [67–71]. In the most general sense, these methodologies require investigators to identify populations of patients who share characteristics, such as postconceptual age, presence or absence of neurological compromise, etc., and then consider the effect of one variable uncommon to these cohorts – such as anesthesia exposure or surgical intervention. As mentioned earlier, when considering any of these sophisticated statistical methods, it is important to only consider confounders that are likely to affect final outcomes and have been hypothesized to impact results.

Missing confounders

Outcome researchers can only compensate for those confounders that are known to exist or have been demonstrated in past studies [68,69,71]. Unfortunately, there may be a host of other influences that are not known or have not been identified. As an example, investigators may account for age of a neonate at the time of surgery as a major influence on long-term outcome. On the other hand, it may be impossible to completely understand and codify the social context in which these patients subsequently live after birth, or possible drug use by the patient's mother during gestation – even though these factors may heavily influence the long-term outcome for a given patient. The known factor (age at the time of surgery) will be used as a primary factor in the analysis of outcomes, while the numerous other confounders (e.g. environment and prenatal drug exposure) would go unknown and unappreciated in the analysis. Since the patients in observational registries are not randomized, it is easy for these unknown issues to unevenly influence outcomes in groups that are being considered. Many authors will report the issues that were "controlled" for in their analysis of surgical outcomes as if these represent the complete list of all possible influences. In fact, it is always possible that confounders exist, and caution is advised in considering the possible unknown influences on surgical results.

Confounders versus mediators

In any registry is it important to distinguish between variables that are potentially confounders and those that are mediators. Confounders can affect outcome but are unrelated to the primary factor of interest [68,71], while mediators are actually related to the primary factor and work as mechanisms that change the outcome of interest [70,72]. A mediator, therefore, is necessarily linked to the factor of interest and plays a role in determining the relationship between that attribute or variable and an outcome of interest. Statistically, controlling for known confounders is necessary. On the other hand, adjusting for mediators in the causal pathway can reduce or eliminate real associations. For example, infants of diabetic mothers (IDMs) have multiple abnormalities in the newborn period, one of which is a propensity for hypoglycemia. Hypoglycemia can occur during surgery and injure the patient. If an investigator were to consider the outcomes from neonatal surgery in IDM newborns and control for hypoglycemia, this would underestimate the true impact that birth to a diabetic mother may have on overall risk in this cohort since the hypoglycemia that accompanies IDM status would be lost as a factor. Registry researchers should clearly define confounders versus mediators and only control for those factors that are *not* clearly linked to a fundamental aspect of a patient's state or diagnosis.

Selection and measurement bias

Once again, registries are, by definition, not controlled comparison studies. Selection bias results when the study population is non-randomly selected or distributed from the registry population [73]. For instance, if a study wished to consider the incidence of severe pain after surgery and consider the impact of a specific regional anesthesia intervention versus systemic analgesia, it is very possible that the choice to perform regional versus systemic analgesia could be influenced by the presence of preoperative pain or opioid therapy. If an investigator were to compare the pain outcomes in a surgical cohort, it is quite possible that the distribution of patients into the different intervention cohorts could be biased by the amount of pain or the personality characteristics that were present. Such bias would constitute a selection of patients for each intervention that could easily impact outcomes but would not be apparent to the investigator.

There is a similar issue of bias when comparing data across institutions in large data collaboratives. Fair comparisons require accurate risk adjustment for the types of patients and cases that are performed. In adult medicine there are several of these types of tools including the Risk Quantification Index that was developed as an outgrowth of the NSQIP database [74]. This index is based on assessment of current procedure terminology codes and is transparent in its methods for stratifying risk. Another such risk adjustment strategy was devised in order to compare outcomes from neonatal surgery as described by Lillehei et al in 2012 [75]. For this assessment ICD-9 (*International Classification of Disease*, 9th edition) codes were used to group patients and surgeries into one of four risk categories based on previous data reported on surgical outcomes. The resultant classification scheme was validated in three distinct, large, public health datasets. The specific risk stratification strategy used is less critical than the fact that some effort must be made to understand the data coming from various institutions. The data must be considered in the context of the type of patients that experience care at each location and the inherent bias that is present due to the unequal distribution of complexity.

Interpretation issues

Large observational trials with tens of thousands of patient records will often lead to findings of statistical significance with marginal clinical significance [76]. For example, in a database evaluating 10,000 postoperative pediatric patients, a difference at any one time point of 0.3 units on an observational pain scale (from 0 to 10) will have a p-value of 0.0001. At the same time, many observers might argue that (while the difference is likely real) this does not constitute a difference that would impact clinical care. In fact, the exact same difference would have a p-value of >0.05 in a cohort of 20 patients. Investigators as well as clinicians need to consider clinical versus statistical significance in outcomes that are reported in any study, particularly large data trials. The fact that a given data comparison results in statistical significance must be considered in the context of the clinical importance of the difference described.

There are other methods available to consider the issue of "significance" when evaluating outcome data from large data studies. The calculation of relative risk (RR), numbers needed to treat (NNT), and absolute risk reduction (ARR) [77] all help put the calculations of factor correlation into context. Relative risk is the ratio of the risks for a given outcome in a population of interest (by intervention or demographics) versus that in a control group. It is important to recognize that RR is independent of the prevalence of an outcome and therefore (once again) can be misleading to investigators and clinicians. The

RR may be large, but if the baseline prevalence of an outcome is very low, the clinical significance of the effect may be marginal. For instance, the rate of intensive care admission may be five times higher for infants after a given surgery when compared to adolescents. On the other hand, if the rate of admission for adolescents is 0.001%, then even the much higher RR for infants remains so low it would not likely change care parameters. Measures such as the ARR and NNT vary with the rate of an outcome in a population. The ARR is calculated as the difference in the absolute risk rates between a treated cohort and the controls. In the above example it would be 0.005%. The NNT is the number of patients that need to be treated with a given intervention (or in a given demographic group) in order to see a difference of one adverse outcome. This is numerically equivalent to 1/ARR. Both the NNT and ARR can be viewed as methods for avoiding the problem of overvaluing statistical versus clinical significance in large registry studies.

Any discussion of the clinical significance of outcomes must include the clinical impact of the outcome in question. Anesthetic interventions that lead to a significantly higher survival rate are clearly of greater interest than those that may slightly decrease the length of the postanesthesia unit stay.

Finally, when considering the studies from datasets, it must be emphasized that observational data yield results that can suggest association, but rarely indicate causation [78]. Given all of the pitfalls and weaknesses inherent in this kind of data analysis, it is important not to assume that relationships are causal until they have been proven in more controlled studies. Data that suggest association can be extremely helpful in the investigation of very rare conditions and may help in the design of controlled trials. Clinicians need to keep in mind the limitations (as well as the advantages) of this kind of study and base practice on a careful consideration of all aspects of this category of data but confirm assumptions with the highest quality data available.

KEY POINTS: DATA REGISTRY CONCERNS

- Data mining research without strictly defining a hypothesis in advance is subject to random data associations that appear to be related statistically even though the finding is simply occurs by chance
- Quality of data, including missing data and differing data field definitions among different instutions, render conclusions ambiguous if these problems are not addressed before setting up a database
- Missing confounders, selection and measurement bias, and interpretation issues are additional problems that can be encountered in using data registries for research

Future uses of large registry data and outcomes analysis

In general, statistical science indicates that clinical trials are most valuable when large numbers of patients are studied in order to best understand the presence of treatment effect. Collecting and managing data on very large cohorts of patients has traditionally been done by direct observation and entered into paper case report forms or CRFs. Given the trend toward electronic data capture and analysis that has become part of the daily operations for anesthesia departments, the data required for clinical trials are generally readily available on any operative patient. As such, if the data can be made available to clinical trialists (after institutional review board approval), very few data need to be recorded on traditional CRFs. The cost of research can be radically decreased since the study essentially only needs to include acquisition of consent and patient randomization – all subsequent outcomes are automatically included in the electronic data collection [6]. Furthermore, this kind of a trial fits well with the concept of the Response Adaptive Clinical Trial where the goal is to place more patients in the better treatment based on patient responses already accrued in the trial [79–81]. While this type of trial design was difficult when relatively small cohort trials were being tracked manually, the advent of large data and electronic data capture makes this type of a trial much more practical and (potentially) more acceptable to institutional review boards.

An extension of this automated study design includes "real-time" randomization based on automated decision support technology. Study designs can include an algorithm that identifies patients eligible for study (based on a specific set of characteristics – such as hypotension) and then, in real time, allocates them to one type of treatment or another. Outcomes would then be collected from the intraoperative or postoperative electronic health data. Such studies require a waiver of consent from institutional review boards, but this has proven possible when treatments arms are considered equal and not harmful or possibly beneficial. Such a strategy has already been used to study use of clinical alerts in the management of low blood pressure, low bispectral index, and low minimal alveolar fraction events [82]. Another innovative strategy for outcomes analysis is the alternating intervention trial where a specific intervention is initiated in a set of operating venues and then switched to a different intervention after a specific period of time. The switch can occur back and forth several times with outcome data collected automatically through the electronic record, thus eliminating some of the bias that is inherent in most time-based trials. Such as design has been used to evaluate the effect of inhaled anesthesia agents on hospital stay [82,783].

Summary

Large data registries, regardless of absolute size of origin, are a rapidly growing and evolving source of information for quality improvement and research in the field of anesthesiology. This information revolution will help shape the specialty in the future as the ability to collect and process data improves. It is critical for pediatric anesthesiologists to understand both the advantages and pitfalls of this resource and help apply this technology in ways that will allow us to improve care and outcomes for our patients. While the data management is exciting, the data must be reliably recorded and applications must be done in a manner that makes sense clinically. Far from making the human anesthesiologist irrelevant, the ability to form appropriate questions, understand the nature of the information, and effectively translate the large data results into clinical improvement, will make pediatric anesthesiologists more important than ever in determining the future of pediatric anesthesia care.

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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CHAPTER 49

Electronic Anesthesia Records: Anesthesia Information Management Systems

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Introduction

Over the past few decades, healthcare organizations and providers have implemented electronic health record (EHR) systems for computerized clinical documentation, order entry, and other functions [1]. EHRs enable the collection of patient data in an electronic format that can be explored and analyzed to improve patient care processes, optimize resource allocation and utilization, and facilitate decision making at the clinical and enterprise levels [1]. Furthermore, recent advances in computer and networking technology, patient monitoring systems, and EHRs have enabled hospitals to collect and store a rapidly accumulating volume and variety of patient data [2,3].

Meanwhile, US physicians and healthcare organizations have adopted EHRs at a steady rate, partly due to the US federal government's passage of the Health Information Technology for Economic and Clinical Health Act in 2009, which incentivized the "meaningful use" of EHRs with the goal of improving healthcare quality and efficiency [4–6]. Thus, an increasing number of anesthesiologists and other healthcare professionals interact with EHRs on a daily basis as they provide patient care.

Anesthesia information management systems (AIMS) are either integrated EHR modules or stand-alone software and hardware products that were developed as a means to document electronically the details of a patient's anesthetic and physiological status while under anesthesia. This chapter will define and describe AIMS and some of their features, explore the benefits and drawbacks of AIMS, discuss the various secondary uses for AIMS data, and present future directions of AIMS research, applications, and utilization.

From paper anesthesia records to anesthesia information management systems

While the origin of medical records goes back to the time of Hippocrates in ancient Greece, the use of paper records to document a patient's physiological status during an anesthetic did not occur until the 1890s, when Drs Cushing and Codman devised the famous "ether chart" in 1894 to record a patient's anesthetic course [7,8]. The practice of paper anesthesia record keeping spread quickly afterward, and the paper record remains in widespread use to this day (Fig. 49.1) [9]. However, manual written paper records are often inaccurate, biased, incomplete, and illegible, and they can divert the attention of the anesthesiologist from more important tasks (Fig. 49.2) [10].

There was growing recognition that automated charting of an anesthetic might address the fallibility and inherent "smoothing" in paper records [11]. Thus, in the 1970s and 1980s, as microcomputers became more affordable and widely available, anesthesia providers sought to use the devices for the capture, storage, and retrieval of electronic perioperative data [12]. Initially, computers were used to manually document patients' physiological data in the 1970s, and in the early 1980s computers were first used to record patients' data from physiological monitors in an automated fashion [13]. These efforts were the precursors to the AIMS that originated in the 1980s as simple, computer-based intraoperative record keepers to complement or replace paper documentation of a patient's anesthetic [14].

AIMS have been adopted gradually over the subsequent decades, particularly in academic hospitals. In 2014, 75% of

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

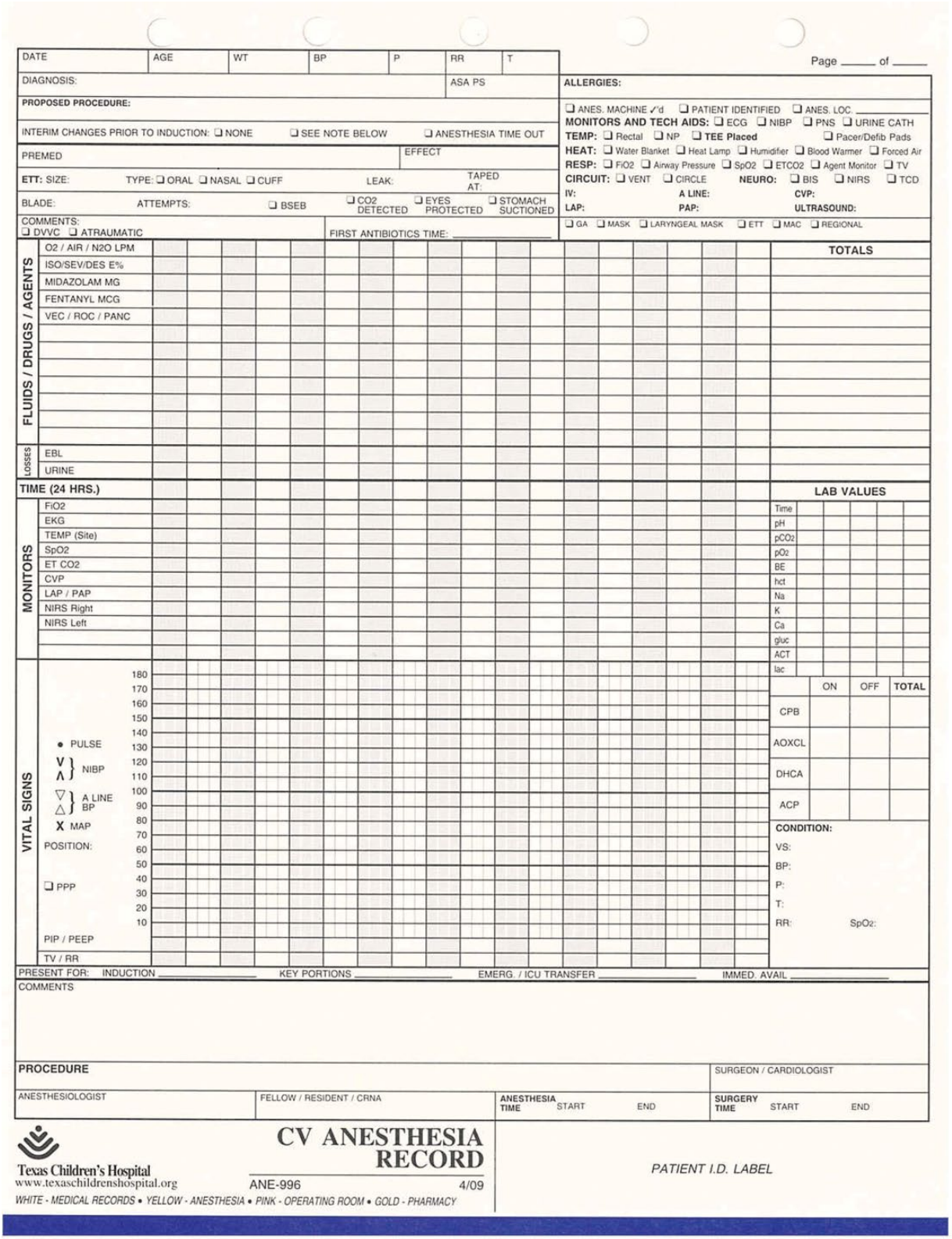

Figure 49.1 Paper anesthetic record. *Source*: Reproduced with permission of Dr Andropoulos, chief of the Texas Children's Hospital department.

academic anesthesiology departments had installed an AIMS, with an 84% AIMS adoption rate anticipated between 2018 and 2020 [15]. Meanwhile, AIMS have evolved from basic anesthesia record documentation software tools to either a stand-alone software product or a component of a hospital's EHR system coupled with hardware components and physiological device interfaces. Most currently available AIMS offer features that enable anesthesia providers to record, view, and share patient information across the entire perioperative continuum [16]. One of the most significant

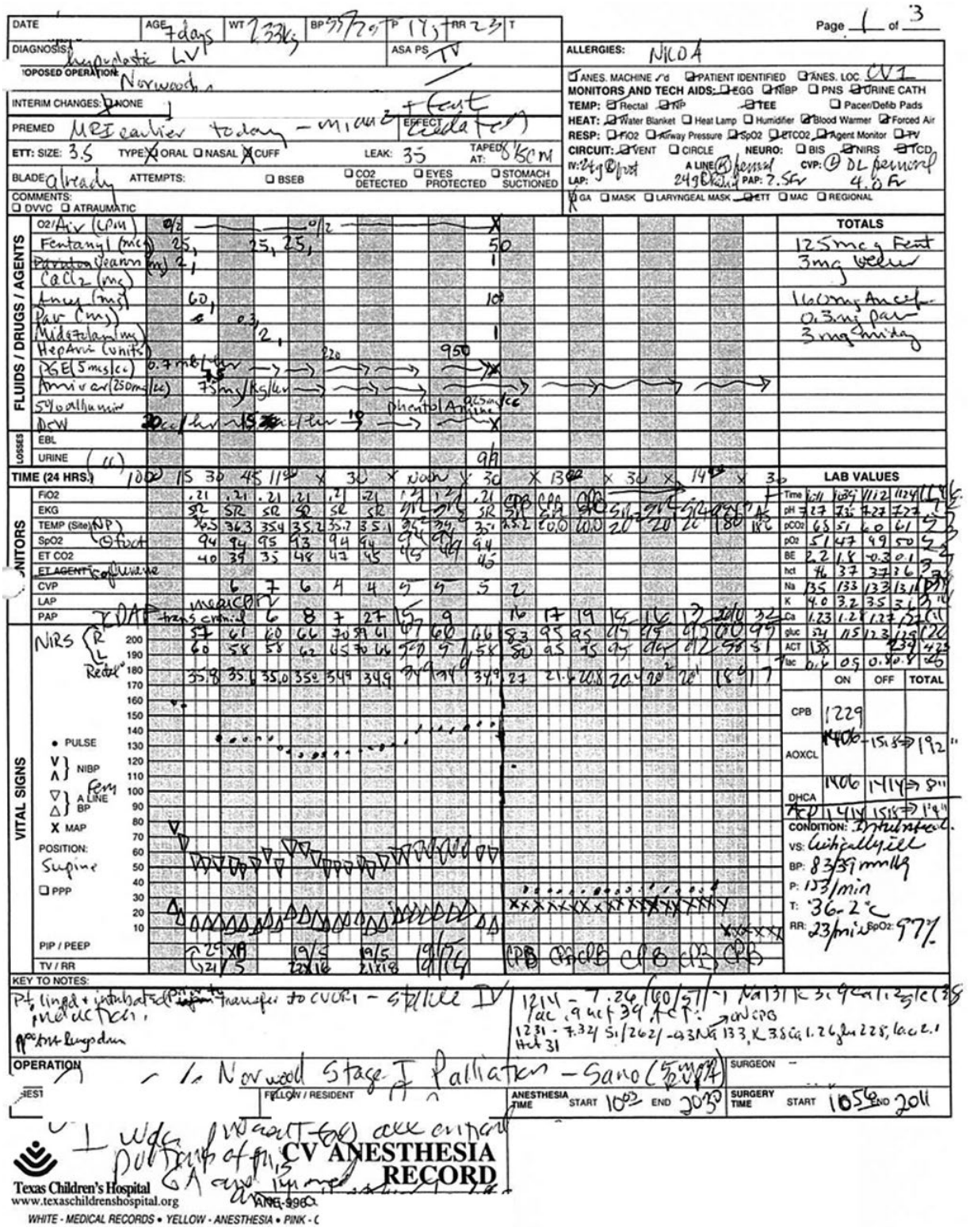

Figure 49.2 Paper anesthetic record completely filled out. *Source*: Reproduced with permission of Dr Andropoulos, chief of the Texas Children's Hospital department.

changes to AIMS over the past several years has been the broad implementation of integrated EHRs such as Cerner (Cerner, Kansas City, MO, USA), Epic (Epic Systems, Verona, WI, USA), and others [17,18]. AIMS are used not only throughout traditional operating room (OR) care (i.e. the preoperative, intraoperative, and postoperative phases), but also throughout the hospital to document acute pain services and the delivery of anesthesia during bedside procedures in intensive care units (ICUs) and the labor and delivery floors [19,20].

KEY POINTS: INTRODUCTION

- AIMs are either integrated EHR modules or stand-alone software and hardware products that document electronically the patient's anesthetic status while under anesthesia, as well as preoperative and postoperative data
- About 75% of academic anesthesiology departments had adopted AIMs by 2014, with an 84% adoption rate anticipated between 2018 and 2020
- Integration of AIMS into broad healthcare EHRs has occurred rapidly over the past several years, and all anesthetic activity, including pain medicine and bedside cases, can now be captured

AIMS software, hardware, and "peopleware"

Most currently available AIMS software offers preoperative patient assessment documentation tools whose features range from rudimentary data entry forms for manually entering free text to comprehensive questionnaires containing richly populated drop-down menus, systems-based assessments, the ability to display patients' photos, and graphical editing tools for annotating images representing patients' dentition and other physical characteristics [18,19]. Entering data into this form enables the creation of a preanesthesia assessment and evaluation note that includes required data elements such as the patient's assigned American Society of Anesthesiologists (ASA) physical status (PS) classification (Fig. 49.3). Stand-alone AIMS that have access to the data within a hospital's EHR and

ROS/MED HX
General: Patient has no history of anesthetic complications (no prior h/o surgery or GA; deny fmhx of GA issues) or fever (no recent illness).
Perinatal: Patient was preterm (36 WGA, prenatal dx of CHD, NICU x 44 days-did not require intubation and remained on CPAP as well as HFNC).
Cardiovascular: Patient has a murmur and hypertension (captopril). Patient has no cyanosis or syncope. Patient has dyspnea at rest. She has no diaphoresis. Patient has a history of congenital heart defect. She has tetralogy of Fallot (large perimembranous VSD, moderate valvar and supravalvar pulmonary stenosis, moderate ASD, mild override of the aorta, small PDA). It is unrepaired. Patient has tricuspid regurgitation (mild). She has congestive heart failure (Lasix). Patient has no decreased myocardial function (mild to moderate RVH). Cardio comments:
-prenatal dx of large perimembranous VSD, moderate valvar and supravalvar pulmonary stenosis, moderate ASD, mild override of the aorta, small PDA
-CHF- Lasix TID
-+ suprasternal and subcostal retractions at rest
Respiratory: Negative respiratory ROS. Patient has no cyanosis or reactive airway disease. The patient does not snore. Patient has dyspnea at rest. The patient did not have a recent URI.
HEENT: Negative HEENT ROS.
Neurological: She has no seizures.She has developmental delays.
Musculoskeletal: She has hypotonia.
Integumentary: Patient does not have a rash.
Gastrointestinal: She has no diarrhea or vomiting. Patient has no esophageal reflux. Patient does not have liver disease. She has hyperbilirubinanemia (s/p phototherapy). She has failure to thrive (NGT feeds).
Genitourinary: She does not have chronic renal disease.
Endocrine/Metabolic: The patient does not have diabetes mellitus. Patient has no hyperthyroidism or hypothyroidism. Endo/other comments:
-NBS- normal per parents.
Syndromes: She has trisomy 21.
Hematological/Lymphatic: Patient does not have bleeding disorder or anemia.
Hematologic/Lymphatic comments:
-deny fmhx of bleeding of clotting issues
Additional ROS/Med Hx Findings:

Procedure: ASD/VSD Closure, PDA ligation, inspection of the PV,

3 mo former 36 wk'er female w/ Trisomy 21 and h/o:
-prenatal dx of large perimembranous VSD, moderate valvar and supravalvar pulmonary stenosis, moderate ASD, mild override of the aorta, small PDA
-CHF- Lasix TID
-+ suprasternal and subcostal retractions at rest

Non-cardiac issues:
-FTT- followed by GI, NGT feeds- EBM with Neosure to 27 kcal 65 ml for 8 feeds, recent visit to GI w/ increased wt gain, so now taking 24kcal Neosure
-chronic nasal congestion- seen by ENT, completed 2 weeks of nasal cipro and receives nasal saline
-s/p phototherapy for hyperbilirubinemia

Allergies: NKA
Meds:
-captopril PO SUSP 1 mg/mL (Compounded - TCH)Give 0.38 mL by mouth 2 times daily for 30 days. 22.8 mL 0
-furosemide PO SOLN 10 mg/mL Give 0.4 mL by mouth 3 times daily for 30 days. 36 mL 0
-multivitamins with iron (POLY-VI-SOL WITH IRON) PO DROP Give 1 mL by mouth daily.
-potassium CHLORide PO SOLN 10% (20 mEq/15 mL) Give 3.2 mL by mouth 2 times daily.

SOCIAL HISTORY: Lives in with biological parents and two elder sisters aged 3 and 7 yrs. Both sisters are healthy.Pet dog, no smoke exposure, no daycare.

Studies:
ECHO
Follow-up study.
Small patent ductus arteriosus with continuous left to right shunting by color doppler(unable to obtain a peak velocity).
There is a prominent anterior ridge seen at the aortic isthmus with no obstruction to flow (image 118); normal color and pulsed wave doppler in the descending and abdominal aorta.
Large perimembranous ventricular septal defect with aortic outlet extension, low-velocity bidirectional shunting (predominantly left to right, with some right to left in diastole). Peak velocity <1.5 meters per second.

Figure 49.3 Portion of a screen image capture of a preoperative evaluation for cardiac surgery in an infant. Text in black font is either imported from other portions of the integrated EMR, copied and pasted, or scripted. Text in red font is entered by the provider. *Source*: Reproduced with permission of Dr Andropoulos, chief of the Texas Children's Hospital department.

AIMS that are a component of a hospital's EHR can retrieve pertinent patient data such as medications, allergies, and procedure information into the preoperative assessment and the intraoperative record [19,21]. Other typical features in preoperative AIMS modules include the ability to peruse a patient's previous anesthesia records, record a review of systems and physical examination, and document an anesthetic assessment and plan [19].

The primary function of every AIMS is the generation of an electronic anesthesia record that captures data in an automated fashion from devices, such as the anesthesia machine and the patient's monitors, and allows the user to manually document a variety of data: administered medications, fluids, and blood products; clinical events such as anesthesia induction, patient positioning, and lines placed; required documentation for billing or regulatory guidelines (e.g. anesthesia start and stop times, procedure notes); and other relevant data that is not captured in automated fashion, such as train-of-four counts [18,19,22]. To accomplish these tasks, AIMS display the anesthesia record in a user interface that the clinician uses to access, review, and edit the record as it is generated.

The intraoperative user interface of most current AIMS consists typically of a grid for vital signs and administered medications that resembles the traditional paper record, with other patient data available in panels surrounding the vital sign grid (Fig. 49.4). The patient data that are displayed varies across AIMS, but data that are typically shown include the patient's name, date of birth, and medical record identifier. Other crucial information such as allergies and recent medications are displayed in some AIMS. Action buttons and drop-down menus are used to access data entry forms to record items such as administered medications and blood products. Procedure notes, such as for regional nerve blocks, can also be entered via the AIMS interface (Fig. 49.5). If the AIMS is a component of an EHR, then the user is often able to access the patient's full EHR record via the software interface.

Most AIMS enable users to document a patient's postoperative status using a computer workstation at the patient's

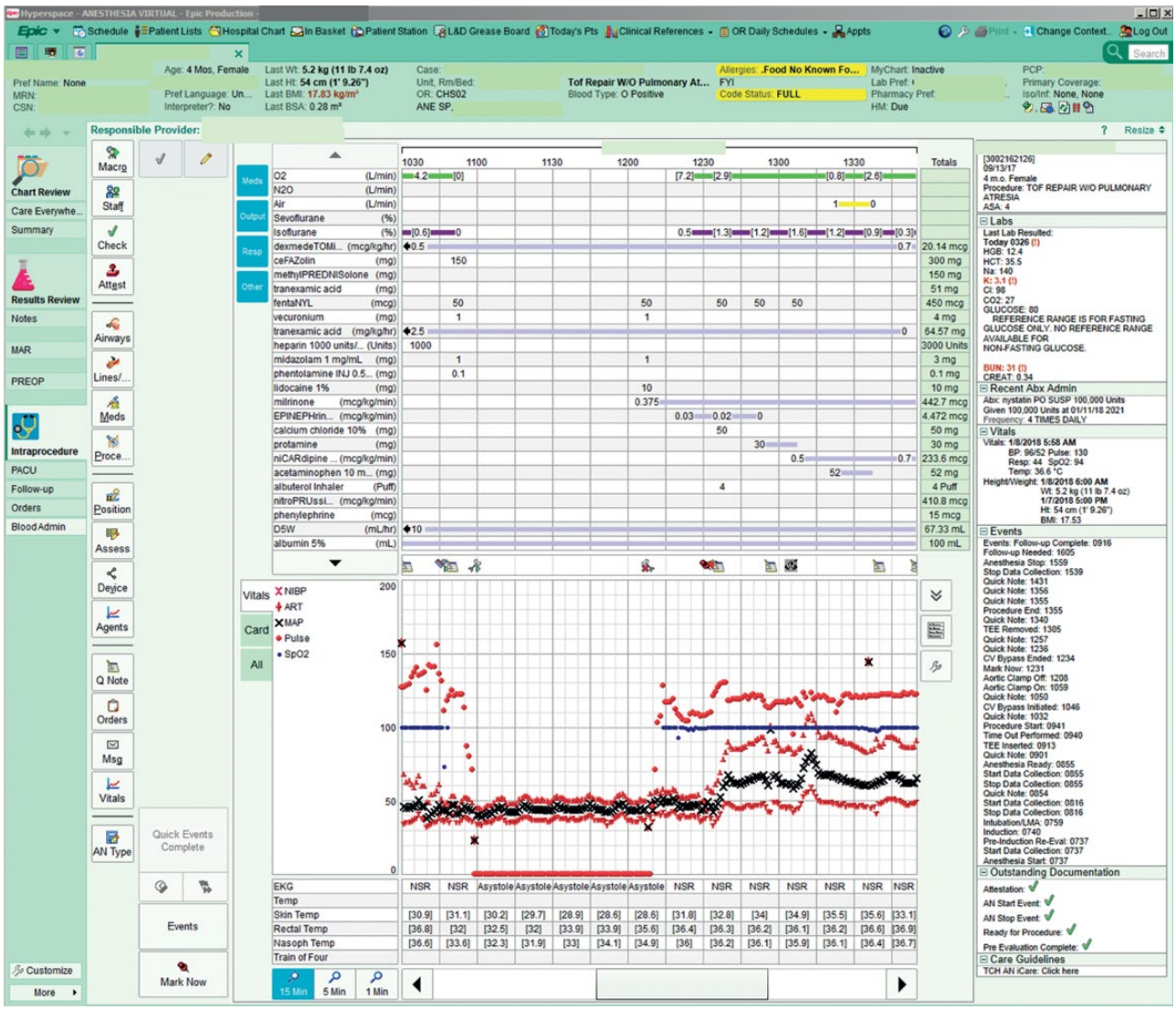

Figure 49.4 Portion of a screen image capture of an intraoperative anesthesia record for a cardiac surgery case in an infant. Even a complex case with multiple medications and interventions can be rendered organized and legible. Other parameters can be accessed by scrolling to other parts of the record or by activating icons along the sides of the screen. This is an example of an AIMS that is part of an integrated system-wide EHR, and the patient's entire medical record can be accessed from this screen. *Source*: Reproduced with permission of Dr Andropoulos, chief of the Texas Children's Hospital department.

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Anesthesia Line Placement - Right Internal jugularCVC
Procedure Note

Location
Patient location during procedure: OR
Start time: 1/10/2018 8:30 AM
End time: 1/10/2018 8:45 AM

Staff
Anesthesiologist: **Fellow/Resident:**
Procedure performed by: Fellow/resident

Anesthesia Checklist
Completed: patient identified, IV checked, risks and benefits discussed, monitors and equipment checked, pre-op evaluation, anesthesia consent given and all elements of maximal sterile barrier technique followed

Line/Catheter
Non-tunneled single lumen CVC
Skin Prep: Skin prepped with 2% chlorhexidine

Indications
central pressure monitoring

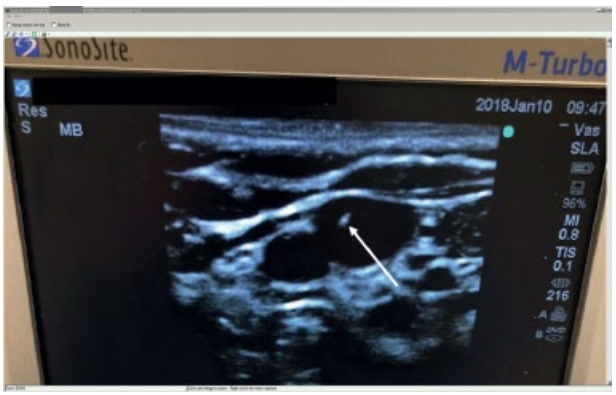
Sedation/Anesthesia

Procedure
Orientation: Right
Size: 3Fr
Location: Internal jugular
Patient position: Flat
Pre Procedure: Landmarks identified
Ultrasound Guided? Ultrasound guided Sterile gel and sterile probe cover used.
Number of Attempts: 1

Post Procedure
Placement Verification: Guidewire, Blood Return and Ultrasound Ultrasound guidance. All relevant anatomy identified. Needle position visualized. Inadvertent cannulation of adjacent structures avoided. An image was obtained and saved.
Secured with: Clear adhesive and Sutured

Notes

(A)

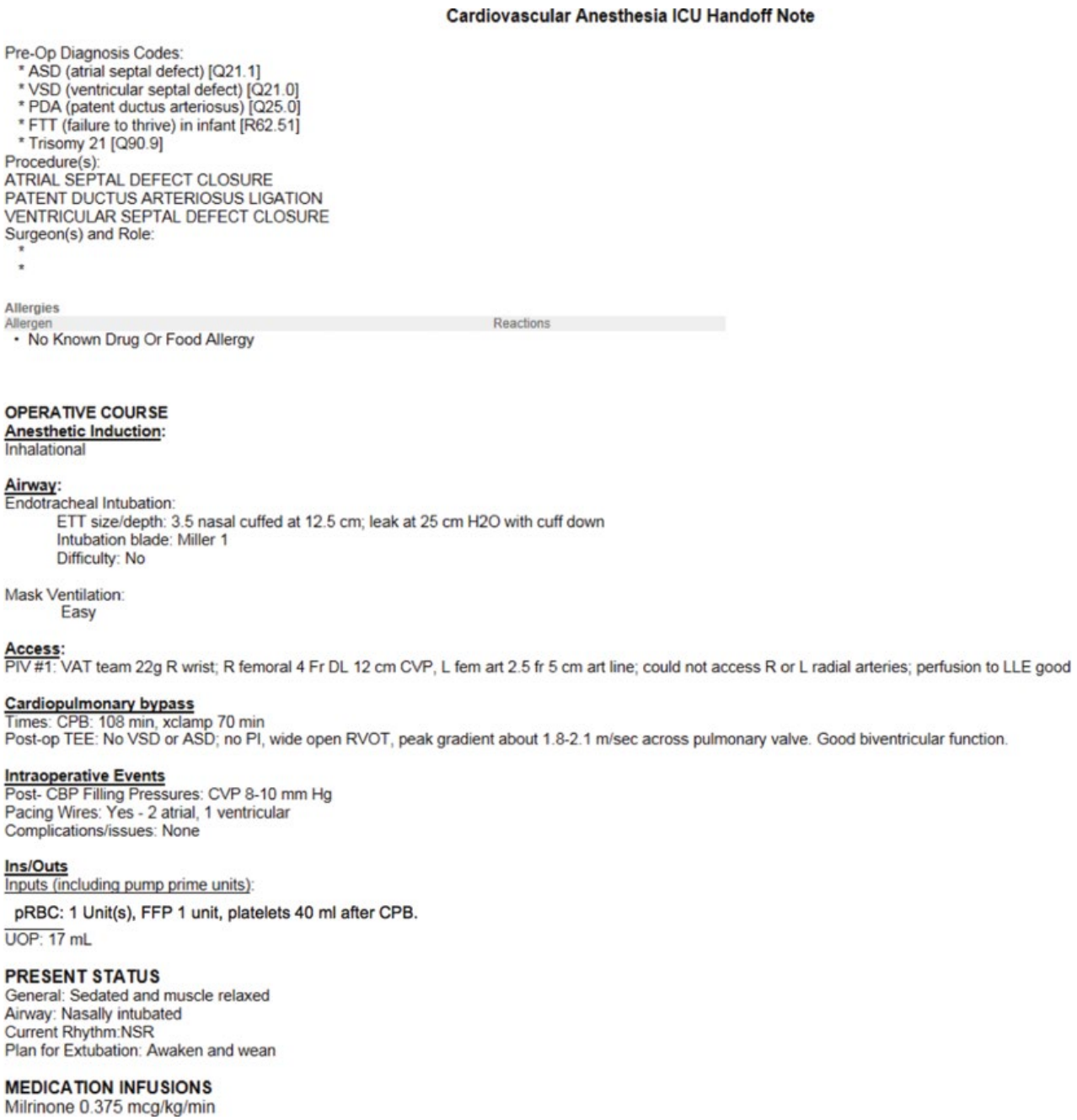


(B)

Figure 49.5 (A) Central line procedure note. Most elements are entered via drop-down menus. (B) Image stored in AIMS for documentation and billing purposes. Arrow, guidewire in right internal jugular vein in cross-sectional view. *Source*: Reproduced with permission of Dr Andropoulos, chief of the Texas Children's Hospital department.

recovery location, such as the postanesthesia care unit (PACU) or ICU. The patient's preoperative and intraoperative data that have been recorded up to that point can be used during the hand-off of patient care to the receiving clinician, and postoperative vital signs can be recorded [19]. A postoperative ICU transfer note can also be documented (Fig. 49.6). Some AIMS can prompt the clinician to enter quality improvement data on relevant perioperative events [23]. Automated documentation checks can trigger notifications via real-time alerts or automated e-mail or text messaging to inform user of any deficiencies that need to be corrected [24].

AIMS hardware components include a computer workstation and mounting equipment and/or a wheeled mobile stand, and might also include vendor-specific devices such as special keyboards, bar code scanners, or syringe pumps [19]. AIMS hardware should meet the hospital's infection control guidelines (i.e. be easy to disinfect) and be durable, ergonomic, water resistant, and usable in multiple environments [19]. The device data flow from the devices to the client and then the server – or first to the server and then the client workstations – depending on the AIMS set-up. Physiological device interfaces are crucial for enabling patient physiological



Cardiovascular Anesthesia ICU Handoff Note

Pre-Op Diagnosis Codes:
* ASD (atrial septal defect) [Q21.1]
* VSD (ventricular septal defect) [Q21.0]
* PDA (patent ductus arteriosus) [Q25.0]
* FTT (failure to thrive) in infant [R62.51]
* Trisomy 21 [Q90.9]

Procedure(s):
ATRIAL SEPTAL DEFECT CLOSURE
PATENT DUCTUS ARTERIOSUS LIGATION
VENTRICULAR SEPTAL DEFECT CLOSURE

Surgeon(s) and Role:
*
*

Allergies

Allergen	Reactions
• No Known Drug Or Food Allergy	

OPERATIVE COURSE

Anesthetic Induction:
Inhalational

Airway:
Endotracheal Intubation:
ETT size/depth: 3.5 nasal cuffed at 12.5 cm; leak at 25 cm H2O with cuff down
Intubation blade: Miller 1
Difficulty: No

Mask Ventilation:
Easy

Access:
PIV #1: VAT team 22g R wrist; R femoral 4 Fr DL 12 cm CVP, L fem art 2.5 fr 5 cm art line; could not access R or L radial arteries; perfusion to LLE good

Cardiopulmonary bypass
Times: CPB: 108 min, xclamp 70 min
Post-op TEE: No VSD or ASD; no PI, wide open RVOT, peak gradient about 1.8-2.1 m/sec across pulmonary valve. Good biventricular function.

Intraoperative Events
Post- CBP Filling Pressures: CVP 8-10 mm Hg
Pacing Wires: Yes - 2 atrial, 1 ventricular
Complications/issues: None

Ins/Outs
Inputs (including pump prime units):
pRBC: 1 Unit(s), FFP 1 unit, platelets 40 ml after CPB.
UOP: 17 mL

PRESENT STATUS
General: Sedated and muscle relaxed
Airway: Nasally intubated
Current Rhythm:NSR
Plan for Extubation: Awaken and wean

MEDICATION INFUSIONS
Milrinone 0.375 mcg/kg/min

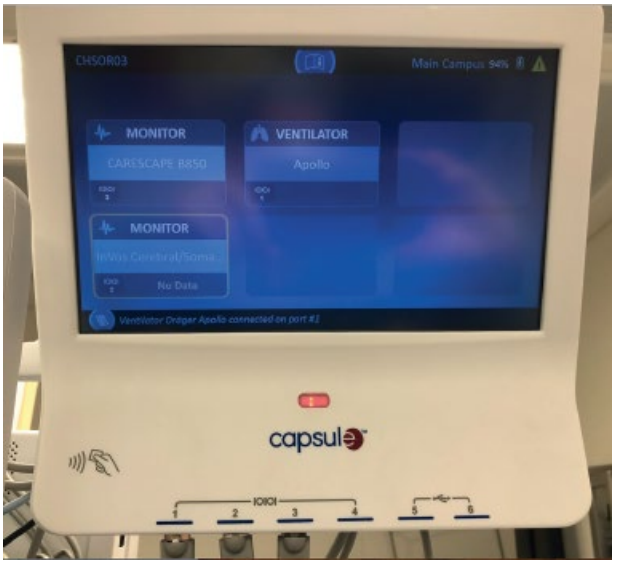
Figure 49.6 Screen image capture of part of an ICU postoperative hand-off note. *Source*: Reproduced with permission of Dr Andropoulos, chief of the Texas Children's Hospital department.

monitors, anesthesia machines, ventilators, and other monitors to communicate and record automatically via the AIMS hardware and software.

Thus, AIMS software is installed on AIMS hardware at sites of anesthetic care, such as computers attached to the anesthesia machine in the OR (Fig. 49.7), PACU, or even on mobile workstations in the ICU (Fig. 49.8) [19,20]. The AIMS hardware and software obtains physiological data via interfaces with the monitoring devices. Stand-alone AIMS software on a workstation is typically in the form of a "thick client" that stores the anesthesia data on that workstation; the data are then filed periodically to a central server. With AIMS that are components of EHRs, the software on the workstation is typically a front-end user interface – also called a "thin client" – with most or all of the data filed directly to a central server [18].

Successful AIMS implementations require not only the appropriate hardware and software, but also a substantial investment of time and "peopleware" – that is, clinicians with sufficient expertise within a department to lead the AIMS installation decision-making and implementation processes. The cost of an AIMS implementation will depend on many factors, including its level of sophistication, the hardware and software needed to attain that level of sophistication, and most significantly, the implementation team's time as clinicians are taken from the clinical setting to guide the AIMS implementation efforts through site visits, meetings, and other time-consuming efforts [18]. The personnel and

(A)



(B)

Figure 49.7 (A) Configuration of AIMS at a children's hospital. Data from the physiological monitors and the anesthesia machine are integrated through the capsule device into the AIMS. The software on this computer workstation (visible at bottom center) is a front-end user interface – also called a "thin client" – with most or all of the data filed directly to a central server. Additional data for medications, procedures, and other parameters can be entered using a mouse, or by a touchscreen function where an additional window opens for the required data field. (B) Detail of wired interface between anesthesia machine and monitors, and the AIMS. *Source*: Reproduced with permission of Dr Andropoulos, chief of the Texas Children's Hospital department.

expertise required for successful basic and advanced AIMS implementation are displayed in Box 49.1.

KEY POINTS: AIMS SOFTWARE, HARDWARE, AND "PEOPLEWARE"

- AIMS software varies but all will at least be able to retrieve data about medications, allergies, and procedure information for the preoperative assessment
- The primary function of every AIMS is to generate an electronic anesthesia record that captures data from the anesthesia machine and patient monitors and allows manual documentation of medications, fluids, and all the other events of a case
- A successful AIMS implementation also requires substantial investment of time and expertise of clinicians to design and implement the system

Figure 49.8 Wireless AIMS portable workstation for a bedside case in a neonatal ICU. The bedside monitor data is transmitted wirelessly to the portable workstation for creation of the anesthetic record. *Source*: Reproduced from Simpao AF, Galvez JA, England WR, et al. A technical evaluation of wireless connectivity from patient monitors to an anesthesia information management system during intensive care unit surgery. *Anesth Analg* 2016; 122: 425–9 with permission of Wolters Kluwer.

Box 49.1: People and expertise required within a department for successful implementation of basic and advanced anesthesia information management systems (AIMS)

Minimum requirements for a basic implementation

- One or more physician clinical champions to guide decision-making processes and inform clinical workflow requirements for the AIMS installation team
- Support from biomedical engineering and information technology personnel for the software and hardware interfaces between devices, the AIMS, and the hospital's electronic health record (HER) system

Advanced requirements for a state-of-the-art AIMS implementation within an institution

- Requirements listed in "minimum requirements"
- Data scientists with expertise in visual and advanced analytics for descriptive and predictive AIMS data analytics [35,38]
- Database system administrator to handle AIMS data queries for research and quality improvement
- Physicians with informatics expertise to spearhead clinical decision support and data analytics efforts
- EHR and AIMS programmers for implementing clinical decision support tools
- Project manager

Source: Reproduced from Simpao and Rehman [18] with permission of Wolters Kluwer.

Clinical decision support in AIMS and EHRs

Computer-assisted decision making, or clinical decision support (CDS), has been used widely in EHRs to improve patient care quality and safety [25,26]. Several systematic reviews have described how CDS alerts and tools that are embedded within hospitals' EHRs can improve clinical performance, resource utilization, and patient care [27,28]. CDS tools can provide clinicians with patient-specific assessments or recommendations to assist with making clinical decisions [29]. The critical features for successful CDS systems are often summarized as the five "rights": delivering the right information, to the right person, in the right intervention format, through the right channel, at the right time in workflow [30].

AIMS have similarly incorporated CDS in order to accomplish the same or similar goals, and CDS tools have been increasingly integrated within AIMS to provide clinicians with near real-time alerts and post hoc reports to enhance patient care processes, documentation compliance, and resource utilization [31–33]. There are numerous narrative and systematic reviews of AIMS-based CDS that have described the extent to which CDS tools can impact aspects of clinical performance and patient care, particularly if the CDS is smoothly integrated into clinical workflow and comprised of evidence-based recommendations rather than assessments [4,33–38]. Some examples of AIMS-based CDS include alerts, reminders, and notifications to modify the behavior of anesthesia practitioners with the goal of enhancing various perioperative processes [39]: improving intraoperative glucose monitoring and management [40–42], addressing intraoperative hypothermia [43], restoring suspended alarms after cessation of cardiopulmonary bypass [44], correcting OR location errors [45], improving β-blocker medication compliance, and informing clinicians of the optimal postoperative nausea and vomiting and antibiotic prophylaxis [46,47]. Decision support can also consist of post hoc reports to clinicians to impact many aspects of clinical care and documentation [33].

AIMS: potential benefits and perceived drawbacks

In addition to CDS, AIMS offer many additional benefits. Box 49.2 lists the areas where peer-reviewed literature has supported the positive impact of AIMS on patients, anesthesia departments, and hospital systems [48].

There are several perceived drawbacks to installing and using an AIMS: a reluctance to abandon familiar paper anesthesia record forms, unacceptable or unsustainable costs of installation and maintenance, electronic distraction of anesthesia providers, and medicolegal concerns due to AIMS automatically recording all physiological data, as well as

Box 49.2: Benefits of anesthesia information management systems published in peer-reviewed literature

Improving the safety and quality of patient care
- Automated recording of vital signs offloads cognitive burden, enabling anesthesia providers to focus on the patient
- Provides automatic notification of operating room location errors
- Enables automated drug diversion surveillance systems
- Warns users of potential drug allergy and blood transfusion reactions
- Facilitates implementation of and adherence to departmental protocols (such as perioperative antibiotic prophylaxis administration)
- Provides point-of-care clinical decision support (such as perioperative glucose and insulin management and ventilator management)
- Enables real-time surveillance of patient monitors
- Provides timely clinical feedback via post hoc reports to impact clinicians' behavior

Improved documentation
- Precise, accurate capture of intraoperative data and patients' hemodynamic responses to anesthesia
- Generates high-resolution anesthetic records that are more easily searched, accessed, and used for post hoc analysis than paper records
- Automated, real-time, or near real-time notification of missing or incomplete documentation
- Enhanced legal fortification due to unbiased, precise records
- Facilitates risk management and quality assurance activities

Improved operations management
- Improves billing personnel workflow when reviewing anesthesia records
- Enhances anesthesiology department's administrative role in the perioperative setting
- Facilitates faculty and staff scheduling
- Generates a real-time surgical whiteboard to improve situational awareness and workflow
- Enables operating room modeling for administrative decision support
- Facilitates individual anesthesia provider and departmental performance tracking
- Allows verification of Accreditation Council for Graduate Medical Education case requirements for residents and fellows
- Provides post hoc reports to residents with a log of their anesthesia experiences to guide requests for next day's cases

Improved cost containment and reimbursement
- Accurate accounting of anesthesia supplies and medications
- Decreases costs and utilization of anesthesia medications and supplies
- Facilitates resource management in the operating room
- Enhances anesthesia billing and charge capture
- Increases hospital reimbursement
- Merges financial systems with clinical documentation to improve efficiency

Improved clinical research
- Enables researchers to search for rare events or specific occurrences across a large number of cases
- Helps develop evidence-based medicine guidelines from validated datasets of clinical practice
- Facilitates linking of perioperative data to outcomes data for research (such as the National Surgical Quality Improvement Program)
- Enhances the sharing of data in national and international consortiums (such as the Multicenter Perioperative Outcomes Group or Anesthesia Quality Institute)

Sources: Adapted from Ehrenfeld and Rehman [21], Kadry et al [22], Epstein et al [35], Simpao and Rehman [18], Simpao et al [45], and O'Sullivan et al [54].

hospital, departmental, or clinicians' resistance to changes in established clinical workflow [18,49–51]. However, studies have established that electronic records are more accurate and reliable than paper records [52,53]. AIMS implementations indeed bear significant costs, and the return on investment depends on an institution's financial, billing, and management practices. AIMS can produce a positive net return on investment in four ways: (1) decreased anesthesia medication costs; (2) decreased staffing costs due to more efficient staff scheduling; (3) enhanced charge and billing capture; and (4) increased hospital reimbursement from improvements in hospital coding [54]. As for AIMS distracting anesthesia providers in the OR, studies have reported no significant effect of AIMS on clinicians' vigilance [55–57]. With respect to medicolegal concerns, some have indeed argued that failure to recognize a loss of incoming data into an AIMS may increase medical liability [58]. However, the majority of 24 anesthesia departments reported in a survey that AIMS were useful for risk management, and there were no cases in which AIMS hindered the defense process [59].

Secondary use of AIMS data

Countless clinical research, quality improvement, and collaborative projects across myriad institutions and anesthesia practices have utilized AIMS data [60]. For example, studies have been published using data from multi-institutional AIMS registries such as the Anesthesia Quality Institute's National Anesthesia Clinical Outcomes Registry and the Multicenter Perioperative Outcomes Group [61,62]. It is important to note that collecting vast amounts of data does not necessarily ensure valid, high-quality data, as the quality and reliability of the AIMS data is dependent on the clinicians recording it [63]. Truly valid and reliable perioperative documentation requires clear, consistent definitions of perioperative events and outcomes that can enhance billing, reporting, and clinical decision support processes. However, these definitions vary routinely across and sometimes even within institutions. For instance, a few different events can be considered the "induction of anesthesia," such as administration of a hypnotic, provision of anxiolytics, or start of preoxygenation [18]. Research, administrative, and quality improvement initiatives that are based on AIMS data must factor in any inconsistent definitions as well as other issues such as physiological monitoring artifacts in order to avoid arriving at invalid, faulty conclusions ("garbage in, garbage out") [64,65]. Chapter 48 presents further discussion about using AIMS data for contribution to large national databases and local databases for quality and outcomes projects and research.

AIMS data quality and outcomes

The massive amount of data collected by AIMS can be used for quality and safety initiatives. One approach is visual analytics, a category of computational tools that integrate data analytics with interactive visual interfaces and can be used to navigate and manipulate large data [1]. Parameters of interest, such as medication alerts and the number of times they are over-ridden, can be tracked over time to assess their appropriateness and proper use. Point-and-click functionality allows the user to access the data, often in near real time, for periodic assessment of progress. An example of a quality program to increase reliability of medication alerts is displayed in Figure 49.9 [1]. Intraoperative blood transfusion is another area of pediatric anesthetic practice that has significant variability, and risk and

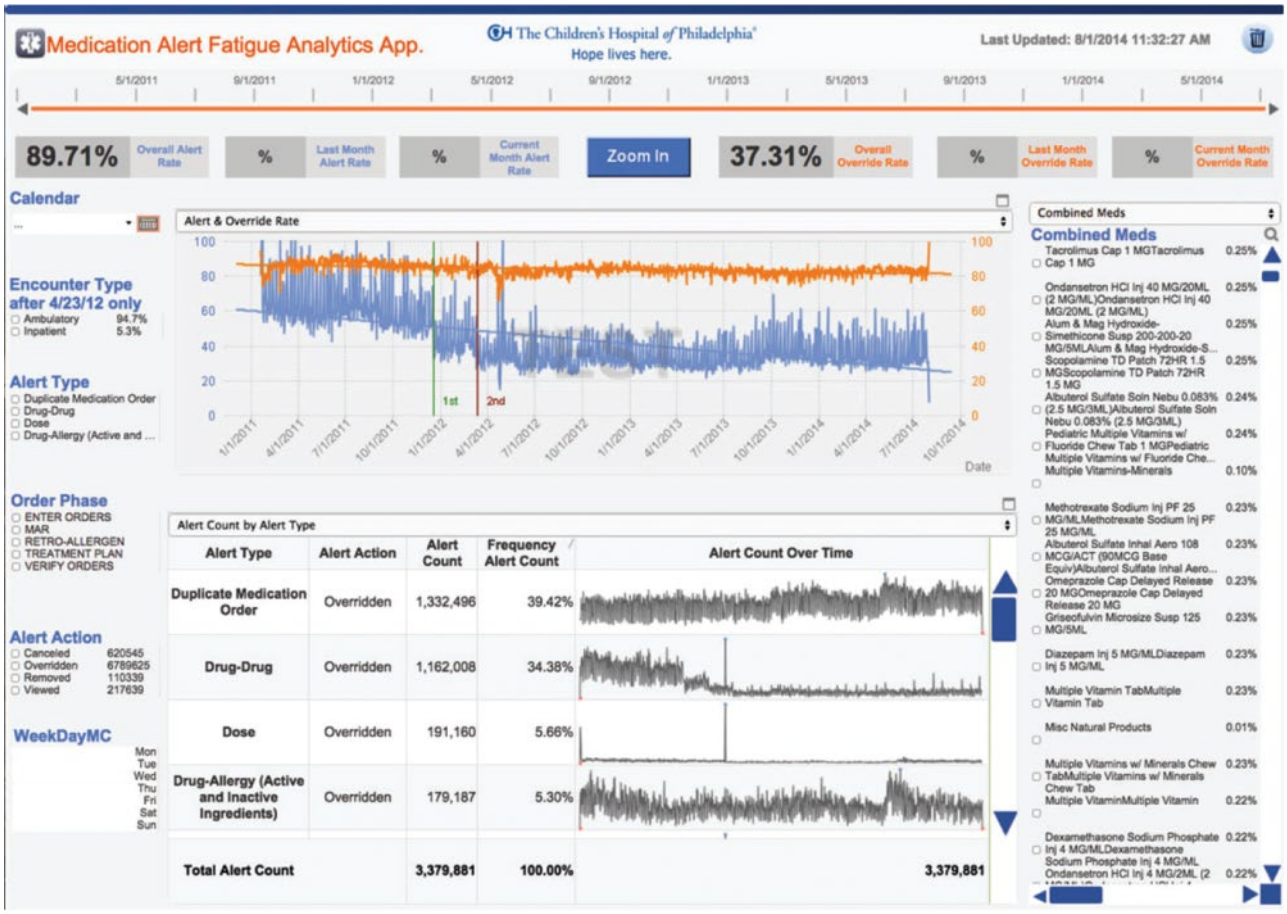


Figure 49.9 Screen image capture of the Children's Hospital of Philadelphia medication alert fatigue visual analytics dashboard. This enables the user to explore electronic health record medication alert data. *Source*: Reproduced from Simpao et al [1] with permission of Elsevier.

cost to the patient and hospital, and the AIMS and EHR can be mined to display contemporaneous data about this important aspect of practice (Fig. 49.10) [1].

Quality and adverse event reporting is another area in which AIMS can facilitate reporting and analysis of adverse events and outcomes. The Children's Hospital of Philadelphia initiated a quality improvement program designed to improve response to, and reporting of, anesthesia emergencies where additional personnel were called to assist in critical events, for example, significant laryngospasm. These events were termed Anesthesia Now! (AN!), and were documented in the AIMS [66]. The purpose of the project was to categorize these emergency events, and then plan programs that targeted their prevention and rapid response. Rates and outcomes could be compared to national data as part of the overall quality improvement program. Of 213 AN! calls, 67% were for airway emergencies, with laryngospasm the leading cause (Table 49.1). Overall prevalence was 1:234, and AN! events were inversely proportional to age and ASA physical status. Critical event response algorithms have been designed and electronically formatted for operating room use as a result of these data. Team response efficacy is being studied using these emergency algorithms and simulation scenarios.

In the USA, data collected for quality and outcomes analysis are legally protected from discovery for malpractice purposes in most states, and so quality and outcomes databases are not considered part of the patients' EHRs. One approach to this issue used by some children's hospitals is an electronic quality improvement reporting screen that appears after the anesthetic and must be filled out before formal closure of the electronic anesthesia record for the case. The data, however, are sent to a separate database and not the EHR for later quality analysis (Fig. 49.11).

KEY POINTS: DECISION SUPPORT, BENEFITS AND DRAWBACKS, AND SECONDARY USE OF AIMS DATA

- Clinical decision support tools such as electronic reminders for antibiotic dosing can improve the processes of delivering appropriate clinical care
- Drawbacks of AIMS include their considerable costs, and reluctance to change well-accepted workflows of paper records
- Advantages include legible and accurate records, and ability to capture a myriad of data related to cost and quality of care
- Secondary use of AIMS data for quality and research does not occur automatically; knowledgeable clinicians working with information technology professionals must work together to determine how to mine these data

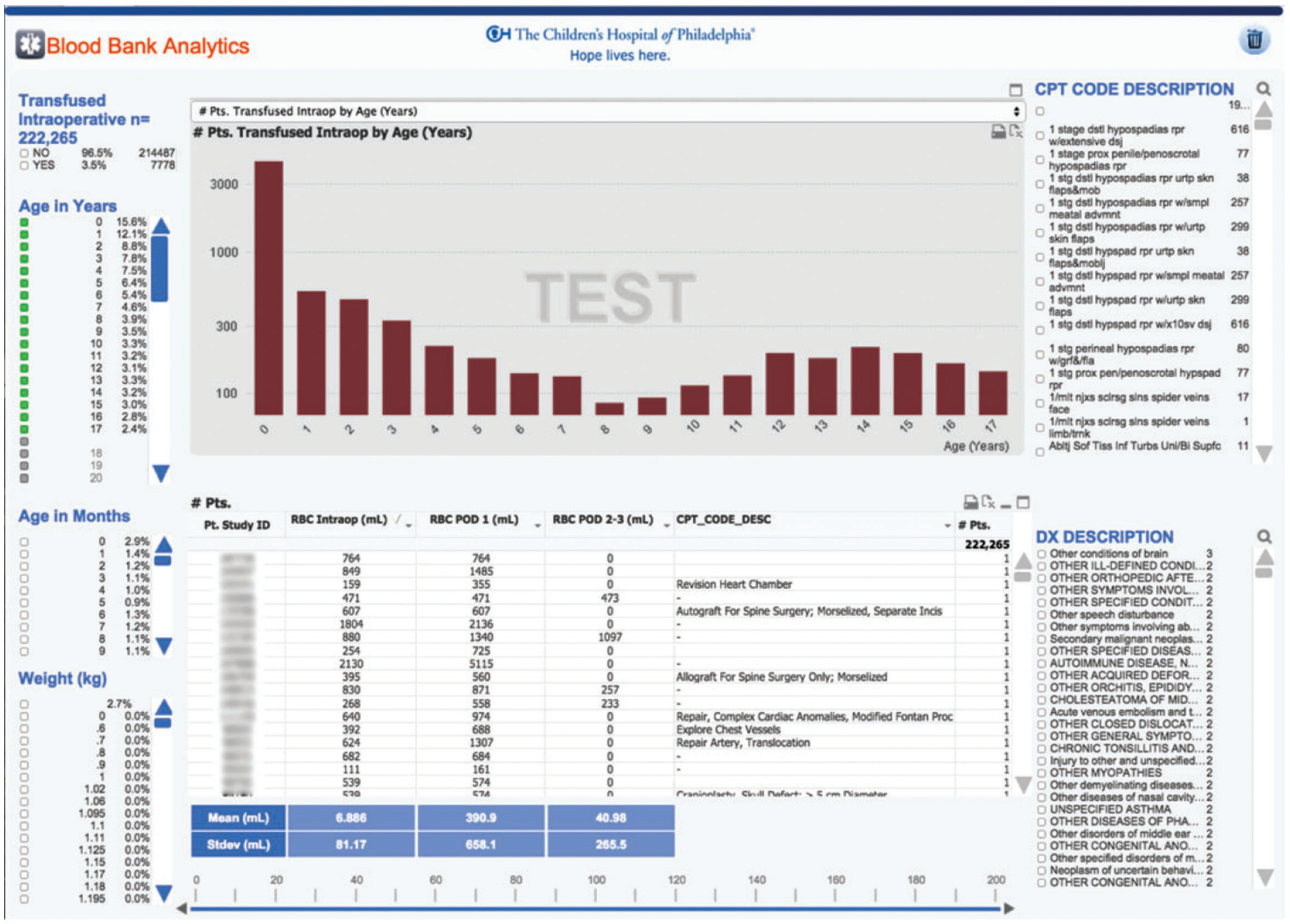


Figure 49.10 Screen image capture of the Children's Hospital of Philadelphia perioperative blood transfusion visual analytics dashboard. This enables the user to explore historic blood transfusion data (based on patient characteristics and procedure type). *Source*: Reproduced from Simpao et al [1] with permission of Elsevier.

Table 49.1 Adverse event classification

Event	*n* (%)
Respiratory	143 (67.1)
Laryngospasm*	63 (29.6)
Bronchospasm*	20 (9.4)
Difficult ventilation	18 (8.5)
Airway obstruction	12 (5.6)
Desaturation	11 (5.2)
Respiratory failure after extubation	11 (5.2)
Breath holding	7 (3.3)
Other	5 (2.3)
Cardiac	23 (10.8)
Bradycardia	11 (5.2)
Arrhythmia	4 (1.9)
Arrest	3 (1.4)
Hypotension	2 (0.9)
Other	3 (1.4)
Accidental extubation	14 (6.6)
Hemorrhage	11 (5.2)
Emesis	10 (4.7)
Difficult airway	4 (1.9)
Anaphylaxis	3 (1.4)
Communication error	3 (1.4)
Air embolism	1 (0.5)
High spinal blockade	1 (0.5)

* There were four cases of combined laryngospasm/bronchospasm included in each.

AIMS and pediatric anesthesia research

With the appropriate analytical tools and programs, the anesthesia electronic record has been mined for a number of research reports that have documented a number of important pediatric anesthetic practices, or characteristics and outcomes of particular patient groups. One such example assessed the significantly higher incidence of bradycardia and hypotension during sevoflurane induction in patients with Down syndrome than in patients without Down syndrome. Data were analyzed for the induction period from 8 years of AIMS records, and bradycardia and hypotension was present in 57% of the 209 patients with Down syndrome versus 12% of the 268 control patients without (odds ratio 9.56, 95%CI 6.06–15.09), and this was independent of the presence of congenital heart disease, age, sevoflurane concentration, or cyanosis [67].

The potential for pediatric anesthesia research within the anesthesia EHR is great, and is just beginning to be realized. With the considerable expense, time, and complexity of prospective clinical trials in pediatrics, the data already residing in the AIMS can be utilized to construct a "trial within a database" on a number of clinical questions including superiority of one drug versus another, or outcomes of different anesthetic approaches. It must be emphasized that AIMS in general are excellent clinical documentation systems, but are not

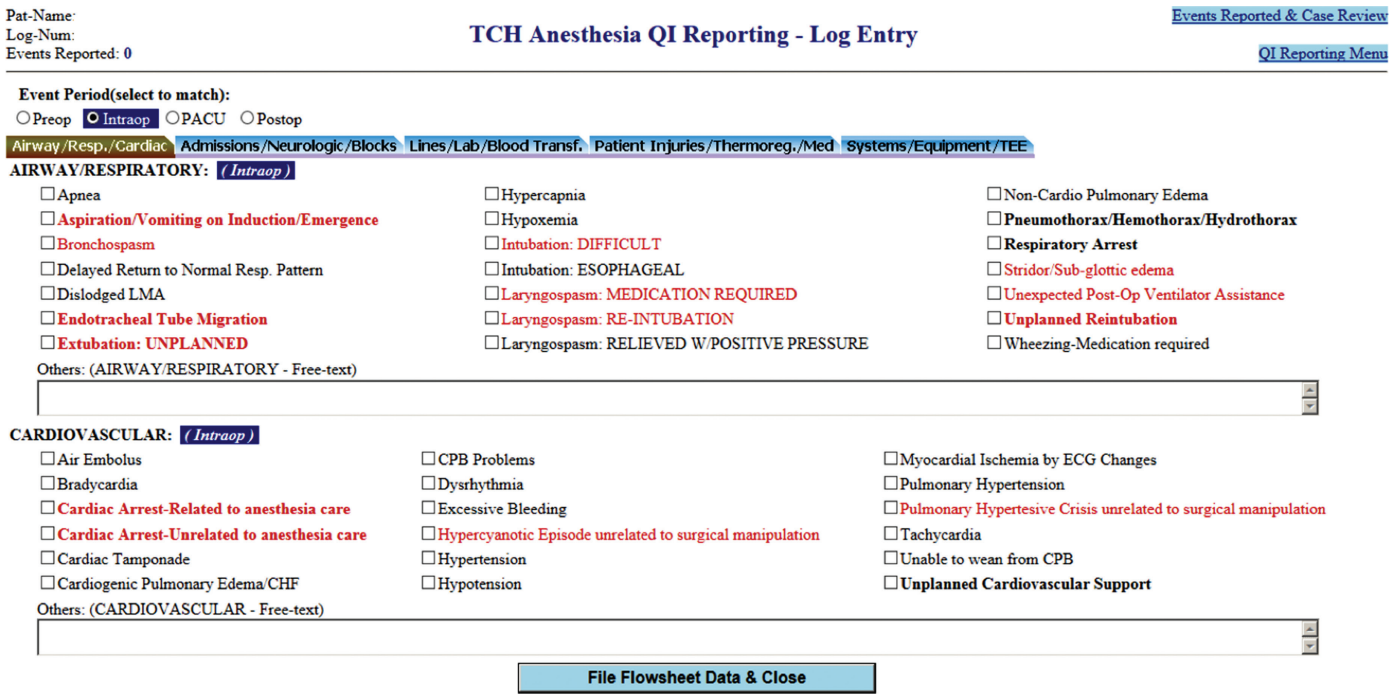


Figure 49.11 Screen image capture of a mandatory quality improvement screen documenting adverse events before closure of the anesthesia record. The data are not part of the medical record, and are sent to a separate, legally protected quality and outcomes database. *Source*: Reproduced with permission of Dr Andropoulos, chief of the Texas Children's Hospital department.

commonly equipped with the analytical programs that are able to perform the data mining described above for quality and research purposes. Significant informatics expertise, coupled with clinical and research knowledge and experience, is required to write meaningful programs or utilize sophisticated software applications to extract and analyze these complex datasets.

Future directions

In the future, AIMS should improve in terms of user interface and either interoperability with or functionality within EHRs. Useful AIMS functionality on portable devices such as tablet computers and smartphones in the perioperative period should continue to expand (Fig. 49.12) [68]. As new hospitals adopt EHRs, integrated AIMS should also become more widely available, and automated data capture will be feasible from a continually growing array of devices, such as barcode medication labeling systems and "smart" medication infusion pumps [18,69,70].

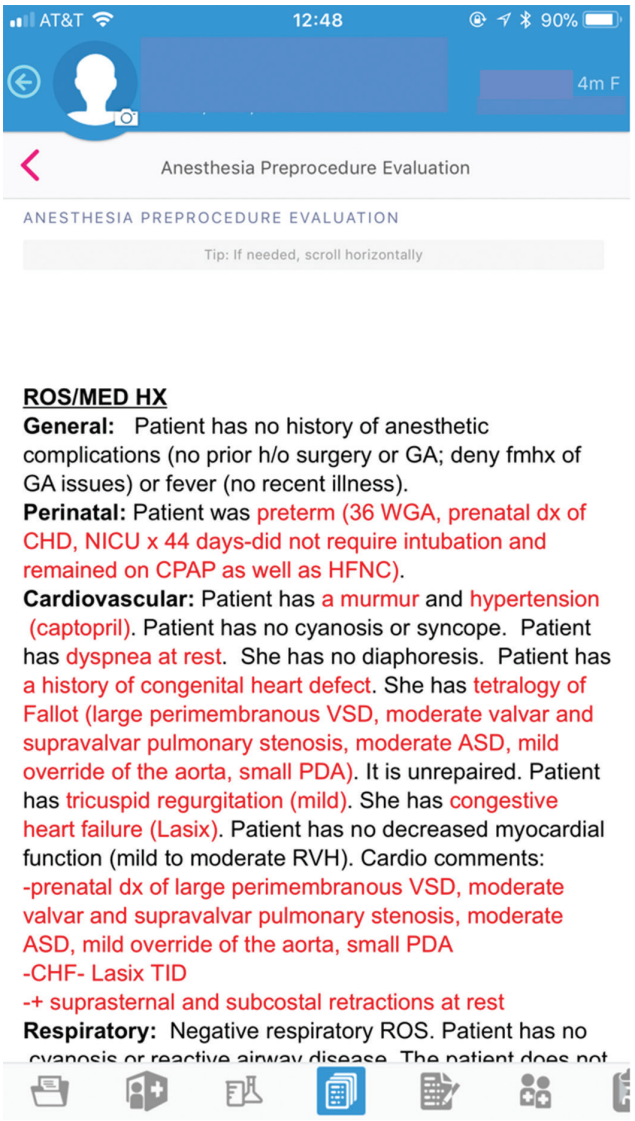
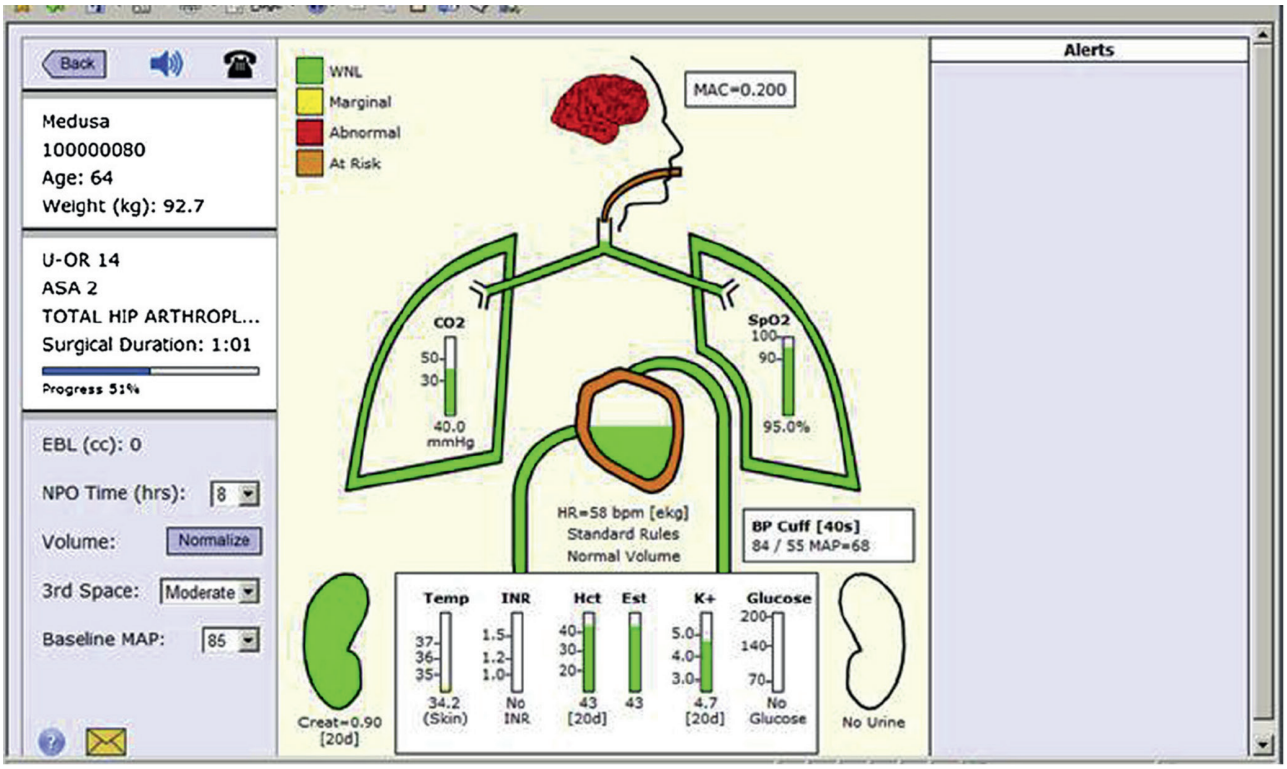


Figure 49.12 Screen image capture of a smartphone remote EHR access application that allows viewing of the medical record from a cellular phone or tablet, with proper access credentials. *Source*: Reproduced with permission of Dr Andropoulos, chief of the Texas Children's Hospital department.

Analytical techniques such as visual analytics, natural language processing, and machine learning will be applied to large AIMS datasets for meaningful insights and to drive quality and clinical performance improvement efforts [1]. Visual analytics consist of interactive visual interfaces driving analytical reasoning, and have been utilized to enhance the evaluation of large, complex datasets within healthcare fields. AIMS can generate prohibitively large datasets that can be navigated and represented visually in near real time using visual analytics software tools [65]. One possible use of visual analytics is for advanced integrated real-time clinical displays that use sophisticated computer algorithms (artificial intelligence) to synthesize information from a patient's clinical history, current status of physiological monitor and anesthesia machine parameters, and evidence-based decision support to produce a display of patient "well-being" somewhat akin to current advanced avionics "cockpit" displays that a commercial airline pilot sees (Fig. 49.13) [71]. This visual analytical display approach was used to inform decision support algorithms in a retrospective study that compared 7954 adult surgical anesthetics that used this system to 10,933 parallel controls, and 7882 historical controls [72]. After propensity score adjustment and compared with the parallel controls, the decision support approach was associated with improvements in the three process measures (excessive fluid administration, minutes of hypotension, and tidal volumes >10 mL/kg, all $p < 0.001$), but did not improve the postoperative outcome measures of 30-day mortality, myocardial or renal injury, or hospital length of stay. Hospital charges were about US$3000 less with decision support, which was a statistically significant difference.

Natural language processing involves the software-based retrieval and extraction of information from unstructured, semistructured, and structured text, such as detecting surgical site infections using unstructured text in EHR clinical notes [73,74]. Machine learning consists of computer algorithms that can be trained to recognize meaningful patterns in large datasets. Thus, these algorithms can be applied to AIMS data to automate perioperative event annotation or to ascertain the clinical relevance of physiological data [73].

Real-time analysis of patient data across various health information systems via the application of sophisticated clinical decision support and surveillance systems is another promising application of technology to AIMS data [74]. AIMS-based clinical decision support will continue to be developed in a more sophisticated and meaningful fashion to enhance various facets of patient care. As AIMS continue to proliferate in pediatric anesthesia practice settings, clinicians should feel empowered to envision ways that these tools can be used to improve clinical workflow and enhance the care of children.



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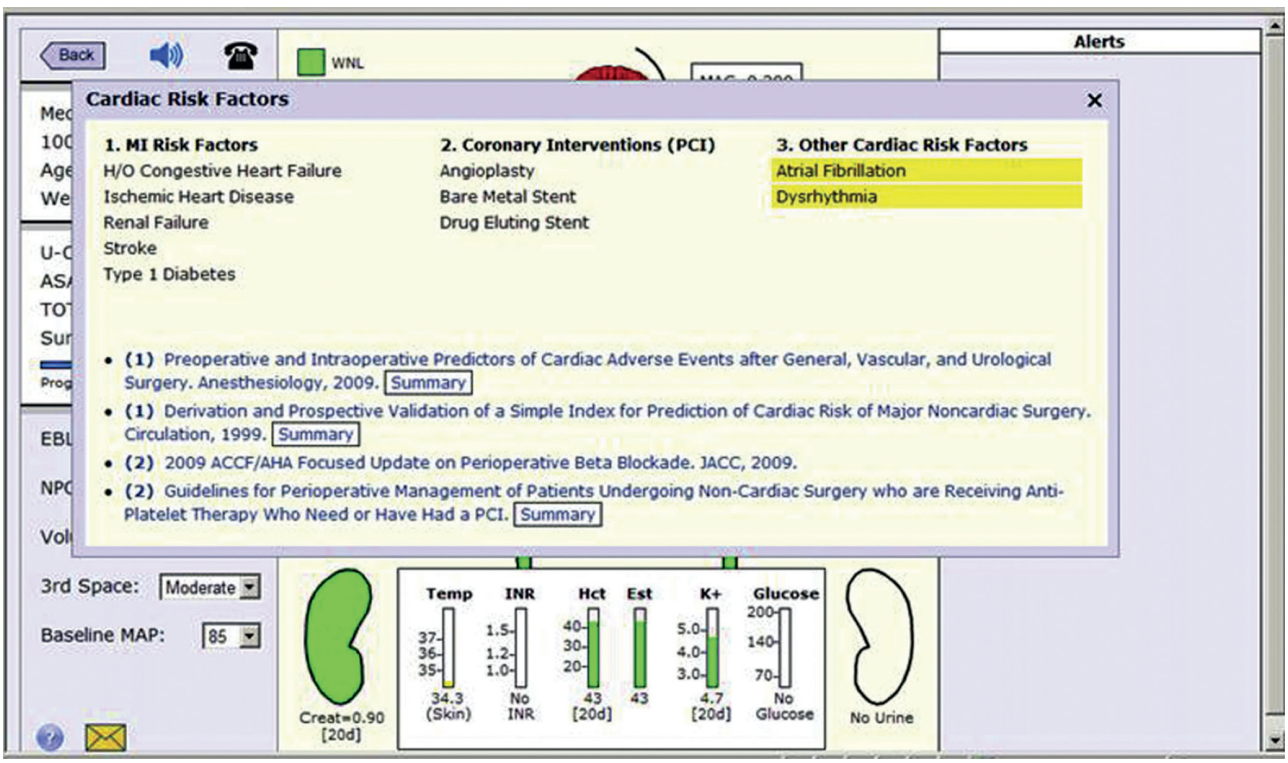

(B)

Figure 49.13 (A) Alertwatch display of one patient; the icons for each organ are self-evident, the lungs ventilate up and down with respiration, and the heart beats with heart rate. The left side of the screen shows case information, including current progress of case and percent completion, estimated blood loss (EBL), nil per os (NPO) hours, and preoperative baseline mean arterial pressure (MAP). Colors: green is normal (WNL), yellow is marginal, red is abnormal, and brown demonstrates organ system at risk. In this case, part of the patient's brain is orange, which indicates that he or she has a history of stroke; and the heart is orange, designating a cardiac history. This figure shows the heart volume to be low, which is based on an input/output calculation unless there is an objective measure, such as systolic pressure variation (SPV), central venous pressure, or pulmonary artery wedge pressure. The box at the bottom between the kidneys shows the current laboratory values and the last time they were drawn. There is also an alert portion of the screen on the right. BP, blood pressure. (B) If any organ at risk is selected (the screen is touched), a window will open; in this case it is the heart. On the left, the myocardial infarction (MI) risk factors are listed; the history of coronary intervention is in the middle; and a list of other cardiac problems is on the right. If the patient has these risk factors, they are highlighted in yellow. Below this are pertinent references and guidelines for cardiac care. In this case, the patient has a history of atrial fibrillation. H/O, history of; PCI, percutaneous coronary intervention. *Source*: Reproduced from Kruger et al [71] with permission of Elsevier.

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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71 Kruger GH, Tremper KK. Advanced integrated real-time clinical displays. Anesthesiol Clin 2011; 29(3): 487–504. A very interesting article explaining the massive amount of data input and integration required to produce advanced integrated real-time clinical displays, and their potential utility in anesthesia care.

CHAPTER 50

Operating Room Safety, Communication, and Teamwork

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Introduction

"In solo or group practice, teamwork is a major part of the anesthesiologist's life. Whether a vital part of a surgical team, a member of an interdisciplinary group of diagnosticians at a pain clinic, or a partner on a research team or teaching faculty, an anesthesiologist works continuously with a variety of medical professionals."

This quote from the American Society of Anesthesiologists (ASA) career information webpage summarizes the importance of teamwork in the daily life of all anesthesiologists [1]. Teamwork can be defined as "the ability of team members to work together, communicate effectively, anticipate and meet one another's demands, and inspire confidence resulting in a coordinated collective action" [2]. In 2000, The Institute of Medicine published a report titled, *To Err Is Human: Building a Safer Health System* [3]. This report highlighted the fact that systemic failures in healthcare delivery account for more errors than poor performance by individuals. The Institute of Medicine recommended interdisciplinary team training to reduce the incidence of such medical errors. Effective teamwork can provide a safety net that can often prevent human errors from becoming patient safety issues. This chapter reviews the basic principles of operating room and anesthesia safety as they apply to pediatric patients, emphasizing the non-technical skills of communication and teamwork as crucial to patient outcomes.

Non-technical skills

In the 1970s, the investigation of several airplane crashes concluded that no mechanical failure of the aircraft or technical failure of the pilot had occurred. So why did these planes crash? The investigators blamed deficits in other human factors characterized as non-technical skills [4]. Non-technical skills are defined as "the cognitive, social, and personal resource skills that complement technical skills, and contribute to safe and efficient task performance" [5]. These skills do not directly relate to medical knowledge, technical expertise, drugs, or equipment. For example, a surgeon could demonstrate excellent technical skills during the amputation of the wrong foot (a lack of situational awareness). Non-technical skills have been increasingly recognized as crucial to maintaining patient safety. Non-technical skills can be classified as: (1) cognitive and mental skills (such as decision making, planning, and situational awareness); and (2) social and interpersonal skills (such as communication, teamwork, and leadership) [6]. Traditionally, medical training has not formally taught these skills and deficiencies in these skills have been reported amongst anesthesiologists [6,7]. Medical team training focuses on the cultivation of these non-technical skills.

Medical team training

Clinical training usually focuses on the individual execution of tasks. Safe and efficient patient care requires the coordination of activity among physicians, nurses, respiratory therapists, pharmacists, and other healthcare professionals. However, all of these team members are rarely trained together. Effective teamwork is not reliably learned without formal training and cultivation. Team training teaches a set of tools and strategies that requires a mental shift from an individual perspective to a team perspective.

Several different medical team training programs have been developed. Medical team training programs can be categorized into high-fidelity simulator-based programs and classroom-based programs. The high-fidelity simulator-based

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

programs rely upon patient simulators and include courses such as "anesthesia crisis resource management" [7] and "team-oriented medical simulation" [8]. The classroom-based team training programs rely upon lectures, videos, demonstrations, and role play. Classroom-based programs include TeamSTEPPS® (Team Strategies and Tools to Enhance Performance and Patient Safety) [9], MedTeams® [10], Medical Team Management, Lifewings™, and Geriatric Interdisciplinary Team Training.

There is considerable overlap between all of these training programs, and there is no evidence that one training program or method is superior to another. Advocates of high-fidelity simulator-based programs list several advantages [11]. Simulators provide hands-on training in a realistic environment. The environment mandates the integration of decision skills, procedural skills, and teamwork skills in a scenario that actually challenges and stresses the clinician. Advocates of classroom-based programs highlight the lower cost, mobility, and ability to train large numbers of students simultaneously [12]. A detailed discussion of ACRM and TeamSTEPPS follows.

Box 50.1: Anesthesia crisis resource management key points in healthcare

- Know the environment
- Anticipate and plan
- Call for help early
- Exercise leadership and followership with assertiveness
- Distribute the workload
- Mobilize all available resources
- Communicate effectively – speak up
- Use all available information
- Prevent and manage fixation errors
- Cross check and double check
- Use cognitive aids
- Re-evaluate repeatedly
- Use good teamwork – coordinate with and support others
- Allocate attention wisely
- Set priorities dynamically

Source: Reproduced from Rall and Gaba [90] with permission of Elsevier.

Anesthesia crisis resource management

In 1989, David Gaba and his colleagues at Stanford University and the Palo Alto Veterans Affairs Medical Center pioneered the adaptation of aviation crew resource management to the practice of anesthesiology, resulting in the curriculum for anesthesia crisis resource management (ACRM) [7]. The phrases "crew resource management," "crisis resource management," and "cockpit resource management" are used interchangeably throughout the literature. Crew resource management can be defined as a management system that makes optimum use of all available resources (equipment, procedures, and people) to promote safety and focuses on teaching non-technical skills. The ACRM course begins with didactic presentations regarding anesthesia safety, decision making, specific anesthesiology crisis scenarios, and system-related failures that affect patient safety and human performance. Also, course participants critically analyze a video of an aviation accident. The bulk of the course consists of simulations followed by detailed debriefings. The simulator sessions feature a realistic patient simulator in an operating room environment in which each participant is the primary anesthesiologist managing critical event scenarios. Significant interaction between nursing and surgical personnel (role played by instructors) is required during the scenarios. Emphasis is placed on working more effectively with different leadership, followership, and communication styles. The simulation sessions are video recorded and analyzed by the team during debriefing sessions with the help of an instructor. The key points emphasized in ACRM are listed in Box 50.1. See Chapter 47 for a more detailed discussion of simulation in pediatric anesthesiology.

TeamSTEPPS®

TeamSTEPPS is another resource for training healthcare professionals in better teamwork practices. The Patient Safety Program of the Department of Defense and the Agency for Healthcare Research and Quality collaborated for 20 years to explore the field of medical teamwork. TeamSTEPPS is an evidence-based teamwork training system focusing on four complementary competency areas: leadership, situation monitoring, mutual support, and communication [9]. These are all teachable and learnable skills and should not to be viewed as skills that a person "either has or does not have." TeamSTEPPS offers a free public domain toolkit that can be tailored to any healthcare setting [13]. The free educational material on the TeamSTEPPS website includes presentations, group exercises, and videos. The Agency for Healthcare Research and Quality also offers a free TeamSTEPPS instructor course so that an institution can develop in-house expertise on team training. TeamSTEPPS can be used by all healthcare organizations and all medical specialties. This open availability may allow the entire medical field to begin using a common language and approach to team training.

TeamSTEPPS teaches specific tools and strategies to overcome barriers to team effectiveness. The tools and strategies are intimately linked to the four core competencies of the TeamSTEPPS framework: team leadership, situation monitoring, mutual support, and communication shown in Figure 50.1.

Leadership

"Leadership is the ability to direct and coordinate activities of team members, assess team performance, assign tasks, develop team knowledge and skills, motivate team members, plan and organize, and establish a positive team atmosphere" [14]. Effective team leaders organize the team, articulate clear goals, and make decisions through the collective input of members. They also delegate tasks, empower members to speak up and ask questions, actively promote and facilitate good teamwork, and are skillful at conflict resolution. Three strategies that leaders use to promote team information sharing are briefings, huddles, and debriefings.

A *briefing*, also known as a team meeting, is held for planning purposes and lets everyone on the team know what is going on and why. It is a short planning session to discuss subjects such as a patient's current condition, diagnosis, the role of team members, team goals, potential complications, and back-up plans. Briefings open the lines of communication so that everyone can contribute their unique knowledge to the task. The

Figure 50.1 TeamSTEPPS® four core competencies. *Source*: Reproduced from Agency for Healthcare Research and Quality [13] with permission of AHRQ Publications Clearinghouse.

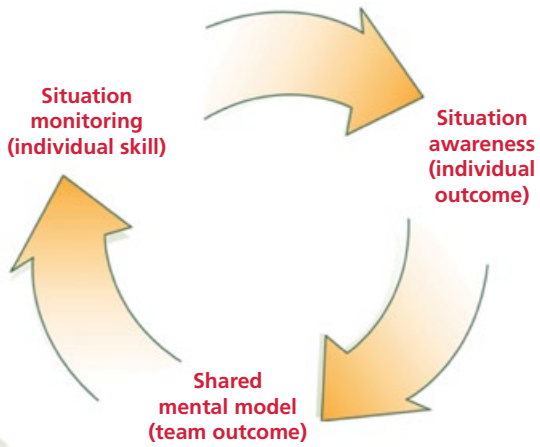


Figure 50.2 Continuum of situation monitoring, situation awareness, and a shared mental model. *Source*: Reproduced from Agency for Healthcare Research and Quality [13] with permission of AHRQ Publications Clearinghouse.

Figure 50.3 The STEP mnemonic for situation monitoring. *Source*: Reproduced from Agency for Healthcare Research and Quality [13] with permission of AHRQ Publications Clearinghouse.

team leader usually initiates the briefing, but any member of the team can do so. A *huddle* is an ad hoc discussion that focuses on problem solving. Huddles provide team members with an opportunity to update each other on changes in the status of the patient so that all team members can adapt. Huddles are used to re-establish situation awareness, reinforce plans already in place, and assess the need to adjust the plan. A *debriefing* takes place after a procedure or event and focuses on process improvement. It is an informal information exchange session designed to improve team performance and effectiveness. Debriefings are most effective in an environment where honest mistakes are viewed as learning opportunities and the focus is not placed on individual blame.

Situation monitoring

Situation monitoring is the process of continually scanning and assessing what is occurring around you to maintain situation awareness [14]. Situation awareness is "knowing what is going on around you." When everyone maintains their situation awareness and shares relevant facts to ensure that all team members are "on the same page," a shared mental model is formed. There is a continuum that begins with the individual skill of situation monitoring that leads to situation awareness and collectively results in a shared understanding of the situation (referred to as a shared mental model) (Fig. 50.2).

Situation awareness can be undermined by one team member's failure to share information, request information, and direct information to specific team members. Cross monitoring involves monitoring the actions of other team members and provides a safety net within a team. It involves "watching each other's back." Cross monitoring can help catch mistakes early before they compromise patient safety. The STEP mnemonic (Fig. 50.3) is a situation monitoring tool that is a mental reminder to constantly monitor the *status of the patient, team members, environment, and progress towards goal*.

Mutual support

Mutual support (or back-up behavior) is the ability to anticipate other team members' needs and to shift workload among members to achieve balance. Task assistance is a form of mutual support where team members protect each other from work overload situations. Some medical professionals are conditioned to avoid asking for help due to the fear of suggesting a lack of knowledge or confidence. Effective teams place all offers and requests for assistance in the context of patient safety and team members foster a climate where it is expected that assistance will be actively sought and offered.

Feedback is another type of mutual support. Feedback provides information to improve team performance. Effective feedback is timely (the behavior is still fresh in the mind of the receiver), respectful (should not be personal and should focus on behavior and not personality), specific (should relate to a specific situation), and directed (goals are set for improvement). Feedback can also be used to reinforce positive behaviors. Personal feedback is more effective when it is given in private as it causes less defensiveness on the part of the recipient.

Advocacy and assertion tools and strategies should be used when a team member's viewpoint does not coincide with that of the decision maker. The team member thus has the opportunity to correct errors or the loss of situation awareness. Failure to advocate and assert is frequently identified as a primary contributor to malpractice cases, sentinel events, and

aviation disasters. If the safety of the patient is at risk, even an unpopular viewpoint that questions authority should be advocated. The two challenge rule was initially developed to help airline pilots prevent disasters caused by momentary lapses in judgment. The two challenge rule states that if there is concern for potential harm to a patient, that concern should be asserted at least twice. If after two attempts the concern is still disregarded, a stronger course of action should be taken using the chain of command. This overcomes the natural tendency to believe the team leader must always be right. If challenged, it is the responsibility of the person challenged to acknowledge the safety concerns and resolve any safety issues. Leaders must foster an environment where all team members feel empowered to speak up when they notice a safety issue, knowing that their inputs are welcomed.

The healthcare environment is susceptible to frequent and sometimes disruptive conflict. This is not surprising given that it is an environment with a number of highly educated, experienced individuals with different training, backgrounds, and priorities. TeamSTEPPS teaches two basic conflict resolution strategies with two different scripts that can aid communication during times of conflict. The CUS script (concerned, uncomfortable, safety) uses signal words to catch an individual's attention. First a *concern* is stated, next the speaker states why they are *uncomfortable*, and finally they state that they believe there is a *safety* issue. The DESC script (describe, express, suggest, consequences) can be used to communicate effectively during all types of conflict. The specific situation is *described*. Concerns about the action are *expressed*. Other alternatives are *suggested*. Finally, potential *consequences* are stated. A private discussion between the individuals who have conflict will lead to more focus on resolving the conflict instead of a focus on saving face. The focus should be on *what* is right, not *who* is right. When resolving conflict, the goal should be to achieve collaboration, which means working together to achieve a mutually satisfying solution yielding a win–win situation.

Communication

Communication includes the efficient exchange of information and consultation with other team members. Communication is defined as the "exchange of information between sender and a receiver … the process by which information is clearly and accurately exchanged between two or more team members in the prescribed manner and with proper terminology and the ability to clarify or acknowledge the receipt of information" [15]. Communication is the lifeline of an effective team and the glue that holds all the team skills together. Improving the quality of information exchange decreases communication-related errors. In order for communication to be effective, it must be complete, clear, concise, and timely. How does communication relate to the other team skills? Effective leaders must communicate clear information so that team members are aware of their roles and responsibilities. Team members monitor situations and communicate any changes to keep the team informed. Finally, communication facilitates a culture of mutual support.

The Joint Commission (formerly the Joint Commission on Accreditation of Healthcare Organizations) has set specific safety goals related to communication including the need for standardized hand-offs with the opportunity to ask and respond to questions. Closed-loop communication is highly recommended and is defined as information exchange behavior whereby a sender initiates a message, a receiver acknowledges the message, and the message is verified by the initial sender.

TeamSTEPPS teaches four communication strategies and tools that have the potential to reduce errors associated with miscommunication. SBAR communication is described as one effective tool to communicate about a patient's condition. SBAR is a mnemonic that stands for s*ituation, background, assessment, and recommendation*. SBAR was originally developed by the United States Navy and adapted for use in the medical setting [16]. Many leading healthcare institutions support the use of SBAR including the Institute for Healthcare Improvement and the Joint Commission. SBAR is a standardized communication technique that allows the speaker to be clear and concise. A call-out is a communication strategy exemplified when a team member verbally states what they are doing, observing, or thinking in real time. A call-out is used to communicate important or critical information during a crisis so that all team members know what is going on. One example of using a call-out is stating the airway status, stating the vital signs, or announcing "clear!" before giving a patient a shock during cardiac arrest. A read-back (check-back) is a process of employing closed-loop communication to ensure that information conveyed by the sender is understood by the receiver as intended. Read-backs avoid orders being given into thin air and ensure proper understanding of orders. Hand-offs are emphasized as important communication processes that can result in patient harm if performed ineffectively. Hand-offs are discussed in detail in the following section. Many barriers to effective communication exist. These include language barriers, distractions, varying communication styles, workload, and conflict. The teamwork tools and strategies can be leveraged to overcome these barriers to effective communication. Figure 50.4 summarizes the barriers to team effectiveness, the tools and strategies to mitigate these barriers, and the desired outcomes of team training as taught by TeamSTEPPS.

KEY POINTS: NON-TECHNICAL AND MEDICAL TEAM TRAINING

- Team training involves multidisciplinary teams and can involve simulation or classroom-based training
- Anesthesia crisis resource management is simulation training that teaches leadership in a crisis and focuses on teaching non-technical skills
- TeamSTEPPS is a classroom-based system that includes team leadership, situation monitoring, mutual support, and communication

Hand-offs

A sentinel event is defined by the Joint Commission as "an unexpected occurrence involving death or serious physical or psychological injury" [17]. Examples of sentinel events include surgery on the wrong body part or the unintended retention of a foreign body such as a surgical instrument. The

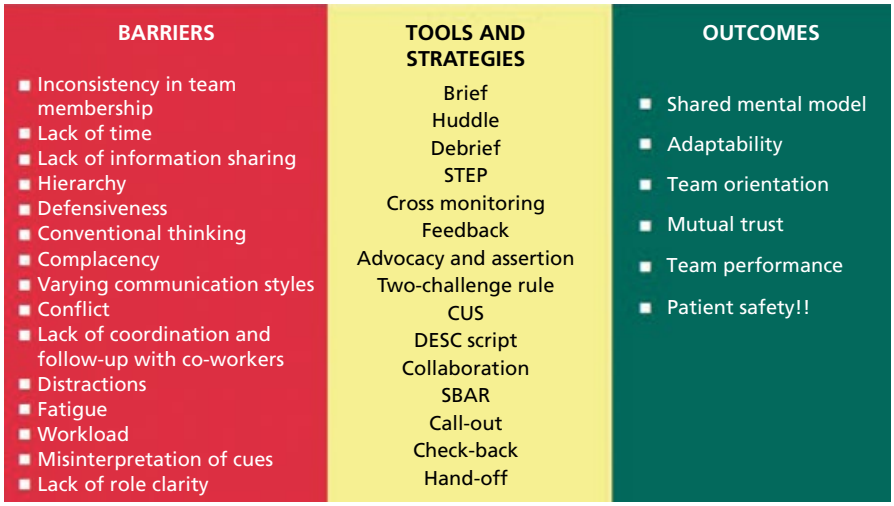


Figure 50.4 Barriers to team effectiveness, tools and strategies to overcome these barriers, and the desired team outcomes. *Source*: Reproduced from Agency for Healthcare Research and Quality [13] with permission of AHRQ Publications Clearinghouse.

Figure 50.5 Frequency of communication problems as the root cause of sentinel events. *Source*: Reproduced from Joint Commission on Accreditation of Healthcare Organizations [19] with permission of Joint Commission Resources.

Joint Commission determined that between 1995 and 2006, nearly 70% of all sentinel events were caused by communication problems (Fig. 50.5) [18,19]. More than half of the communication problems analyzed by the Joint Commission occurred during hand-offs. An analysis of one closed claim database showed that 40% of communication problems occurred during hand-offs [20].

A hand-off (also referred to as a hand-over, sign-out, transition, or sign-over) is defined as the transfer of accountability and responsibility of a patient from one healthcare provider to another. The Joint Commission states that the "primary objective of a handoff is to provide accurate information about a patient's care, treatment, and services, current condition and any recent or anticipated changes. The information communicated during a handoff must be accurate in order to meet patient safety goals" [18]. The daily workflow of anesthesiologists involves had-offs to and from other anesthetists, surgeons, neonatologists, critical care physicians, emergency physicians, respiratory therapists, and perioperative nurses. Pediatric patients are particularly vulnerable to ineffective hand-offs due to their reduced capacity to advocate for themselves and provide information regarding their own medical history [21]. Surprisingly, anesthesiologists are seldom formally taught how to effectively perform this duty. A recently published study of complete intraoperative hand-off of care in over 300,000 adult inpatients undergoing at least 2 h of anesthesia revealed an adjusted increase of 30-day mortality and major complications from 29.1% to 35.9% (relative risk 1.23, 95%CI 1.16–1.32) [22]. As the study authors note, the quality of the intraoperative hand-off was not assessed during this study, but "It is possible that an improved system of anesthesia handovers (in which critical components of handovers are mandated by a checklist) would eliminate the signal of harm while maintaining lifestyle benefits for clinicians."

Many specialties including anesthesiologists, surgeons, pediatricians, internists, and emergency medicine physicians have undertaken the qualitative evaluation of hand-offs, finding that hand-offs frequently lack a formalized structure [23–31]. They also note frequent omissions and distortions of important information. One study noted that pediatric interns overestimated the effectiveness of the hand-offs that they gave [30]. The same study showed that almost 40% of the recipients felt that the most important information about the patient was not reported.

The Joint Commission has commented on the negative consequences of ineffective hand-offs based on the relationship with sentinel events. Analysies of closed claims databases have also demonstrated the contribution of ineffective hand-offs to wrong site surgery, wrong patient surgery, and unintended retention of foreign bodies [20,32]. Ineffective hand-offs have also been shown to result in medication errors, delays in diagnosis and treatment [33], completely missed diagnoses [34], and omission of handed over tasks [26]. Studies have also demonstrated the frequent inability of the oncoming physician to find the missing information by means of the medical record [27].

There are many barriers to effective hand-offs. Most important is the lack of formal teaching of the hand-off process. Other barriers include interruptions, noise, distractions, and the time constraints on performing hand-offs in a busy practice [21,35,36]. Outgoing physician fatigue also can decrease the quality of a hand-off. Social hierarchy can have a negative impact on the quality of a hand-off. It is commonly noted that when receiving a hand-off from a more senior person, the more junior person is reluctant to ask questions and ask for

clarification [21,35,37]. This is because the junior person fears the perception that they are questioning a superior.

There is controversy amongst anesthesiologists regarding whether hand-offs should be formally structured. One survey of anesthesiologists reflected the perspective that standardization is burdensome and not needed, arguing that extra paperwork is an impediment to clinical care [38]. Another group of surveyed anesthesiologists felt that standardization would be valuable [39,40]. Regardless of the desire for or perceived need for the standardization of the hand-off process, it is clear that standardization and inclusion of a written and verbal component decreases omissions, decreases distortion, and improves recipient satisfaction with hand-off quality [23–26,28,29,35,41]. Another feature of high-quality hand-offs is the inclusion of a read-back (also referred to as a check-back) [21,36,42–45]. A read-back takes place by the oncoming provider (recipient of the hand-off) repeating what they heard during the hand-off to the outgoing practitioner who confirms accuracy or clarifies errors. This two-way feedback technique double checks information accuracy and verifies that the recipient was actually listening during the hand-off. Finally, face-to-face communication during a hand-off is ideal due to the non-verbal information that can be conveyed via facial expressions, body language, gestures, and eye contact. Box 50.2 summarizes the characteristics of effective hand-offs described in the literature [31,36,45].

At least 24 different mnemonics for hand-offs have been described in the medical literature [46]. It is recommended that each institution should consistently use one mnemonic throughout the hospital so that when surgeons, nurses, anesthesiologists, neonatologists, critical care physicians, and emergency medicine physicians communicate, they utilize a similar communication structure.

I-PASS system

Nine children's hospitals in the United States studied the effect of a resident hand-off improvement program using the I-PASS mnemonic [47]. I-PASS is a mnemonic that stands for *illness severity, patient summary, action list, suggestions, and synthesis*. I-PASS is copyrighted by Boston Children's Hospital, but the materials are freely available. After implementation of the hand-off improvement program based on I-PASS, the medical error rate decreased by 23% and the rate of preventable adverse events decreased by 30% at the hospitals studied. Box 50.3 shows a sample hand-off protocol in I-PASS format.

Box 50.2: Characteristics of effective hand-offs

- Format is standardized
- Contains a verbal and written component
- Read-back used to verify understanding
- Allows the opportunity to ask questions
- Pending studies are emphasized
- Hierarchy is flattened
- Interactive
- Information is up to date
- Contingency plans discussed
- Free of interruptions
- Quiet environment
- Face to face

Box 50.3: Sample protocol for hand-off in I-PASS format

I *Illness severity*: How sick is the patient?
- Stable, watcher (potential to become unstable), star (unstable)

P *Patient summary*: Brief overview, one liner
- Age, sex, past medical history, past surgical history
- Chief complaint, significant signs and symptoms, working diagnosis or differential
- Diet, meds, support, access, infection sources
- Hospital course so far
- Suggested plan

A *Action list*: To do
- What to do, when to do it, and what to do about it

S *Suggestions*: If/then
- What could happen and what intervention would be needed

S *Synthesis*: Receiver summarizes

Society for Pediatric Anesthesia's intraoperative hand-off tool

The Quality and Safety Committee of the Society for Pediatric Anesthesia (SPA) created an intraoperative hand-off tool and published it online (Fig. 50.6). This tool is helpful for promoting excellent communication during temporary or permanent intraoperative transfer of care from one anesthesia provider to another.

Effective team members are expected to ensure that their colleagues are well informed when sharing the care of a patient. Providing an effective standardized hand-off prevents lapses in information that can lead to mistakes.

KEY POINTS: HAND-OFFS

- Hand-offs are ubiquitous in healthcare, yet as many as 40% of communication problems occur during hand-offs
- Lack of formal teaching and ineffective hand-offs are important sources of error that lead to adverse patient outcomes
- I-PASS stands for illness severity, patient summary, action list, suggestions, and synthesis

Checklists

In 1978, a study revealed that 14% of anesthetic mishaps could be attributed to failure of the anesthesia machine [48]. In 1987, the ASA and the United States Food and Drug Administration (FDA) collaborated to produce a generic anesthesia machine checklist to increase detection of malfunctions.

A checklist is a simple tool designed to reduce error and encourage compliance with best practice. Checklists are memory aids that list action items or criteria that have been determined to be essential to the success of a process or procedure. Indeed, "a short pencil is better than a long memory." Utilization of checklists is considered essential to safety in the industries of aviation, nuclear power, construction, and manufacturing [49]. Recent studies have also demonstrated positive applications in the medical field. Checklists are a proven component of interventions to reduce the incidence of central venous line-associated bloodstream infections, reduce

Intraoperative Handoff Tool

☐ **Provider introductions** ☐ **Attending of record**
☐ **Pt ID** ☐ **Age** ☐ **Weight** ☐ **ASA status**
☐ **Allergies** ☐ **Isolation protocol** ☐ **Premed**

☐ **Surgical procedure** ☐ **Anesthetic technique**
○ Postop disposition

☐ **History**

Airway
☐ Type / size / difficulty / leak
☐ Mode of ventilation
○ Extubation plan

Cardiac
☐ HR / BP / rhythm baseline and trends
☐ Hemodynamic issues / goals

Medications
☐ Controlled substances
☐ Muscle relaxants
☐ Local anesthetics / regional blocks
☐ Antibiotics: last dose / next dose
☐ Medications given by surgeon
☐ Anti-emetics
☐ Independent double check infusions

Fluids
☐ IV access
☐ Type / amount given / dextrose
☐ EBL / blood available / location of blood
☐ Urine output

Monitors
☐ Invasive catheters / BIS / NIRS / ICP / Doppler
☐ Temperature / warming device / setting
☐ Lab data

Other Information
○ Pt anxiety / nickname / development
○ Parent expectation / anxiety

☐ **Complications / Issues not covered**
☐ **Confirmation / questions**
○ Documentation complete

Figure 50.6 Society for Pediatric Anesthesia intraoperative handoff tool. *Source*: Reproduced with permission of Society for Pediatric Anesthesia.

intensive care unit (ICU) length of stay, and reduce surgical morbidity and mortality.

Central line-associated bloodstream infections occur too frequently, may result in death, and are now considered mostly preventable [50]. In 2001, Pronovost and colleagues undertook a quality improvement project aimed at reducing the incidence of line-associated infections [51]. The project included a checklist designed to ensure adherence to the infection control protocol. The checklist contained infection control guidelines that most practitioners recognize but do not always follow. Use of the checklist resulted in a reduction in the mean rate of infections from 7.7 per 1000 catheter-days to 1.4 per 1000 catheter-days. Subsequent studies have reproduced these results showing significant reductions in line-associated infection rates when a checklist is used [52–56]. Typical components of a central line insertion checklist are shown in Box 50.4.

The ICU is an environment where multidisciplinary coordination and communication are vital to patient safety and throughput. The entire care team must clearly understand the goals of care, list of tasks, and communication plan. The ICU daily goals form is a type of checklist designed to improve communication between team members [57–59]. The top two priorities of the daily goals form are the conditions necessary to discharge the patient from the ICU and reducing the patient's greatest safety risk. Several studies have demonstrated that the use of this form results in significant improvements in team understanding of the daily goals for a patient and significant reductions in length of stay for the patient [57,59,60].

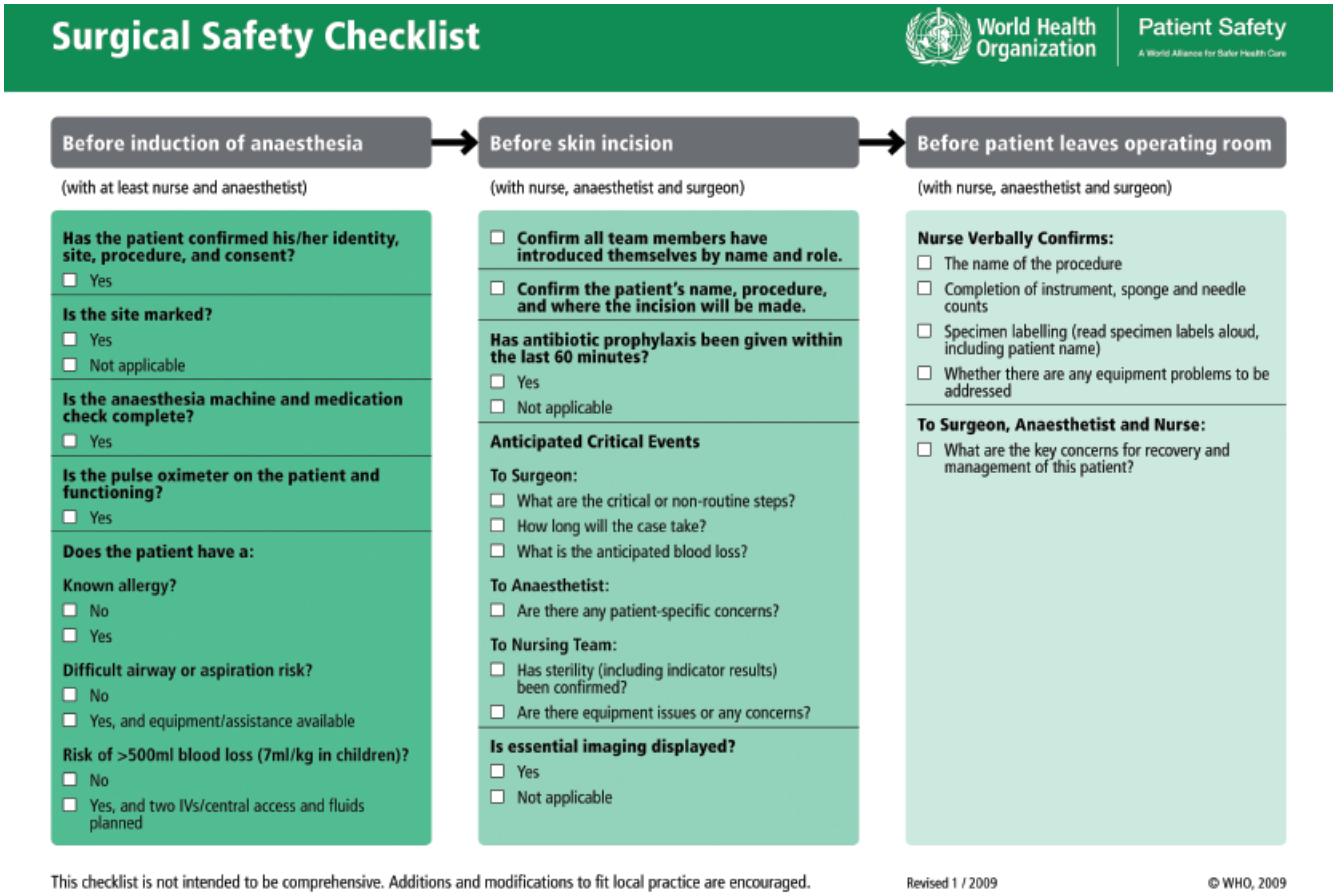
Box 50.4: Central venous line insertion checklist

- Equipment assembled and supplies verified before procedure begins
- Nurse observes procedure and is empowered to intervene to ensure compliance
- Provider washes hands with antibacterial soap or waterless hand cleaner
- Provider wears hat, mask, sterile gown, and sterile gloves
- Insertion site scrubbed with 2% chlorhexidine (age >2 months) or povidone-iodine (<2 months)
- Patient covered from head to toe with sterile drape
- Sterile dressing applied and dated immediately after procedure

The World Health Organization (WHO) recognizes that surgical complications are common and often preventable. It has been estimated that over 230 million major surgeries take place per year [61]. Of these, 7 million major complications occur including 1 million deaths. A team of experts worked to create a checklist designed to improve teamwork and prevent common causes of perioperative morbidity and mortality. The WHO surgical safety checklist is shown in Figure 50.7.

The WHO surgical safety checklist promotes and facilitates good teamwork by helping the team develop a shared mental model with the use of a brief before anesthesia induction and a time out before skin incision. Before the procedure begins, the entire team introduces themselves by name in order to flatten hierarchy. The checklist also empowers team members to speak up if they notice any safety concerns. Several components of the checklist are related to the practice of anesthesiologists. The checklist specifically encourages vigilance related to the presence of a difficult airway, risk of aspiration, risk of significant blood loss, the presence of allergies, and timely administration of prophylactic antibiotics. The effect of the WHO surgical safety checklist was evaluated in eight hospitals across the world, including several in developing nations, and others in highly developed academic teaching settings. Implementation of the checklist resulted in a reduction of death from 1.5% to 0.8% and a reduction in inpatient complications from 11.0% to 7.0% [62]. Considering the high volume of worldwide surgeries and the high complication rates [61], global implementation of the WHO surgical safety checklist could lead to substantial reductions in surgical mortality and morbidity. One criticism of this landmark safety study is that although there was improvement in all hospitals, more of the improvement in outcome could be attributed to the hospitals in developing nations.

A recent study of a comprehensive perioperative safety checklist was conducted in six intervention hospitals, and five control hospitals in the Netherlands, all tertiary care and academic hospitals with previously demonstrated high standards and quality of care [63]. In 3760 patients studied before implementation of the checklist, and 3820 patients after implementation, the total number of complications decreased from 27.3 to 16.5 per 100 patients ($p < 0.001$), and in-hospital mortality decreased from 1.5% to 0.8% ($p < 0.001$). These outcomes did not change in the control hospitals. Surgical safety checklists should be modified according to local institutional needs, including those of a children's hospital, where the



Surgical Safety Checklist

World Health Organization | Patient Safety
A World Alliance for Safer Health Care

Before induction of anaesthesia
(with at least nurse and anaesthetist)

Has the patient confirmed his/her identity, site, procedure, and consent?
- ☐ Yes

Is the site marked?
- ☐ Yes
- ☐ Not applicable

Is the anaesthesia machine and medication check complete?
- ☐ Yes

Is the pulse oximeter on the patient and functioning?
- ☐ Yes

Does the patient have a:

Known allergy?
- ☐ No
- ☐ Yes

Difficult airway or aspiration risk?
- ☐ No
- ☐ Yes, and equipment/assistance available

Risk of >500ml blood loss (7ml/kg in children)?
- ☐ No
- ☐ Yes, and two IVs/central access and fluids planned

Before skin incision
(with nurse, anaesthetist and surgeon)

- ☐ **Confirm all team members have introduced themselves by name and role.**
- ☐ **Confirm the patient's name, procedure, and where the incision will be made.**

Has antibiotic prophylaxis been given within the last 60 minutes?
- ☐ Yes
- ☐ Not applicable

Anticipated Critical Events

To Surgeon:
- ☐ What are the critical or non-routine steps?
- ☐ How long will the case take?
- ☐ What is the anticipated blood loss?

To Anaesthetist:
- ☐ Are there any patient-specific concerns?

To Nursing Team:
- ☐ Has sterility (including indicator results) been confirmed?
- ☐ Are there equipment issues or any concerns?

Is essential imaging displayed?
- ☐ Yes
- ☐ Not applicable

Before patient leaves operating room
(with nurse, anaesthetist and surgeon)

Nurse Verbally Confirms:
- ☐ The name of the procedure
- ☐ Completion of instrument, sponge and needle counts
- ☐ Specimen labelling (read specimen labels aloud, including patient name)
- ☐ Whether there are any equipment problems to be addressed

To Surgeon, Anaesthetist and Nurse:
- ☐ What are the key concerns for recovery and management of this patient?

This checklist is not intended to be comprehensive. Additions and modifications to fit local practice are encouraged.

Revised 1 / 2009

Figure 50.7 World Health Organization's surgical safety checklist. *Source*: Reproduced from World Health Organization Surgical Safety Checklist (www.who.int/patientsafety/safesurgery/en/index.html) with permission of WHO.

surgical briefing may need to be done in the preoperative holding area with the parent present. One such modification is shown in Figure 50.8.

Checklists are important components of comprehensive patient safety interventions. It would be an oversimplification to state that checklists alone reduce central venous line-associated infections, ICU length of stay, and surgical morbidity [64]. Team education must first take place to build faith in the practices reinforced by the checklist. Barriers to the use of the checklist must be identified and eliminated or the checklist will often be left unused. Outcomes must be measured and feedback should be provided. Institutions should customize checklists to fit the needs and culture of their own organization.

One survey revealed that some physicians remain skeptical about whether or not checklists truly improve patient safety. The fact that almost all of those same skeptics wanted the checklist used if they themselves were having surgery speaks for itself [49]. The use of checklists that have shown evidence in improvements in patient outcomes should be embraced.

Society for Pediatric Anesthesia's critical events checklists

The Quality and Safety Committee of the SPA have developed a collection of checklists and cognitive aids to facilitate optimal management of common perioperative emergencies [65] which are available in PDF format and as a mobile application. Several institutions have incorporated these checklists into their anesthesia information management systems. These checklists compile the latest evidence-based and expert opinion-based management strategies that can be used in real time by the entire care team to help manage a patient with optimal teamwork. It is recommended that a paper or digital copy of the checklists be available in all anesthetizing locations. If an emergency occurs, the anesthesiologist, nurse, or any other person in the room should go to the appropriate checklist in real time and verbally call out the recommended therapies listed or diagnoses to be considered. The table of contents of the checklists, and a checklist for anaphylaxis, are shown in Figure 50.9. The SPA critical events checklists are available at http://www.pedsanesthesia.org/critical-events-checklist/ (accessed May 2019).

KEY POINTS: CHECKLISTS

- Checklists have long been utilized in high reliability industries and now are common in healthcare; their use can lead to lower adverse event rates such as central line-associated bloodstream infection
- The surgical safety checklist, including preoperative briefing, intraoperative time out, and intraoperative debriefing are now required in most institutions and their use can lead to decreased perioperative complications
- Intraoperative critical events checklists, or memory aids, can lead to more complete incorporation of all necessary steps in a crisis such as anaphylaxis

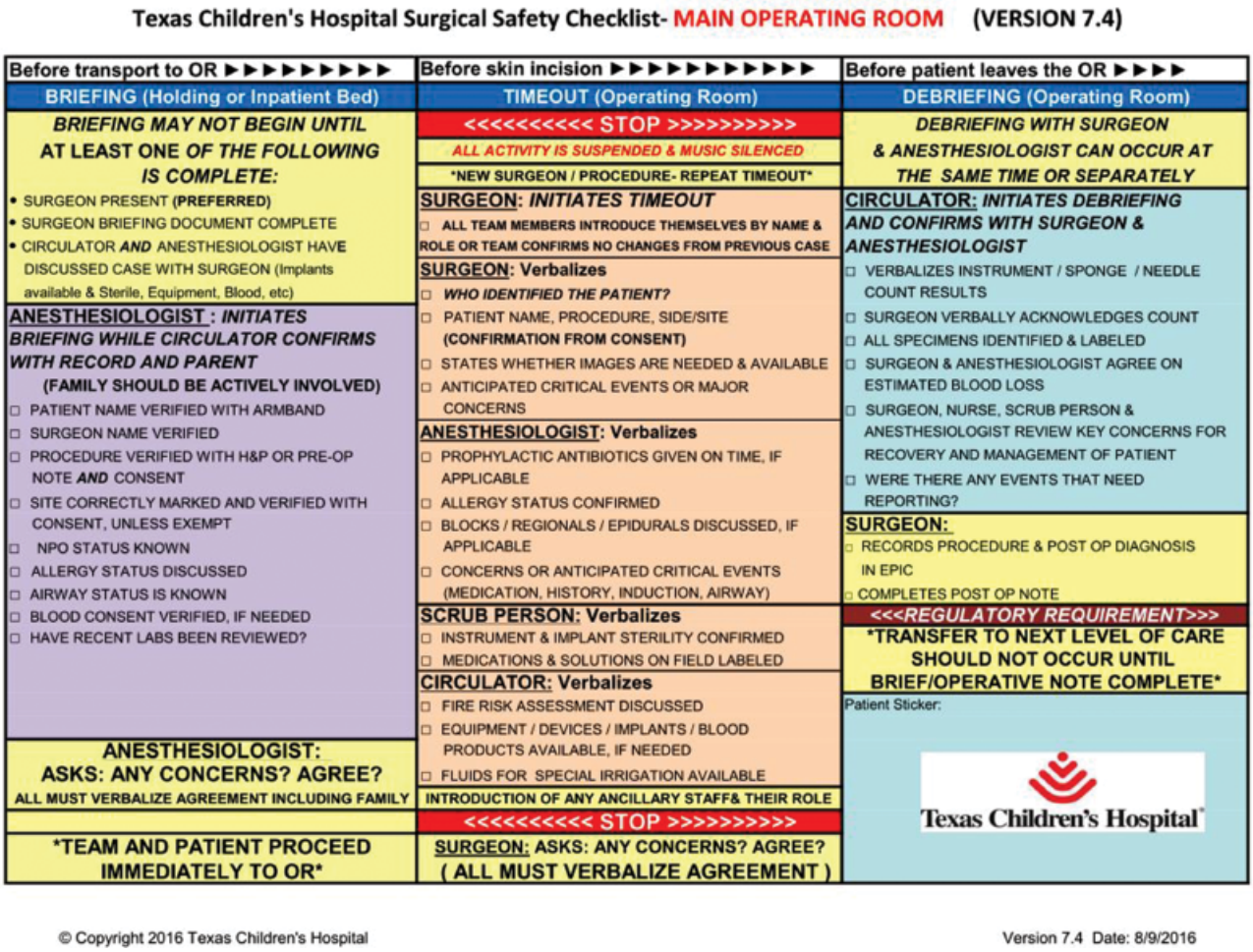


Figure 50.8 Texas Children's Hospital surgical safety checklist. The surgical briefing is done in the holding area, or intensive care unit bedside, and initiated by the anesthesiologist with the parent present to verify information. The surgeon must be present for the briefing, or have communicated to the anesthesiologist verbally or via written communication his/her plans and concerns for the case. *Source*: Reproduced with permission from Dr Andropolous.

Medication safety

The perioperative environment is unique with regards to medication administration since anesthesia providers are singlehandedly responsible for prescribing, preparing, administering, and documenting medications without a second person to cross check. In addition to the numerous medications needed to safely anesthetize a patient, providers must have immediate access to emergency medications should a life-threatening situation arise. Pediatric patients are particularly vulnerable to medication dosing errors since most medications are administered on a dose per weight basis. Incorrect measurement of weight, recording of weight, or calculation of dose can lead to significant over- or underdosing of medications.

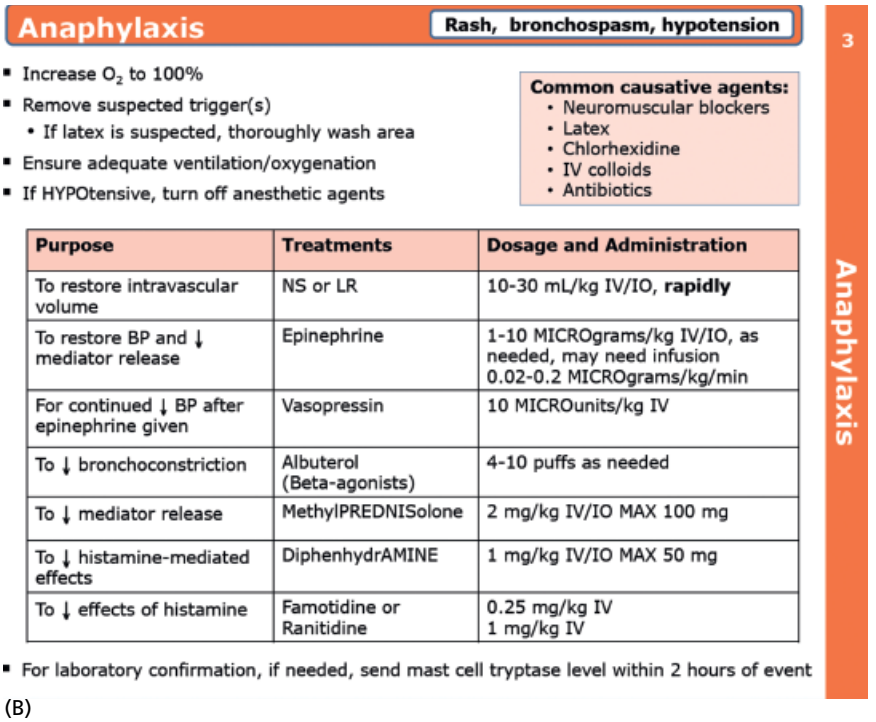
Incidence

Unfortunately, medication errors are a common occurrence in healthcare systems and are reported to be the seventh most common cause of death overall. The FDA reports medication errors as the cause of approximately 1.3 million injuries each year and one death every day in the United States [66]. These numbers are believed to be severely underestimated as most data sources rely on voluntary reporting. A survey of members of the Canadian Society of Anaesthesiologists from 2001 reported that 85% of respondents experienced at least one drug error or near miss [67]. However, another study determined that a medication error or adverse drug event occurred in approximately one in 20 perioperative medication administrations, and every second surgical procedure [68]. More than one-third of these errors led to patient harm, and the remaining two-thirds had the potential for patient harm. Of note, pediatric patients were excluded from this study.

Types of medication errors

Various groups have classified medication errors, and Table 50.1 is one proposed classification system [69]. Wake Up Safe is a multi-institutional quality improvement initiative for reporting and analyzing anesthesia and surgery safety events sponsored by the SPA. A recent report from the Wake Up Safe Quality Improvement Initiative revealed that medication errors occurred most frequently during the administration phase of the anesthetic, particularly with administration of the wrong dose and syringe swaps. Patient harm occurred in half of the reported medication errors that reached the patient, and a large majority of the reported errors were deemed preventable [70]. These findings are consistent with a 2010 report from New Zealand that also identified incorrect dosing as the most common medication error type [69].

(A)



(B)

Figure 50.9 (A) Table of contents of Society for Pediatric Anesthesia critical events checklists. (B) Checklist for intraoperative anaphylaxis. The checklists are available without charge at http://www.pedsanesthesia.org/critical-events-checklist/ (accessed May 2019). *Source*: (A) Reproduced with permission from Dr Andropolous.

Risk factors

A large study from New Zealand evaluated contributing factors to medication errors, finding a failure to check to be the most common (23%), followed by distraction (16%), inattention (13%), and haste or production pressure (10%) [69]. Interestingly, several other studies have evaluated the risk of emergency surgery and this does not appear to be a contributing factor with medication errors.

Table 50.1 Types of medication error

Medication error	Definition
Omission	Drug not given
Repetition	Extra dose of an intended drug
Substitution	Incorrect drug instead of the desired drug: a swap
Insertion	A drug that was not intended to be given at a particular time or at any time
Incorrect dose	Wrong dose of an intended drug
Incorrect route	Wrong route of an intended drug
Others	Usually a more complex event, not fitting the above categories

Prevention

One study evaluated the baseline incidence of medication errors in two hospitals, both of which used a standard color-coding labeling system for medications used by anesthesiologist [69]. They instituted a new system designed to reduce medication errors in one of the hospitals. This improvement strategy included: (1) labels with the class and generic name of each drug in large, clear lettering and incorporating a bar-code; (2) alerts for known allergies and expired drugs; (3) custom software and a barcode scanner to allow a drug identity cross check before each administration, by redisplay of the drug name and its international color code on a computer screen and an auditory announcement of the drug name; (4) reorganization of the workspace using syringe trays and a color-coded drug tray; (5) prefilled, standardized syringes for many commonly used medications; (6) a complete, automated anesthetic record; and (7) operational rules designed to decrease human error and facilitate safe practice. The two principal operating rules were: to scan each drug before administration and to retain used ampules and syringes in designated zones on the new trays as a physical "record" of what had been given; and an additional labeling system for the accurate preparation of infusion drugs. The new system using these strategies resulted in a relative reduction of 35% in drug errors.

On January 26, 2010, the Anesthesia Patient Safety Foundation (APSF) convened a consensus conference of 100 stakeholders from many different backgrounds to develop new strategies for "predictable prompt improvement" of medication safety in the operating room. Their recommendations are summarized in Box 50.5 [71].

Medication labeling systems

The Joint Commission requires that each medication syringe be labeled with the medication name, concentration, preparation time and date, expiration time and date, and preparer's initials. The Safe Label System SLS 500i™ (Codonics Inc., Middleburg Heights, OH, USA) is a computerized drug labeling system (Fig. 50.10). This system scans the barcode on medication vials, provides auditory feedback to confirm the drug name and concentration, and prints a color-coded syringe label. These labels facilitate compliance with Joint Commission regulations and achieve many of the strategies recommended by the APSF to improve medication safety. One study showed that implementation of this medication labeling system increased labeling compliance from 36% to 88% [72].

Further studies are needed to assess the effectiveness of proposed strategies for medication error reduction. However, accepting the current rates of medication errors is unacceptable. Anesthesia providers must remain vigilant and continue to strive to reduce harm to patients. Fostering a culture focused on safety in the perioperative setting and promotion of non-punitive, voluntary reporting of errors is important to foster a better understanding of the true scope of this issue.

KEY POINTS: MEDICATION SAFETY

- Anesthesiologists are some of the only providers who prepare, label, and administer medications frequently without a second person to cross check
- A recent Wake Up Safe study documented a rate of medication error of about 1.2 per 10,000 cases, with patient harm occurring in half the errors that reached the patient
- Prevention strategies include a drug scanning and labeling system, pharmacy premixed and prefilled syringes when possible, and special procedures for high-risk medications

Value-based programs

Many evidence-based clinical processes that are known to improve patient outcomes are not consistently achieved or are implemented slowly [73]. In the United States, the Centers for Medicare and Medicaid Services (CMS) and many other healthcare plans have adopted value-based purchasing programs (also referred to as pay-for-performance) methods to incentivize the reporting of quality data and achieving quality goals. Value-based purchasing initiatives create financial incentives for physicians to achieve quality goals by linking a portion of payments to reporting quality data and performance on quality measures. The Physician Quality Reporting System (PQRS) was established by the CMS in 2006. In 2017, the CMS began transitioning from the PQRS to the Merit-based Incentive Payment System (MIPS) which is a part of the CMS Quality Payment Program. Since January 2019, CMS adjusts payments from +4% to –4% based on satisfactory reporting of quality data and achieving quality goals. In other words, payments to a practice may be reduced by up to 4% or may be increased by up to 4%. That payment adjustment is scheduled to gradually increase to ±9% by 2022 [74]. The ASA has partnered with the Anesthesia Quality Institute to develop a Qualified Clinical Data Registry that can be a basis of performance measures [75]. A selection of MIPS measures related to anesthesiology is shown in Box 50.6.

The actual effect that value-based purchasing has on quality improvement is currently unclear. Studies have generally shown that such initiatives have no effect or minimal effect on improving quality measures [76–79]. Even as many third party payers are moving forward with value-based purchasing initiatives, caution may be warranted due to the fact that the data regarding effectiveness is weak at best.

Safe systems in the operating room

Operating room (OR) safety can potentially be improved through the application of technology and knowledge. Recent advances in technology have moved the traditional surgical

Box 50.5: Consensus recommendations for improving medication safety in the operating room

Standardization

1. High alert drugs (such as phenylephrine and epinephrine) should be available in standardized concentrations/diluents prepared by pharmacy in a ready-to-use (bolus or infusion) form that is appropriate for both adult and pediatric patients. Infusions should be delivered by electronically controlled smart device containing a drug library
2. Ready-to-use syringes and infusions should have standardized fully compliant machine-readable labels
3. *Additional ideas*:
   a. Interdisciplinary and uniform curriculum for medication administration safety to be available to all training programs and facilities
   b. No concentrated versions of any potentially lethal agents in the operating room
   c. Required read-back in an environment for extremely high-alert drugs such as heparin
   d. Standardized placement of drugs within all anesthesia workstations in an institution.
   e. Convenient required method to save all used syringes and drug containers until case concluded
   f. Standardized infusion libraries/protocols throughout an institution
   g. Standardized route-specific connectors for tubing (IV, arterial, epidural, enteral)

Technology

1. Every anesthetizing location should have a mechanism to identify medications before drawing up or administering them (barcode reader) and a mechanism to provide feedback, decision support, and documentation (automated information system)
2. *Additional Ideas*:
   a. Technology training and device education for all users, possibly requiring formal certification
   b. Improved and standardized user interlaces on infusion pumps
   c. Mandatory safety checklists incorporated into all operating room systems

Pharmacy/prefilled/premixed

1. Routine provider-prepared medications should be discontinued whenever possible
2. Clinical pharmacists should be part of the perioperative/operating room team
3. Standardized preprepared medication kits by case type should be used whenever possible
4. *Additional ideas*:
   a. Interdisciplinary and uniform curriculum for medication administration safety for all anesthesia professionals and pharmacists
   b. Enhanced training of operating room pharmacists specifically as perioperative consultants
   c. Deployment of ubiquitous automated dispensing machines in the operating room suite (with communication to central pharmacy and its information management system)

Culture

1. Establish a "just culture" for reporting errors (including near misses) and discussion of lessons learned
2. Establish a culture of education, understanding, and accountability via a required curriculum and continuing medical education and dissemination of dramatic stories in the *APSF Newsletter* and educational videos
3. Establish a culture of cooperation and recognition of the benefits of standardization, technology, and culture within and between institutions, professional organizations, and accreditation agencies

Source: Reproduced from Eichhorn [71] with permission of APSF.

suite toward one that is more efficient and safe. However, practice in most ORs does not differ greatly from that of 50 years ago. The Health Information Technology for Economic and Clinical Health Act, as part of the American Recovery and Reinvestment Act of 2009, pledged billions of dollars to improve access to data through technology and improve overall quality of care [80,81]. Yet, to date, electronic information systems do not have a common platform and do not effectively share data elements (pertinent patient information). Effective anesthesia information management systems (AIMS) should enhance patient care more than simply providing a legible record. In fact, although legible, most current information systems produce records that will automatically add data and descriptive text with the push of a button. Such a record may actually lead to inaccurate data entry, or produce a lengthy record that will fatigue users in the same way as inefficiently sorting through a voluminous paper chart. Also, the addition of complex technology to the OR can add hazards by distracting the anesthesiologist from the patient and surgical procedure. An effective AIMS is easy to use and provides decision support to the user in order to enhance patient care. See Box 50.7 [82] and Chapter 49 for a more detailed presentation of the electronic anesthesia record.

Other technologies that are being tested in the OR to improve patient safety include the use of barcodes, radiofrequency identification (RFID), and smart imaging. As described earlier, barcodes can be used to perform as a second check on medication administration. Additionally, barcodes can track instruments used in the surgical field. Most commercial warehouses and supermarkets track their inventories more effectively than supplies and equipment are tracked in the perioperative environment. Retailing giants closely track the location of their one dollar paper towel inventory, but a charge nurse in a typical operating

Figure 50.10 Codonics Medication Safety System. The device audibly reads the barcode on a medication vial, and prints out a color-coded medication label with all required information: drug name, concentration, preparation and expiration dates, and initials of preparer. *Source*: Courtesy of Codonics, Inc.

Box 50.6: Merit-based incentive payment system measures related to anesthesiology

- Perioperative temperature management
- Patient-reported experience with anesthesia
- Nausea/vomiting prevention with combination therapy
- Prevention of central venous catheter-related bloodstream infections
- Central line ultrasound guidance
- Use of checklist for transfer of care to postanesthetic care unit
- Use of checklist for transfer of care to intensive care unit
- Sleep apnea: assessment of sleep symptoms
- Multimodal pain management
- Pain assessment and follow-up
- Safe opioid prescribing practices
- Documentation of anticoagulant and antiplatelet medications when performing neuraxial anesthesia/analgesia or interventional pain procedures

Box 50.7: Examples of decision support from anesthesia information management systems

Quality assurance
- Maintenance of normothermia notifications
- Presurgical antibiotic management notifications

Medication support
- Drug–drug interaction checking
- Drug–dose calculations
- Drug redosing reminders
- Drug–allergy checking

Regulatory and compliance support
- Concurrency checking
- Ensuring electronic records contain elements required for billing
- Attending physician attestation statements
- Case times (start of anesthesia care, end of anesthesia care)
- Case type (general/monitored anesthesia care/regional)
- Patient details (American Society of Anesthesiologists (ASA) physical status)

Support around critical events
- Algorithm display and guidance (malignant hyperthermia, advanced cardiac life support, ASA difficult airway algorithm)
- Critical event detection:
  - Chaotic electrocardiogram + no pulse oximetry wave form → consider ventricular fibrillation
  - ↓ Blood pressure + ↑ heart rate + ↓ end-tidal CO_2 → consider ↓ cardiac output from hypovolemia

suite might have to search for a $25,000 ultrasound instrument. RFID can be used to track, plan, and send shared equipment for OR procedures thereby improving efficiency. RFID can be inexpensively incorporated into the patient's armband so that when the patient enters the OR the most recent labs, images, planned surgical procedure, ordered antibiotics, and allergies are automatically displayed on a common screen. Adding RFID tags to surgical sponges and instruments could potentially eliminate retained foreign material in the surgical wound; and an RFID label on blood products could identify an incorrect unit as it is brought into the OR. At the writing of this chapter, these technologies remain in a state of development.

Distractions in the anesthetic and operating room environments

The anesthetic and OR environments require that the anesthesiologist's primary focus of attention be on the patient: closely following the physiological monitoring parameters, anesthetic delivery, and requirements for the surgery or procedure to deliver safe and effective anesthetic care, often for medically complex and unstable patients. At times there are long periods of relative calm and stability where less intervention on the part of the anesthesiologist is required. The anesthesia environment is full of potential distractions diverting one's attention away from the patient. A direct observational study of 30 anesthetics comprising over 31 h of anesthetic time revealed 424 distracting events, or about one every 4 min [83].

Events included unrelated conversations, music, noises outside the room, personnel entering the room to locate equipment, OR teaching activities, the anesthetist briefly leaving the room to locate equipment, and many others. Twenty-two percent of events were judged to potentially have a negative effect on patient care, including deterioration in physiological variables, delays in procedures, and repeated attempts at procedures.

In recent years the ubiquitous presence of computers in the anesthesia work area, including workstations for AIMS and personal laptops, tablets, and the now omnipresent smartphone, have increased the potential for electronic distractions in the OR [84]. There are just a few published studies of electronic distraction in the anesthesia environment, and as yet no clear data that the presence of these electronics has adverse effects on patient care. In a study of 1061 anesthetics where the AIMS computer also had access to the internet for use not directly related to the case, 16% of anesthetic time had the computer accessing the internet for non-AIMS applications [85]. In a clever analysis of hemodynamic instability during those times, there was no increase in hemodynamic variability or instability. Another large observer study of 319 anesthetics targeting self-initiated non-clinical distractions revealed that they occurred in 54% of cases [86]. The most common distraction was personal internet use; but these distractions only accounted for 2% of case time, and were not deemed to be the cause of any adverse events. It should be noted that the study subjects knew they were being observed and data for this recently published paper were collected from 2007 to 2009, before the pervasive presence of smartphones and social media in the OR.

Over the past several years, the presence of powerful handheld computers with increasingly fast processing speeds, known as smartphones, has revolutionized daily life. They have become an indispensable aid to anesthesiologists' ability to stay in touch, both professionally and personally, with the people and activities that are important to them. However, the easy ability to connect to the internet, social media, electronic mail, and text messaging applications makes it tempting for some anesthesia providers to be in near continuous interaction with their phones when they are not directly engaged in performing a procedure. Smartphone addiction is now an established diagnosis with validated criteria, and a recent study from China of 1440 medical students noted a prevalence of 29.8% of this disorder [87]. A survey from Turkey of 955 anesthesia providers of all levels including anesthetic nurses, residents, and attending anesthesiologists, revealed that 93.7% used smartphones during anesthetized patient care [88]. The most frequent use was phone calls (65%), text messaging (46%), social media (35%), and internet access (34%); 97% of respondents indicated that smartphones were never or seldom used during critical stages of anesthesia care; 87% said that they were never distracted because of smartphone use but 41% responded that they had witnessed their colleagues being distracted at least once.

Besides the obvious issue of possible distraction from high-quality patient care, the unprofessional appearance to others (surgeons, nurses, trainees) in the OR environment, as well as the perception of medicolegal risk if the anesthesiologist is seen engaging with their electronic device during a time when an adverse event occurs, should caution the anesthesiologist to limit these activities and to focus on the needs of the patient during all phases of anesthetic care [84]. Although the ASA has a general statement on distractions in the OR that includes electronic devices, more study is needed before specific recommendations can be made, such as limiting electronic device access to matters directly relevant to patient care [89].

KEY POINTS: SAFE SYSTEMS IN THE OPERATING ROOM

- Appropriate anesthesia information management systems can improve care and documentation
- Barcode reading for medications and instruments, and radiofrequency identification to track sponges and other equipment, could enhance operating room safety
- Minimizing distractions, including personal use of electronic devices, can lead to more focused and possibly improved safety in the operating room

Summary

The Institute of Medicine's seminal report, *To Err is Human*, first published in 2000 [3], started the patient safety revolution in healthcare that continues to this day. That study used previously collected data from large population-based studies to determine that there were between 44,000 and 98,000 preventable hospital deaths, and up to 1 million patient injuries each year in the United States during the decade of the 1990s. In a recent report retrospectively reviewing adverse events from 2002 to 2007 in 10 randomly selected North Carolina general acute care hospitals, there was no reduction in patient harms on an annual basis over the 6 years of the study [82], with an average of 25.1 harms per 100 admissions. The perioperative period was a significant source of patient harms. These new data demonstrate that despite all the recent emphasis on patient safety and improving outcomes, that medical error is still common and that there is still a very significant amount of work to be done. The Institute of Medicine's stated goal of 50% reduction in medical error has clearly not been met. Although data specific to pediatric care are sparse, the same issues are identified in pediatric practice as in medical care in general. Pediatric anesthesiologists are in a unique position, interfacing with all members of the perioperative care team, to take a leadership role in teamwork, communication, and patient safety, to prevent adverse events and deaths in the vulnerable pediatric population.

Annotated references

A full reference list can be found in the Wiley Companion Digital Edition of this title (see inside front cover for login instructions).

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APPENDIX A

Appendix: Pediatric Anesthesia Drugs and Other Treatments in the Perioperative Period

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Drug doses and treatments are those commonly recommended; each patient's treatment must be individualized, drug doses double checked for accuracy, and drug concentrations and modes of administration used according to local guidelines. Information is current at the time of publication; however, the practitioner must always be aware of new recommendations, and is responsible for determining the best course of treatment. Consult the textbook, hospital formulary, or authoritative internet resources, for a complete listing of indications, contraindications, interval dosing schedules, and side-effects of these drugs and treatments. All drugs are intravenous (IV) unless otherwise noted. Source for dosing information is the Texas Children's Hospital Drug Formulary, current as of November 2019, except where otherwise noted in the references.

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

Category	Drug/treatment	Bolus/loading dose	Infusion/continuous dose
Anesthetic, sedative, and analgesic agents			
Opioids	Fentanyl	1–10 μg/kg; 50–200 μg/kg total dose	5–20 μg/kg/h
	Remifentanil	0.25–1 μg/kg	0.05–2 μg/kg/min
	Sufentanil	0.1–5 μg/kg	0.1–3 μg/kg/h
	Morphine	0.03–0.2 mg/kg	0.01–0.05 mg/kg/h
	Meperidine (shivering)	1–2 mg/kg	NA
	Methadone	0.1 mg/kg	NA
	Hydromorphone	0.02 mg/kg	0.006 mg/kg/h
Benzodiazepines	Midazolam IV	0.03–0.1 mg/kg	0.05–0.1 mg/kg/h
	Midazolam PO	0.5–1 mg/kg	NA
	Lorazepam	0.25–0.1 mg/kg	NA
	Diazepam IV	0.05–0.3 mg/kg, max. 10 mg	NA
	Diazepam PO	0.04–0.3 mg/kg, max. 10 mg	NA
Barbiturates	Thiopental	1–6 mg/kg	NA
	Pentobarbital	1–6 mg/kg	NA
	Methohexital	1–3 mg/kg	NA
Other sedative/analgesic agents	Ketamine IV	1–2 mg/kg	NA
	Ketamine IM	5–10 mg/kg	NA
	Etomidate	0.1–0.3 mg/kg	NA
	Propofol	1–3 mg/kg	50–200 μg/kg/min
	Scopolamine	10 μg/kg	NA
	Dexmedetomidine	0.3–1 μg/kg	0.3–0.7 μg/kg/h
Neuromuscular blocking drugs and reversals	Vecuronium	0.1–0.3 mg/kg	0.05–0.1 mg/kg/h
	Rocuronium IV	0.6–1.2 mg/kg	NA
	Rocuronium IM	2 mg/kg	NA
	Atracurium	0.4–0.5 mg/kg	NA
	Cisatracurium	0.15–0.2 mg/kg	NA
	Pancuronium	0.1–0.2 mg/kg	NA
	Succinylcholine IV	1–2 mg/kg	NA
	Succinylcholine IM	4 mg/kg	NA
	Neostigmine	40–80 μg/kg	NA
	Glycopyrrolate	8–16 μg/kg	NA
	Sugammadex [1]	2–4 mg/kg, 16 mg/kg for emergency reversal of profound block	NA
Vasoactive drugs			
Inotropes/vasoconstrictors	Epinephrine	0.5–10 μg/kg	0.03–0.1 μg/kg/min
	Atropine IV	10–20 μg/kg	NA
	Atropine IM	20–40 μg/kg	NA
	Phenylephrine	0.5–3 μg/kg	0.05–0.5 μg/kg/min
	Ephedrine	0.05–0.2 mg/kg	NA
	Calcium chloride	10 mg/kg	5–10 mg/kg/h
	Calcium gluconate	30 mg/kg	NA
	Dopamine	NA	3–20 μg/kg/min
	Dobutamine	NA	3–20 μg/kg/min
	Milrinone	25–75 μg/kg	0.25–0.75 μg/kg/min
	Norepinephrine	NA	0.05–0.1 μg/kg/min
	Vasopressin	NA	0.02–0.05 units/kg/h
	Isoproterenol	NA	0.01–0.1 μg/kg/min
	Levosimendan [2–5]	6–12 μg/kg	0.05–0.2 μg/kg/min
	Triiodothyronine (T3) [6]	NA	0.05 μg/kg/h
Vasodilators/antihypertensives	Sodium nitroprusside	NA	0.3–5 μg/kg/min
	Nitroglycerine	NA	0.3–5 μg/kg/min
	Prostaglandin E1	NA	0.0125–0.05 μg/kg/min
	Epoprostenol	100–500 μg/kg	1–2 ng/kg/min; increase every 4–8 h to 25–40 ng/kg/min
	Treprostinil		1–2 ng/kg/min, increase every 8–12 h to 20–40 ng/kg/min
	Nesiritide	NA	0.01–0.03 μg/kg/min
	Fenoldepam	NA	0.025–0.3 μg/kg/min initially, titrate to max. 1.6 μg/kg/min
	Nicardipine	NA	0.5–3 mg/kg/h, max. 15 mg/h
	Clevidipine [7]	10–15 μg/kg	0.5–7 μg/kg/min
	Hydralazine	0.1–0.2 mg/kg	NA
	Phentolamine	0.1–0.2 mg/kg on CPB	NA
	Phenoxybenzamine	0.25–1 mg/kg on CPB	NA

Category	Drug/treatment	Bolus/loading dose	Infusion/continuous dose
	Labetalol	0.25–0.5 mg/kg	NA
	Enalaprilat	5–10 μg/kg	NA
	Sildenafil [8,9]	0.35–0.44 mg/kg over 1–3h	0.067 mg/kg/h
Antiarrhythmics/β-blockers	Lidocaine	1–2 mg/kg	20–50 μg/kg/min
	Procainamide	10–15 mg/kg	20–80 μg/kg/min
	Esmolol	250–500 μg/kg	50–300 μg/kg/min
	Propranolol	0.01–0.1 mg/kg	NA
	Amiodarone	5 mg/kg over 10–15 min, may repeat × 2 to max. 15 mg/kg	NA
	Verapamil	0.1–0.3 mg/kg	NA
	Adenosine	25–50 μg/kg; double if ineffective	NA
	Magnesium sulfate	25–50 mg/kg over 30–60 min	NA
	Digoxin	8–10 μg/kg first loading dose	NA
Antibiotics	Cefazolin	25 mg/kg, max. 1 g	NA
	Ampicillin	50 mg/kg, max. 1 g	NA
	Vancomycin	15 mg/kg, max. 1 g	NA
	Gentamycin	2.5 mg/kg, max. 120 mg	NA
	Nafcillin	50 mg/kg, max. 2 g	NA
	Clindamycin	10 mg/kg	NA
	Cefuroxime	25–30 mg/kg	NA
	Cefoxitin	30–40 mg/kg, max. 2 g	NA
	Pipericillin/tazobactam	100 mg/kg piperacillin component, max. 4 g	
Non-steroidal anti-inflammatory drugs/non-opioid analgesics	Ketorolac	0.5 mg/kg, max. 30 mg every 6 h	NA
	Acetaminophen PO	15 mg/kg, max. 1000 mg	NA
	Acetaminophen PR	20–30 mg/kg (one time)	NA
	Acetaminophen IV	12.5–15 mg/kg, max. 60–75 mg/kg/24 h or 3000 mg/24 h	NA
	Ibuprofen IV	5–10 mg/kg, max. 400 mg	NA
	Ibuprofen PO	5–10 mg/kg, max. 400 mg	NA
Malignant hyperthermia treatment	Dantrolene (use Ryanodex®; dilute 250 mg vial in 5 mL sterile water)	2.5 mg/kg; may repeat × 3 up to 10 mg/kg	NA
Local anesthetics	Lidocaine	Max. 5 mg/kg	NA
	Bupivacaine	Max. 2.5 mg/kg	NA
	Levobupivacaine	Max. 2.5 mg/kg	NA
	Ropivacaine	Max. 2 mg/kg	NA
	Tetracaine (spinal – infants <6 months)	0.4–0.8 mg/kg	NA
Local anesthetic toxicity	20% intralipid [10]	1 mL/kg; repeat × 2 to max. 3 mL/kg	0.25 mL/kg/min
Corticosteroids	Methylprednisolone	1–30 mg/kg depending on indication	5.4 mg/kg/h × 23 h for spinal cord injury
	Dexamethasone	0.25–1 mg/kg, max. 20 mg	NA
	Hydrocortisone	1–2 mg/kg	NA
Anticoagulants	Heparin	CPB: 300–400 units/kg	NA
	Bivalrudin [11,12]	Interventional cardiac catheter: 0.75 mg/kg	Catheter: 1.75 mg/kg/h
		CPB: 1 mg/kg; plus 1 mg/kg CPB prime	CPB: 2.5 mg/kg/h
	Argatroban	CPB: 35–100 μg/kg (ACT >400 s)	2–10 μg/kg/min
	Antithrombin III	50 units/kg; target levels 80–120% of normal	NA
Hemostasis agents	ε-aminocaproic acid [13]	Neonate 0–4 weeks: 40 mg/kg weight of patient; 0.1 mg/mL of CPB prime	30 mg/kg/h
		Neonate >4 weeks: 75 mg/kg weight of patient; 75 mg/kg CPB prime	75 mg/kg/h
	Tranexamic acid [14,15]	5–10 mg/kg	2.5–5 mg/kg/h
	Recombinant factor VIIa	30–90 μg/kg; may repeat × 2	NA
	Fibrinogen concentrate(RiaStap®)	70 mg/kg	NA
	Prothrombin complex concentrate-4 (KCentra®)	25–50 units/kg, max. 5000 units	
	Anti-inhibitor coagulant complex (FEIBA)	50–100 units/kg	

Category	Drug/treatment	Bolus/loading dose	Infusion/continuous dose
Diuretics	Furosemide	0.5–1 mg/kg, max. 40 mg	0.1–0.4 mg/kg/h
	Bumetanide	0.015–0.1 mg/kg, max. 2.5 mg	NA
	Mannitol	0.25–1 g/kg	NA
Perioperative nausea and vomiting/ gastrointestinal prophylaxis	Ondansetron	0.1 mg/kg, max. 4 mg	NA
	Granisetron	10–20 μg/kg	NA
	Metaclopromide	0.1–0.2 mg/kg, max. 10 mg	NA
	Promethazine (over age 2 years only)	0.25–0.5 mg/kg, max. 25 mg	
	Sodium citrate PO	30 mL	NA
Antihistamines	Diphenhydramine	1–2 mg/kg, max. 50 mg	NA
	Ranitidine	1 mg/kg, max. 50 mg	NA
	Famotidine	0.5 mg/kg, max. 40 mg	NA
Alkalinizing agents	Sodium bicarbonate (dilute 1:1 sterile H_2O for neonates)	1–2 meq/kg	NA
	Tromethamine (THAM) 0.3 M solution	3–6 mL/kg	NA
Inhaled agents/bronchodilators			**Inspired dose**
	Sevoflurane		1–8%
	Isoflurane		0.5–3%
	Desflurane		2–12%
	Nitrous oxide (N_2O)		50–75%
	Nitric oxide (iNO)		5–20 ppm
	Levalbuterol	8–12 MDI puffs per ETT; 0.075–0.15 mg/kg nebulized in 3 mL normal saline	NA
	Racemic epinephrine	0.25–0.5 mL of 2.25% racemic epinephrine in 3 mL normal saline	NA
	Prostacyclin (iloprost, PGI_2) [16]	2.5–5 μg nebulized in 3 mL normal saline	NA
Electrolytes/dextrose			**Infusion/continuous dose**
	25% dextrose in water (50% dextrose diluted 1:1)	0.25–0.5 mL/kg	NA
	Potassium chloride (KCl)	0.5–1 meq/kg	NA
	3% NaCl	3–5 mL/kg	NA
Insulin (regular)	Insulin (regular): dose based on plasma glucose levels	0.02–0.1 units/kg	0.02–0.1 units/kg/h
Sedation/analgesia reversal	Naloxone	1–10 μg/kg	NA
	Flumazenil	1–5 μg/kg; repeat as needed, max. dose 1 mg	NA
Immunosuppressants (transplant)	Basiliximab	<35 kg: 10 mg; >35 kg: 20 mg	NA
	Mycophenolate	15 mg/kg, max. 1.5 g	NA
Miscellaneous drugs	Caffeine citrate	10–20 mg/kg	NA
Transfusions	Packed red blood cells	10–15 mL/kg	NA
	Whole blood	10–15 mL/kg	NA
	Platelets	1 unit/5 kg will increase platelet count by 50,000; 1 pheresis unit = 6 random donor units	NA
	Cryoprecipitate	1 unit per 5 kg, max. 4 units	NA
	Fresh frozen plasma	10–20 mL/kg	NA
Intravascular volume expansion	5% albumin	10–20 mL/kg	NA
	25% albumin	2–4 mL/kg; 0.5–1 g/kg	NA
Direct current cardioversion/ defibrillation	External synchronized cardioversion	0.5 J/kg; increase to max. 1 J/kg; max. 100 kg	NA
	External defibrillation	2–5 J/kg; increase if ineffective; max. 200 J biphasic; 360 J monophasic	NA
	Internal defibrillation	5 J; increase to 10 J if ineffective	NA
	Internal synchronized cardioversion	2 J; increase to 5 J if ineffective	NA

ACT, activated clotting time; CPB, cardiopulmonary bypass; ETT, endotracheal tube; IM, intramuscular; IV, intravenous; J, joules; max., maximum; MDI, metered dose inhaler; meq, milliequivalents; mg, milligram; μg, microgram; ng, nanogram; NA, not applicable; PO, per os; ppm, parts per million; PR, per rectum.

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APPENDIX B

Appendix: Pediatric Normal Laboratory Values

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Values are reference values from Texas Children's Hospital Clinical Laboratory, current as of November 2019. All practitioners are urged to consult the normal laboratory values for their local laboratory, as these may differ from those listed below. They are also advised to continually check for updated normal ranges.

For conversion of conventional (US) units to SI units, see: http://www.soc-bdr.org/content/rds/authors/unit_tables_conversions_and_genetic_dictionaries/e5196/index_en.html (accessed May 2019).

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.

Clinical chemistry reference values (United States/conventional units)

Test	Reference range	
Albumin (CSF)	10–30 mg/dL	
Albumin (random urine)	<37 mg/L or <3.7 mg/dL	
Albumin (S, P)		
Age	*Male/female (g/dL)*	
0–14 days	2.6–4.2	
15–364 days	2.3–4.8	
1–7 years	3.5–4.7	
8–14 years	3.7–5.0	
	Male (g/dL)	*Female (g/dL)*
15–18 years	3.9–5.3	3.5–5.2
	Male/female (g/dL)	
≥19 years	3.5–5.0	
Albumin/creatinine ratio (random urine)	<16 mg/g	
Alanine aminotransferase (S, P)		
Age	*Male/female (U/L)*	
0–11 months	6–50	
1–3 years	6–45	
4–6 years	10–25	
7–9 years	10–35	
	Male (U/L)	*Female (U/L)*
10–11 years	10–35	10–30
12–13 years	10–55	10–30
14–15 years	10–45	6–30
16–18 years	10–40	6–35
≥19 years	21–72	9–52
Alkaline phosphatase (S, P)		
Age	*Male (U/L)*	*Female (U/L)*
0–7 days	77–265	65–270
8–30 days	91–375	65–365
1–3 months	60–360	80–425
4–6 months	55–325	80–345
7–12 months	60–300	60–330
1–3 years	129–291	129–291
4–6 years	134–346	134–346
7–9 years	156–386	156–386
10–11 years	120–488	116–515
12–13 years	178–455	93–386
14–15 years	116–483	62–209
16–19 years	58–237	45–116
≥20 years	38–126	38–126
Allergen-specific IgE	*kU/L*	
Class scoring 0: normal	≤0.34	
Class scoring 1: low level of allergy	0.35–0.69	
Class scoring 2: moderate level of allergy	0.70–3.49	
Class scoring 3: high level of allergy	3.50–17.49	
Class scoring 4: very high level of allergy	17.50–49.99	
Class scoring 5: very high level of allergy	50.00–99.99	
Class scoring 6: very high level of allergy	≥100	
Alpha-1-antitrypsin (S)		
Age	*mg/dL*	
0–1 years	92–282	
1–4 years	94–156	
4–13 years	102–159	
>14 years	97–203	

Test	Reference range	
Alpha-fetoprotein (S)		
Age	*ng/mL*	
0–30 days	50–100,000	
1–3 months	40–1000	
4 months–18 years	0–12	
Adult (≥19 years)	<10	
Ammonia (P)		
Age	*μmol/L*	
0–7 days	54–94	
8–30 days	47–80	
1–12 months	15–47	
1–15 years	22–48	
≥16 years	9–26	
Amylase (S, P)	30–115 U/L	
Amylase (U) – random	No reference range	
Amylase (U) – timed	4–37 U/2 h	
Asparate aminotransferase (S, P)		
Age	*Male/female (U/L)*	
0–5 days	35–140	
6 days–3 years	20–60	
4–6 years	15–50	
7–9 years	15–40	
	Male (U/L)	*Female (U/L)*
10–11 years	10–60	10–40
12–15 years	15–40	10–30
16–18 years	10–45	5–30
≥19 years	17–59	14–36
Beta-hydroxybutyrate (S, P)	<0.30 mmol/L (12 h fasting)	
Beta 2-microglobulin	1.1–2.5 mg/L	
Bilirubin (S, P)	*Premature (mg/dL)*	*Full-term (mg/dL)*
Age	*Total*	*Total*
Up to 23 h	1–8	2–6
24–48 h	6–12	6–10
3–5 days	10–14	4–8
≥1 month	*mg/dL*	
Bu unconjugated	<1.0	
Total	0.2–1.0	
All ages		
Bc conjugated	<0.3	
Blood gases: pH		
Capillary/arterial		
Age		
Newborn	7.33–7.49	
1 day	7.25–7.43	
2–30 days	7.32–7.43	
1 month	7.34–7.43	
2 months–1 year	7.34–7.46	
≥2 years		
Male	7.35–7.45	
Female	7.36–7.44	
Venous		
All ages	7.32–7.42	
Blood gases: pCO_2		
Capillary/arterial		
Age	*mmHg*	
0–1 month	27–40	
2 months–1 year	26–41	

(*Continued*)

Test	Reference range		
≥2 years			
Male	36–46		
Female	33–43		
Venous			
All ages	40–50		
Blood gases: pO_2	*mmHg*	*mmHg*	*mmHg*
Age	*Capillary*	*Arterial*	*Venous*
0–1 year	60–70	65–76	25–40
≥2 years	80–90	88–105	40–47
Oxygen saturation	85–100%		
B-type natriuretic peptide or BNP (EDTA plasma)	0–100 pg/mL		
BUN – see Urea nitrogen			
C3, C4 (S)	*C3*	*C4*	
Age	*mg/dL*	*mg/dL*	
0–30 days	54–128	8–28	
1 month	60–153	8–32	
2 months	66–134	10–31	
3 months	63–179	9–43	
4 months	66–171	8–41	
5 months	75–176	10–48	
6–8 months	77–170	12–42	
9–11 months	86–179	14–45	
1 year	83–174	10–39	
2 years	78–176	12–41	
3–4 years	89–170	14–36	
5–7 years	90–160	14–36	
8–9 years	92–200	12–45	
≥10 years	86–182	17–51	
Ca^{2+} (ionized) (WB)			
Age	*mmol/L*		
0–30 days	0.90–1.45		
1–5 months	0.95–1.50		
≥6 months	1.10–1.30		
Calcium (S)			
Age	*mg/dL*		
Premature	6.0–10.0		
0–11 months	8.0–10.7		
1–3 years	8.7–9.8		
4–11 years	8.8–10.1		
12–13 years	8.8–10.6		
14–15 years	9.2–10.7		
≥16 years	8.9–10.7		
Calcium (U) – random	No reference range		
Calcium (U) – timed	42–353 mg/24 h		
Carboxyhemoglobin (WB)	<1.5% of total Hb		
Ceruloplasmin (S)			
Age	*mg/dL*		
0–1 month	3–25		
1–11 months	14–44		
1–9 years	23–51		
≥10 years	18–46		
Chloride (CSF)	122–132 mmol/L		
Chloride (S, P)	95–105 mmol/L		
Chloride (U) – random	No reference range		
Chloride (U) – timed			
Age	*mmol/24 h*		
0–11 months	5–10		
1–15 years	15–40		
≥16 years	110–250		

Test	Reference range	
Chloride sweat test (SWT)	Cystic fibrosis unlikely : ≤29 mmol/L Intermediate: 30–59 mmol/L Indicative of cystic fibrosis : ≥60 mmol/L	
Cholesterol (S, P)		
Age	*Male (mg/dL)*	*Female (mg/dL)*
0–14 days	50–109	50–125
	Male/female (mg/dL)	
15–364 days	64–237	
1–18 years	112–208	
≥19 years		
Desirable	<200	
Borderline high	200–239	
High	≥240	
Cholesterol, HDL (S, P)		
Age	*Male (mg/dL)*	*Female (mg/dL)*
0–14 months	8–61	8–61
1–5 years	35–80	35–80
6–15 years	38–75	35–73
≥16 years	30–64	35–80
Cholesterol, LDL		
Age	*Male (mg/dL)*	*Female (mg/dL)*
0–14 months	32–117	32–117
1–5 years	38–140	38–140
6–15 years	64–130	60–140
≥16 years	65–145	60–155
CO_2 content (S, P)		
Age	*mmol/L*	
0–15 years	20–28	
≥16 years	25–35	
Cortisol (S)		
Age	*μg/dL*	
1–7 days	2–11	
1–12 months	2.8–23	
1–16 years (8 am)	3–21	
≥16 years (8 am)	8–19	
(4 pm)	4–11	
C-peptide (S)		
Age	*ng/mL*	
0–12 months	0.2–4.4	
1–5 years	0.4–4.5	
6–18 years	0.8–6.8	
≥19 years	0.8–3.85	
C-reactive protein (S, P)	<1.0 mg/dL	
Creatine kinase (S, P)		
Age	*Male/female (U/L)*	
0–3 years	60–305	
4–6years	75–230	
7–9 years	60–365	
	Male (U/L)	*Female (U/L)*
10–11 years	55–215	80–230
12–13 years	60–330	50–295
14–15 years	60–335	50–240
16–18 years	55–370	45–230
≥19 years	55–170	30–135
CKMB (S, P)		
Normal	<5 ng/mL	
Borderline	5–10 ng/mL	
Abnormal	>10 ng/mL	

(*Continued*)

Test	Reference range	
CKMB activity – West Campus only (P)	CKMB enzymatic (CKMBE): CKMB activity <16 U/L should be considered a negative finding in the context of a suspected ED MI CKMB percent (CKMBP): CKMB percentage of <4% or *greater than* 25% of total CK activity is likely not the consequence of an increase in plasma CKMB. A positive result should be confirmed by ordering the CK index (mass assay – test code CKMBI) available through the main campus	
Creatinine (S, P)		
Age	*Male/female (mg/dL)*	
0–14 days	0.3–0.9	
15 days–1 year	0.1–0.4	
2–4 years	0.2–0.4	
5–11 years	0.3–0.6	
12–14 years	0.5–0.8	
	Male (mg/dL)	*Female (mg/dL)*
15–18 years	0.6–1.0	0.5–0.8
≥19 years	0.66–1.25	0.52–1.04
Creatinine (U) – random	<500 mg/dL	
Creatinine (U) – timed	0.8–2.8 g/24 h (800–2800 mg/24 h)	
Creatinine clearance (U)		
Age	*mL/min*	
0–30 days	25–55	
1–5 months	50–90	
6–11 months	75–125	
≥1 year	90–150	
Cystatin C		
Age	*mg/L*	
0–3 months	0.8–2.3	
4–11 months	0.7–1.5	
1–17 years	0.5–1.3	
≥18 years	0.5–1.0	
Deamidated gliadin peptide antibody IgG	*U/mL*	
Negative	≤6.0	
Equivocal	7.0–10.0	
Positive	≥10.1	
DHEA-S		
Age	*Male/female (μg/dL)*	
0–59 days	>1110.0	
2–5 months	30.0–600.0	
6–11 months	10.0–180.0	
1–5 years	3.0–120.0	
6–8 years	10.0–160.0	
9–12 years	30.0–280.0	
13–15 years	60.0–480.0	
	Male (μg/dL)	*Female (μg/dL)*
16–18 years	130.0–700.0	150.0–590.0
≥19 years	238.4–539.3	134.2–407.4
Estradiol	*Male (pg/mL)*	*Female (pg/mL)*
	11–44	
Follicular phase	–	21–251
Midcycle phase	–	38–649
Luteal phase	–	21–312
Postmenopausal phase (no hormone replacement therapy)	–	<10–28
Postmenopausal phase (hormone replacement therapy)	–	<10–144

Test	Reference range	
Ferritin (S)		
Age	*Male/female (ng/mL)*	
1day–6 weeks	0–400	
7 weeks–12 months	10–95	
1–9 years	10–60	
	Male (ng/mL)	*Female (ng/mL)*
10–17 years	10–300	10–70
≥18 years	18–464	
18–49 years		6–137
≥50 years		11–264
Folate (S)	*ng/mL*	
Deficient	≤3.5	
Indeterminate	3.6–5.9	
Normal	≥6.0	
Follicle-stimulating hormone (S)	*Male (mIU/mL)*	*Female (mIU/mL)*
Infants	<10	<50
Prepubertal	<7	<11
Adult	1.6–17.2	0.4–15.1
Follicular/luteal	–	3.5–16.9
Midcycle	–	11.9–32.7
Follicular phase	–	1.98–11.6
Midcycle peak	–	5.14–23.4
Luteal phase	–	1.38–9.58
Postmenopausal	–	21.5–131
Normal (age 19–65 years)	1.55–9.74	–
Gamma-glutamyl transferase (S, P)		
Age	*Male/female (U/L)*	
0–5 days	34–263	
6 days–2 months	10–160	
3–11 months	11–82	
1–3 years	10–19	
4–6 years	10–22	
7–9 years	13–25	
	Male (U/L)	*Female (U/L)*
10–11 years	17–30	17–28
12–13 years	17–44	14–25
14–15 years	12–33	14–26
16–18 years	11–34	11–28
≥19 years	10–78	10–78
Glucose (CSF)	50–70% of serum glucose	
Glucose (S, P) (WB)		
Age	*mg/dL*	
0–5 months	Fasting 50–120	
≥6 months	Fasting 70–100	
Level of 30–50 mg/dL may be common in 0–2-day-old neonates		
Glucose (U) – random	<30 mg/dL	
Glucose (U) – timed	<500 mg/24 h	
Haptoglobin (S)		
Age	*mg/dL*	
0–1 year	34–175	
2–3 years	30–140	
4–5 years	30–191	
≥6 years	35–181	
HCG (S)	*Postconception normals (mIu/mL)*	
1 week	5–50	
2 weeks	40–1000	
3 weeks	100–5000	

(*Continued*)

Test	Reference range		
4 weeks	600–10,000		
5–6 weeks	1500–100,000		
7–8 weeks	16,000–200,000		
2nd trimester	24,000–55,000		
3rd trimester	6000–48,000		
Hematocrit (B)			
Age	*%*		
0–30 days	44–70		
1 month	32–42		
2–6 months	29–41		
7 months–2 years	33–39		
3–6 years	34–40		
7–12 years	35–45		
13–18 years/female	36–45		
13–18 years/male	37–49		
≥19 years/female	36–46		
≥19 years/male	41–53		
Hemoglobin (B)			
Age	*g/dL*		
0–30 days	15.0–22.0		
1 month	10.5–14.0		
2–6 months	9.5–13.5		
7 months–2 years	10.5–14.0		
3–6 years	11.5–14.5		
7–12 years	11.5–15.5		
13–18 years/female	12.0–16.0		
13–18 years/male	13.0–16.0		
≥19 years/female	12.0–16.0		
≥19 years/male	13.5–17.5		
Hgb A1c			
Non-diabetic	≤5.6%		
Diabetic	≥6.5%		
Prediabetic	5.7–6.4%		
Hemoglobin fractionation, HPLC (WB)	A	A_2	F
Age	*(%)*	*(%)*	*(%)*
0–30 days	10–35	–	65–90
1–3 months	30–50	–	50–70
4–5 months	>90	<4	<10
≥6 months	>90	<4	≤3
Homocysteine			
Age	*Male/female (μmol/L)*		
0–2 months	3.0–8.5		
2 months–10 years	3.3–8.3		
11–15 years	4.7–10.3		
16–18 years	4.7–11.3		
	Male (μmol/L)		*Female (μmol/L)*
≥19 years	5.9–16.0		3.4–20.4
IgE (S)			
Age	*IU/mL*		
0–1 years	<15		
1–5 years	<60		
6–9 years	<90		
10–15 years	<200		
>16 years	<100		
IgG (CSF)	0.4–5.2 mg/dL (10% of total protein)		

Test	Reference range			
IgG subclasses (S)	*IgG1*	*IgG2*	*IgG3*	*IgG4*
Age	*mg/dL*	*mg/dL*	*mg/dL*	*mg/dL*
0–1 months	240–1060	87–410	14–55	4–55
1–4 months	180–670	38–210	14–70	3–36
4–6 months	180–700	34–210	15–80	3–23
6–12 months	200–770	34–230	15–97	3–43
1–1.5 years	250–820	38–240	15–107	3–62
1.5–2 years	290–850	45–260	15–113	3–79
2–3 years	320–900	52–280	14–120	3–106
3–4 years	350–940	63–300	13–126	3–127
4–6 years	370–1000	72–340	13–133	3–158
6–9 years	400–1080	85–410	13–142	3–189
9–12 years	400–1150	98–480	15–149	3–210
12–18 years	370–1280	106–610	18–163	4–230
>18 years	490–1140	150–640	20–110	8–140
Immunoglobins (S)	*IgG*	*IgA*	*IgM*	
Age	*mg/dL*	*mg/dL*	*mg/dL*	
0–30 days	252–909	10–50	18–80	
1 month	207–904	10–45	15–96	
2 months	177–583	10–43	22–82	
3 months	196–560	10–69	25–93	
4 months	173–817	10–80	30–99	
5 months	216–706	10–65	32–94	
6–8 months	218–907	10–85	31–116	
9–11 months	346–1217	13–100	40–159	
1 year	425–1054	13–116	44–155	
2 years	442–1139	21–150	43–184	
3–4 years	464–1240	22–146	40–180	
5–7 years	635–1284	32–191	44–190	
8–9 years	610–1577	42–223	48–222	
≥10 years	641–1353	66–295	40–180	
Insulin				
Age	*mU/L*			
0–12 months	1.0–23.5			
1–5 years	1.3–40.2			
6–18 years	2.2–49.6			
≥19 years	2.0–19.6			
Iron, total (S,P)	55–150 μg/dL			
Iron-binding capacity (calculated)	250–400 μg/dL			
Lactate (P, WB, CSF)	*mmol/L*			
Plasma (venous)	0.2–2.0			
Plasma (arterial)	0.3–0.8			
CSF	0.6–2.2			
Whole blood	0.2–1.7			
Lactate dehydrogenase(LDH) (S, P)				
Age	*Male/female (U/L)*			
0–5 days	934–2150			
6 days–3 years	500–920			
4–6 years	470–900			
7–9 years	420–750			
	Male (U/L)	*Female (U/L)*		
10–11 years	432–700	380–770		
12–13 years	470–750	380–640		
14–15 years	360–730	390–580		
16–18 years	340–670	340–670		
≥19 years	313–618	313–618		
Lipase (S, P)				
Age	*U/L*			
0–9 years	25–120			
10–13 years	15–110			
14–18 years	25–110			
≥19 years	23–300			

(*Continued*)

Test	Reference range	
Luteinizing hormone (S)	*Male (mIU/mL)*	*Female (mIU/mL)*
Infants (0–7 days)	<5	<5
Infants (week 2–1 year)	3–22	1.8–13
Prepubertal	1.0–3.5	1.0–3.5
Adult	2.0–9.0	–
Follicular	–	2.5–12.0
Midcycle peak	–	27.0–97.0
Luteal phase	–	0.8–16.0
Postmenopausal	–	13.1–86.5
Magnesium (S, P)		
Age	*mg/dL*	
0–6 days	1.2–2.6	
7–30 days	1.6–2.4	
1 month–1 year	1.6–2.6	
2–5 years	1.5–2.4	
6–9 years	1.6–2.3	
10–13 years	1.6–2.2	
≥14 years	1.5–2.3	
Magnesium (U) – random	No reference range	
Magnesium (U) – timed	12.4–191.9 mg/24 h	
Methemoglobin (WB)	<2% of total Hb	
Microalbumin (random urine)	0–30 mg/L or 0–3.0 mg/dL	
Microalbumin (U) – timed	<20 ug/min <30 mg/24 h	
Microalbumin/creatinine ratio	<30 mg microalbumin/g creatinine	
N-terminal prohormone B-type natriuretic peptide	<125 pg/mL	
Osmolality (S, P)	275–295 mOsm/kg H_2O	
Osmolality (U)	300–1000 mOsm/kg H_2O	
Parathyroid hormone intact (intact PTH)		
Age	*pg/mL*	
0–5 days	No reference range	
6 days–12 months	6.4–88.6	
1–8 years	16.2–63.0	
9–16 years	21.9–87.6	
≥17 years	16.0–60.4	
Phosphorus, inorganic (S, P)		
Age	*mg/dL*	
Premature	5.6–8.0	
Term	5.0–7.8	
0–3 months	4.8–8.1	
4–11 months	3.8–6.7	
1–4 years	3.5–6.8	
5–7 years	3.1–6.3	
8–11 years	3.0–6.0	
12–16 years	2.5–5.0	
≥17 years	2.3–4.8	
Phosphorus, inorganic (U) – random	No reference range	
Phosphorus, inorganic (U) – timed	0.9–1.3 g/24 h (900–1300 mg/24 h)	
Plasma hemoglobin (P)	<30 mg/dL	
Potassium (S, P)		
Age	*mmol/L*	
0–30 days	4.5–7.0 (venous or arterial) 4.5–7.5 (heel stick)	
1–2 months	4.0–6.2	
3–11 months	3.7–5.6	
≥1 year	3.5–5.5	
Potassium (U) – random	No reference range	

Test	Reference range	
Potassium (U) – timed	40–80 mmol/24 h	
Potassium (WB)		
Age	*mmol/L*	
Premature	4.5–7.0	
0–11 months	5.0–5.7	
≥1 year	3.5–5.5	
Prealbumin (S)		
Age	*mg/dL*	
0–6 days	4–20	
7–41 days	8–25	
≥42 days	18–44	
Procalcitonin (PCT)	0.05–2.00 ng/mL	
Progesterone	*Male (ng/mL)*	*Female (ng/mL)*
	0.0–0.2	
Follicular phase	–	0.0–0.3
Luteal	–	1.2–15.9
Postmenopausal	–	0.0–0.2
Pregnancy		
1st trimester (4–12 weeks' gestation)	–	2.8–147.3
2nd trimester (13–24 weeks' gestation)	–	22.5–95.3
3rd trimester (25–36 weeks' gestation)	–	27.9–242.5
Prolactin (S)	*ng/mL*	
Newborn	>10 × adult levels	
Nursing female	<40	
Follicular female	<23	
Luteal female	5–40	
Pregnancy		
1st trimester	<84	
2nd trimester	18–306	
3rd trimester	34–386	
Protein (CSF)		
Age	*mg/dL*	
Premature	40–300	
0–30 days	<100	
≥1 month	15–45	
Protein, total (S, P)		
Age	*g/dL*	
0–14 days	5.5–8.8	
15–364 days	4.5–7.4	
1–5 years	6.3–7.9	
6–8 years	6.7–8.1	
9–18 years	6.8–8.5	
≥19 years	6.3–8.2	
Protein, total (U) – random	No reference range	
Protein, total (U) – timed	28–141 mg/24 h	
Renin, direct	2.5–45.7 pg/mL	
Sex hormone-binding globulin (SHBG) (S, P)	*nmol/L*	
Male	11.2–78.1	
Female	11.7–137.2	
Sodium (S, P) (WB)		
Age	*mmol/L*	
Premature	132–140	
0–11 months	133–142	
≥1 year	136–145	

(*Continued*)

Test	Reference range	
Sodium (U) – random	No normals	
Sodium (U) – timed		
Age	*mmol/24 h*	
0–11 months	0.3–3.5	
1–15 years	40–180	
≥16 years	80–200	
T3 (S)		
Age	*ng/dL*	
Cord blood	30–70	
0–7 days	65–275	
8 days–9 years	90–260	
10–14 years	80–210	
≥15 years	115–195	
T3 uptake (S)	25–35%	
Free T4 (S)		
Age	*ng/dL*	
0–3 days	2.0–5.0	
3–30 days	0.9–2.2	
31 days–18 years	0.8–2.0	
≥19 years	0.71–1.40	
Pregnant euthyroid patients: levels trend 23–38% lower than reference mean and the lowest point typically occurs between 34 and 36 weeks of gestation		
T4 (S)		
Age	*μg/dL*	
0–3 days	8.0–20	
3–30 days	5.0–15	
31–365 days	6.0–14	
1 years–5 years	4.5–11.0	
6–17 years	4.5–10	
≥18 years	5.0–12.0	
T7 (S)	T7 = (T4 × T3 uptake)/100	
Age		
0–7 days	9.1–26.6	
8 days–4 years	5.5–16.6	
5–9 years	5.1–14.7	
≥10 years	4.0–13.3	
Testosterone	*Male (ng/dL)*	*Female (ng/dL)*
Tanner stage I	≤17.87	≤19.31
Tanner stage II	≤24.50	≤19.88
Tanner stage III	≤543.23	≤41.79
Tanner stage VI	8.65–636.31	8.93–41.50
Tanner stage V	99.71–759.65	3.75–49.57
Age		
4 days–5 months	8.65–298.85	
6 months–8 years	<35.73	
9 years–10 years	<23.34	
11 years–13 years	<444–38	
14 years–15 years	36.02–632.28	
16 years–18 years	147.84–793.95	
≥19 years	250–1100	
4 days–8 years		1.15–61.96
9 years–12 years		<28.24
13 years–14 years		10.37–44.38
15 years–18 years		14.12–48.99
≥19 years		5–45

Test	Reference range	
Free testosterone index		
Age	*Male*	*Female*
0–12 months	0.0–32.7	–
0–8 years	–	0.0–1.3
1–8 years	0.0–0.6	–
9–13 years	0.2–34.7	0.1–2.6
14–18 years	3.6–83.3	0.6–6.5
≥19 years	Not available	0.7–13.5
Thyroid-stimulating hormone (TSH) (S)		
Age	*μIU/mL*	
Cord blood	3–22	
0–3 days	1–20	
4–30 days	0.5–6.5	
1–5 months	0.7–4.8	
6 months–14 years	0.7–4.1	
15–18 years	0.5–3.4	
Adults (≥19 years)	0.4–4.9	
Pregnant, euthyroid females (≥19 years):		
1st trimester:	0.1–2.5	
2nd trimester:	0.2–3.0	
3rd trimester:	0.3–3.0	
Thyroperoxidase Ab	≤5.6 IU/mL	
Tissue transglutaminase Ab IgA	*U/mL*	
Negative	≤6.0	
Equivocal	7.0–10.0	
Positive	≥10.1	
Tissue transglutaminase Ab IgG	*U/mL*	
Negative	≤6.0	
Equivocal	7.0–10.0	
Positive	≥10.1	
Transferrin (S)	169–300 mg/dL	
Transferrin saturation (S)		
Age	*%*	
0–11 years	15–39	
12–17 years/male	16–44	
12–17 years/female	11–44	
>18 years/male	21–52	
>18 years/female	11–44	
Triglycerides (S, P)		
Age	*mg/dL*	
0–14 days	84–266	
15–364 days	54–265	
1–18 years	45–203	
≥19 years		
Normal	<150	
Borderline high	150–199	
High	200–499	
Very high	≥500	
Troponin I (S, P)	<0.03 ng/mL	
Troponin I – West Campus only	<0.05 ng/mL	
Urea nitrogen (S, P)		
Age	*mg/dL*	
0–15 years	2–23	
≥16 years	4–18	
Urea nitrogen (U) – random	No reference range	
Urea nitrogen (U) – timed	12–29 mg/24 h	
Uric acid (S, P)	2.0–6.2 mg/dL	
Uric acid (U) – random	No reference range	
Uric acid (U) – timed	250–750 mg/24 h	

(*Continued*)

Test	Reference range
Vitamin B_{12}	*pg/mL*
Deficient	≤212
Normal	213–816
Vitamin D_{25} hydroxy	
Age	*ng/mL*
0–17 years	
Deficient	0–20
Optimum	≥21
≥18 years	
Deficient	0–20
Insufficiency	21–29
Optimum	30–80
Possible toxicity	≥150
Vitamin D, 1, 25-dihydrozy	
Age	*pg/mL*
0–12 months	NA
1–9 years	31–87
10–13 years	30–83
14–17 years	19–83
≥18 years	18–72

CKMB, creatine kinase MB band; CSF, cerebrospinal fluid; DHEA-S, dehydroepiandrosterone-sulfate; ED, emergency department; EDTA, ethylene diamine tetra-acetic acid; Hb, hemoglobin; HCG, human chorionic gonadotropin; HLD, high-density lipoprotein; HPLC, high-performance liquid chromatography; Ig, immunoglobulin; LDL, low-density lipoprotrine; MI, myocardial infarction; P, plasma; S, serum; SWT, sweat; U, urine; WB, whole blood.

Hematology reference ranges (United States/conventional units)

Test	Reference range						
White blood cells (B)							
Age	*×10³/μL*						
0–30 days	9.1–34.0						
1 month	5.0–19.5						
2–11 months	6.0–17.5						
1–6 years	5.0–14.5						
7–12 years	5.0–14.5						
13–18 years	4.5–13.5						
≥19 years	4.5–11.0						
Age	*Seg%*	*Band%*	*Lymph%*	*Monos%*	*Eos%*	*Baso%*	*ANC*
0–30 days	32–67	0–8	25–37	0–9	0–2	0–1	6.0–23.5
1 month	20–46	0–4.5	28–84	0–7	0–3	0–1	1.0–9.0
2–11 months	20–48	0–3.8	34–88	0–5	0–3	0–1	1.0–8.5
1–6 years	37–71	0–1.0	17–67	0–5	0–3	0–1	1.5–8.0
7–12 years	33–76	0–1.0	15–61	0–5	0–3	0–1	1.5–8.0
13–18 years	33–76	0–1.0	15–55	0–4	0–3	0–1	1.8–8.0
≥19 years	33–76	0–0.7	14–54	0–4	0–3	0–1	1.8–7.7
Red blood cells (B)							
Age	*×10⁶/μL*						
0–30 days	4.1–6.7						
1 month	3.0–5.4						
2–6 months	2.7–4.5						
7 months–2 years	3.7–5.3						
3–6 years	3.9–5.3						
7–12 years	4.0–5.2						
13–18 years/female	4.1–5.1						
13–18 years/male	4.5–5.3						
≥19 years/female	4.2–5.4						
≥19 years/male	4.7–6.0						
Hemoglobin (B)							
Age	*g/dL*						
0–30 days	15.0–22.0						
1 month	10.5–14.0						
2–6 months	9.5–13.5						
7 months–2 years	10.5–14.0						
3–6 years	11.5–14.5						
7–12 years	11.5–15.5						
13–18 years/female	12.0–16.0						
13–18 years/male	13.0–16.0						
≥19 years/female	12.0–16.0						
≥19 years/male	13.5–17.5						
Hematocrit (B)							
Age	*%*						
0–30 days	44–70						
1 month	32–42						
2–6 months	29–41						
7 months–2 years	33–39						
3–6 years	34–40						
7–12 years	35–45						
13–18 years/female	36–45						
13–18 years/male	37–49						
≥19 years/female	36–46						
≥19 years/male	41–53						
Mean corpuscular volume							
Age	*fL*						
0–30 days	86–115						
1 month	72–88						

(*Continued*)

Test	Reference range		
2–6 months	72–82		
7 months–2 years	76–90		
3–6 years	76–90		
7–12 years	76–90		
13–18 years	78–95		
≥19 years	78–100		
Mean corpuscular hemoglobin			
Age	*pg*		
0–30 days	33.0–39.0		
1 month	28.0–40.0		
2–6 months	25.0–35.0		
7 months–2 years	23.0–31.0		
3–6 years	25.0–30.0		
7–12 years	26.0–30.0		
13–18 years	26.0–32.0		
≥19 years	27.0–31.0		
Mean corpuscular hemoglobin concentration			
Age	*g/dL*		
0–30 days	32.0–36.0		
1 month	33.0–38.0		
2–6 months	28.0–36.0		
7 months–2 years	30.0–34.0		
3–6 years	32.0–36.0		
7–12 years	32.0–36.0		
13–18 years	32.0–36.0		
≥19 years	32.0–36.0		
Red blood cell distribution width, coefficient of variation			
Age	*%*		
0–30 days	13.0–18.0		
1 month	13.0–18.0		
2–6 months	13.0–18.0		
7 months–2 years	11.5–16.0		
3–6 years	11.5–15.0		
7–12 years	11.5–14.0		
13–18 years	11.5–14.0		
≥19 years	11.5–14.0		
Red blood cell distribution width, size distribution			
Age	*fL*		
0–30 days	38.5–49.0		
1 month	38.5–49.0		
2–6 months	38.5–49.0		
7 months–2 years	38.5–49.0		
3–6 years	38.5–49.0		
7–12 years	38.5–49.0		
13–18 years	38.5–49.0		
≥19 years	38.5–49.0		
Platelet count (B)	150,000–450,000 μL		
Mean platelet volume (B)	6–10 fL		
Immature platelet fraction (B)			
Age		*Female (%)*	*Male (%)*
0–6 months		1.3–6.8	2.0–6.8
6 months–<2 years		1.4–4.5	1.4–3.8
2–<6 years		1.0–3.6	1.1–3.6
6–<12 years		1.0–4.7	1.0–4.9
12–18 years		1.4–6.4	1.6–6.1
≥18 years		1.6–4.9	1.6–7.1

Test	Reference range
Reticulocyte count percentage (B)	
Age	*%*
0–2 days	3.0–7.0
3–4 days	1.0–3.0
>4 days	0.5–1.5
Reticulocyte count absolute (B)	
Age	*× 10^6/μL*
0–2 days	0.140–0.220
3–4 days	0.040–0.110
>4 days	0.020–0.080
Reticulocyte hemoglobin content (B)	
Age	*pg*
<2 years	24.5–35.2
>2 years	27.1–35.4
Sedimentation rate (B)	0–20 mm/h
Urinalysis (U)	
Specific gravity	1.001–1.035
pH	4–9
Protein	Neg
Glucose	Neg
Ketone	Neg
Bilirubin	Neg
Urobilinogen	0.1–1.0
WBC	0–4/ HPF
RBC	0–4/ HPF
EPI (epithelial cells)	0–4/ HPF

ANC, absolute neutrophil count; B, blood; EPI, epithelial cells; RBC, red blood cells; U, urine; WBC, white blood cells.

Clinical coagulation laboratory reference ranges (United States/conventional units)

Test	Reference range
ADAMTS13 (P)	>65% normal activity
Anti-β_2-glycoprotein1 – IgG (S)	<20.1 SGU
Anti-β_2-glycoprotein 1 – IgM (S)	<20.1 SMU
Anti-β_2-glycoprotein 1 – IgA (S)	<20.1 SAU
Anticardiolipin IgG (S)	<23.0 GPL
Anticardiolipin IgM (S)	<11.0 MPL
Antithrombin (P)	
Adult	85–130%
Normal ranges for healthy full-term infants	
Day 1	63% (39–87%)
Day 5	67% (41–93%)
Day 30	78% (48–108%)
Day 90	97% (73–121%)
Day 180	104% (84–124%)
D-dimer (P)	
Adult	≤0.40 μg/mL FEU
Neonatal reference range from cord blood	≤3.40 μg/mL FEU
Dilute Russell viper venom time (DRVVT) test (P)	
DRVVT S/C Ratio	<1.17
DRVVT result	Negative
Factor 2 (P)	50–150%
Factor 5 (P)	59–150%
Factor 7 (p)	58–150%
Factor 8 (P)	47–169%
Factor 9 (P)	67–141%
Factor 10 (P)	65–142%
Factor 11 (P)	48–139%
Factor 12 (P)	41–140%
Fibrinogen (P)	
Adult	220–440 mg/dL
Neonatal reference range from cord blood	135–283 mg/dL
INR (P)	
Adult	0.8–1.2
Neonatal reference range from cord blood	1.0–1.4
Lovenox (P)	
Prophylactic:	0.20–0.40 U/mL
Therapeutic:	0.50–1.00 U/mL
Platelet function assay (WB)	84–183 s
Collagen/epinephrine Collagen/ADP	69–126 s
Protein C (P)	
Adult	80–175%
Normal ranges for healthy full-term infants	
Day 1	35% (17–53%)
Day 5	42% (20–64%)
Day 30	43% (21–65%)
Day 90	54% (28–80%)
Day 180	59% (37–81%)
(AM J Pediatric Hematology Oncol 1990:12:95–104)	
Please note that these ranges were not established using the current ranges and analyzer at TCH Coagulation Lab	
Protein S (P)	
Adult	58–128%
Normal ranges for healthy full-term infants	
Day 1	36% (12–60%)
Day 5	50% (22–78%)
Day 30	63% (33–93%)
Day 90	86% (54–118%)
Day 180	87% (55–119%)
Please note that these ranges were not established using the current ranges and analyzer at TCH Coagulation Lab [1]	
Prothrombin time (P)	
Adult	11.4–15.8 s
Neonatal reference range from cord blood	12.9–16.9 s
Partial thromboplastin time (P)	
Adult	24.8–34.4 s
Neonatal reference range from cord blood	28.7–53.7 s
STACLOT tube 1–tube 2	<9.8
Result	Negative
Reptilase time (P)	16.3–19.8 s
ROTEM (WB)	
INTEM	
Clotting time (CT)	122–208 s
Clot formation time (CFT)	45–110 s
Alpha angle	70–81 degrees
A10	48–63 mm
A20	51–72 mm
Maximum clot firmness (MCF)	51–72 mm
Maximum lysis (ML)	7–21 %
EXTEM	
Clotting time (CT)	43–82 s
Clot formation time (CFT)	48–127 s
Alpha angle	65–80 degrees
A10	48–67 mm
A20	50–70 mm
Maximum Clot Firmness (MCF)	52–72 mm
Maximum lysis (ML)	8–22%
FIBTEM	
A10 A20	8–25 mm
Maximum clot firmness (MCF)	10–23 mm
	10–23 mm
Thrombin time (P)	15.0–19.0 s
VWF antigen (P)	56–176%
VWF ristocetin co-factor (P)	48–142%
VWF activity/antigen ratio	0.7–1.2
Unfractionated heparin (P)	0.35–0.70 U/mL

ADP, adenosine diphosphate; FEU, fibrinogen equivalent units; INR, international normalized ratio; P, plasma; S, serum; WB, whole blood.

Reference

1 Andrew M, Paes B, Johnston M. Development of the hemostatic system in the neonate and young infant. Am J Pediatr Hematol Oncol 1990; 12: 95–104.

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Note: page numbers in *italics* refer to figures, those in **bold** refer to tables and boxes.

Gregory's Pediatric Anesthesia, Sixth Edition. Edited by Dean B. Andropoulos and George A. Gregory.